

SINGH & SINGH LAW FIRM LLP

July 1, 2019

The Controller of Patents
The Patent Office,
Plot No. 32,
Dwarka, Sector 14
New Delhi, Delhi 110075

By Online

Subject: Representation under Section 25(1) read with Rule 55

Indian Patent Application No.: 8222/DELNP/2015
Date of Patent: 10/09/2015
Title of the invention: "TOFACITINIB ORAL SUSTAINED RELEASE
DOSAGE FORMS"
Name of the Patentee: PFIZER INC.
Name of the Opponent: SUJATA SHARMA

Dear Sirs,

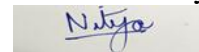
We hereby submit Representation under Section 25(1) read with Rule 55 of the Patents Act, 1970 against Indian Patent Application No. 8222/DELNP/2015 titled "Tofacitinib Oral Sustained Release Dosage Forms" on behalf of **Ms. Sujata Sharma**.

The following documents are enclosed herewith in reference to the same:

1. Form 7A
2. Representation under Section 25(1) along with Annexures (A to G)
3. POA (Form 26)

Thanking you,

Yours sincerely



Nitya Sharma
(IN/PA-3522)

Of Singh & Singh Law Firm LLP
AGENT FOR THE APPLICANT

Encl: As stated Above

BEFORE THE INDIAN PATENT OFFICE, NEW DELHI

In the matter of a representation under Section 25(1) read with Rule 55 of The Patents Act, 1970

IN THE MATTER OF:

Application No.: 8222/DELNP/2015

Date of Filing of Application: 10.09.2015

IN THE MATTER OF:

Sujata Sharma

.....Opponent

VERSUS

Pfizer Inc.

.....Applicant

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Ms. Bitika Sharma, Ms. Anusuya Nigam, Ms. Nitya Sharma (INPA-3522)

Of Singh & Singh Law Firm

Opponent's Agent

New Delhi

Dated: 29th June, 2019

FORM 7A
THE PATENTS ACT, 1970
(39 OF 1970)
AND
THE PATENT RULES, 2003
NOTICE OF OPPOSITION
(See section 25(1); rule 55-A)

I, Sujata Sharma, an Indian Citizen, D/O Lt. Birendranath Paul residing at House No. 328, Chotta Ayma, Po. Nimpura, Dist. Medinipur West, Kharagpur, West Bengal-721304, India, hereby give representation by way of opposition to grant of patent in respect of Patent Application No. **8222/DELNP/2015** dated September 10, 2015 made by **Pfizer Inc.**, having office at **235, East 42nd Street, New York, New York 10017, USA.** and published on August 31, 2016 under Section 11A in the Official Journal of Indian Patent Office on the following grounds:

1. **Section 25(1)(b)**: that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim:
 - i. in any specification filed in pursuance of an application for a patent made in India on or after 1st day of January, 1912; or
 - ii. in India or elsewhere, in any other document:

Provided that the ground specified in sub-clause (ii) shall not be available where such publication does not constitute an anticipation of the invention by virtue of sub-section (2) or sub-section (3) of section 29.

2. **Section 25(1)(e)**: that the invention so far as claimed in any claim of the complete specification is obvious and does not involve any inventive step, having regard to the matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant's claim.
3. **Section 25(1)(f)**: that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act.
4. **Section 25(1)(g)**: that complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
5. **Section 25(1)(h)**: that the applicant has failed to disclose to the Controller the information required by Section 8 or has furnished the information which in any material particular was false to his knowledge.

Our address for service in India is:

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e-mail: bitika@singhandsingh.com

Dated this 29th day of June, 2019

Ms. Bitika Sharma, Ms. Anusuya Nigam, Ms. Nitya Sharma

(INPA-3522)

Of Singh & Singh Law Firm

Opponent's Agent

To,

The Controller of Patents,

The Patents Office,

At Delhi

BEFORE THE PATENTS OFFICE, DELHI

In the matter of a representation under Section 25(1) read with
Rule 55 of The Patents Act, 1970

IN THE MATTER OF:

Application No.: **8222/DELNP/2015**

Date of Filing of Application: **10.09.2015**

IN THE MATTER OF:

Sujata Sharma

.....Opponent

VERSUS

Pfizer Inc.

.....Applicant

**REPRESENTATION BY WAY OF OPPOSITION UNDER SECTION
25(1) OF THE PATENTS ACT, 1970 ON BEHALF OF THE
OPPONENT/PETITIONER.**

1. It is submitted that the present representation is being filed by Ms. Sujata Sharma, (hereinafter referred to as the 'Opponent') opposing the grant of the Indian patent no. 8222/DELNP/2015 (hereinafter referred to as 'IN '222' or the 'impugned application') in favor of Pfizer Inc. (hereinafter referred to as the 'Applicant' or 'Respondent'). The present representation has been signed by the Opponent.

ABOUT THE OPPONENT:

The Opponent Ms. Sujata Sharma is a Post Graduate in Pharmacy. She has 5 years of experience in drug development and formulation. She is also involved in various Research and Development of Generic Drugs.

LOCUS STANDI

2. As per Section 25(1) any person may, in writing, file an opposition to the Ld. Controller against the grant of patent on any of the grounds, available after the publication of the said application and before the grant thereof.

ABOUT THE IMPUGNED PATENT APPLICATION

3. It is submitted that the Applicant has filed for the Indian Patent Application No. IN 8222/DELNP/2015 on September 10, 2015. The details of the said patent are as under:

Application Number	8222/DELNP/2015
Applicant Name	Pfizer Inc.
Title of Invention	TOFACITINIB ORAL SUSTAINED RELEASE DOSAGE FORMS
Priority Date	March 16, 2013
Date of Filing of PCT Application (PCT/IB2014/059689)	March 12, 2014
Date of Filing / Entry to National Phase	September 10, 2015
Date of Publication of Application u/s 11 A	August 31, 2016
Date of filing Request for Examination before the IPO	September 10, 2015
Date of Filing Response to First Examination Report	October 08, 2018

4. The impugned application, as amended, contains the following 25 claims, after the amendment of claims as filed on which are being challenged by the Opponent:

Claim 1:

A once daily pharmaceutical dosage form comprising a core comprising 11 mg of tofacitinib, or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof, and an osmagen, and a semi-permeable membrane coating surrounding the core wherein said coating comprises a water-insoluble polymer, wherein said dosage form is a sustained release dosage form, and when added to a test medium comprising 900 ml of 0.05M pH 6.8 potassium phosphate buffer at 37° C in a standard USP rotating paddle apparatus and the paddles are rotated at 50 rpm, dissolves not more than 30% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 1 hour, and not less than 35% and not more than 75% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 2.5 hours and not less than 75% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 5 hours and wherein said dosage form delivers the tofacitinib, or pharmaceutically acceptable salt thereof, to a subject primarily by osmotic pressure and wherein the water-insoluble polymer is a cellulose derivative that sustains release of the tofacitinib, or pharmaceutically acceptable salt thereof.

Claim 2:

A once daily pharmaceutical dosage form comprising a core comprising 11 mg of tofacitinib, or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof, and an osmagen, and a semi-permeable membrane coating

surrounding the core wherein said coating comprises a water-insoluble polymer, wherein the dosage form is a sustained release dosage form and when administered orally to a subject provides an AUC in the range of 80% to 125% of the AUC of 5 mg of tofacitinib or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof administered as an immediate release formulation BID and provides a ratio of geometric mean plasma C_{max} to C_{min} from about 10 to about 100 and wherein the dosage form delivers the tofacitinib, or pharmaceutically acceptable salt thereof, to the subject primarily by osmotic pressure and wherein the water-insoluble polymer is a cellulose derivative that sustains release of the tofacitinib or pharmaceutically acceptable salt thereof.

Claim 3:

The pharmaceutical dosage form of claim 2, wherein the AUC range is 90% to 110% and the geometric mean plasma concentration C_{max} to C_{min} from about 20 to about 40.

Claim 4:

The pharmaceutical dosage form of claim 3, wherein the geometric mean plasma concentration C_{max} to C_{min} from about 20 to about 30.

Claim 5:

The pharmaceutical dosage form of claim 2, wherein when the dosage form is administered orally to the subject provides a mean plasma C_{max} in the range of 70% to 125% of the mean plasma C_{max} of tofacitinib administered as the immediate release formulation BID at steady state.

Claim 6:

The pharmaceutical dosage form of claim 2, wherein when the dosage form is administered orally to the subject provides a drug holiday in the range of 80% to 110% of the drug holiday of tofacitinib administered as the immediate release formulation BID over a 24 hour period.

Claim 7:

The pharmaceutical dosage form of claim 2, having a drug holiday from about 15 to about 18 hours over the 24 hour period.

Claim 8:

A once daily pharmaceutical dosage form comprising
a core comprising 11 mg of tofacitinib, or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof, and an osmagen,
and a semi-permeable membrane coating surrounding the core wherein said coating comprises a water-insoluble polymer,
wherein said dosage form is a sustained release dosage form, and when administered to a subject has a mean area under the plasma concentration versus time curve following administration from about 17 ng-hr/mL per mg of tofacitinib dosed to about 42 ng-hr/mL per mg of tofacitinib dosed and a ratio of geometric mean plasma C_{max} to C_{min} from about 10 to about 100 and wherein said dosage form delivers the tofacitinib, or pharmaceutically acceptable salt thereof, to the subject primarily by osmotic pressure and wherein the water-insoluble polymer is a cellulose derivative that sustains release of the tofacitinib or pharmaceutically acceptable salt thereof.

Claim 9:

The pharmaceutical dosage form of claim 8, wherein the ratio of geometric mean plasma C_{max} to C_{min} from about 20 to about 40.

Claim 10:

The pharmaceutical dosage form of claim 9, wherein the ratio of geometric mean plasma C_{max} to C_{min} from about 20 to about 30.

Claim 11:

The pharmaceutical dosage form of claim 8, wherein the subject has a single, continuous time above about 17 ng/ml from about 6 to about 15 hours and a single, continuous time below about 17 ng/ml from about 9 to about 18 hours over a dosing 24 hours interval.

Claim 12:

The pharmaceutical dosage form of claim 11, wherein the subject has a single, continuous time above about 17 ng/ml from about 6 to about 9 hours.

Claim 13:

The pharmaceutical dosage form of claim 11, wherein the subject has a single, continuous time below about 17 ng/ml from about 15 to about 18 hours.

Claim 14:

The pharmaceutical dosage form of claim 11, wherein the subject has a single, continuous time above about 17 ng/ml from about 11 to about 15 hours.

Claim 15:

The pharmaceutical dosage form of claim 11, wherein the subject has a single, continuous time below about 17 ng/ml from about 9 to about 13 hours.

Claim 16:

The pharmaceutical dosage form of claim 8, wherein the subject has a mean maximum plasma concentration (C_{max}) from about 3 ng/mL per mg to about 6 ng/mL per mg of tofacitinib dosed.

Claim 17:

The pharmaceutical dosage form of claim 8, wherein said dosage form delivers the tofacitinib, or pharmaceutically acceptable salt thereof, by a system selected from the group consisting of an extrudable core system, a swellable core system, and an asymmetric membrane technology.

Claim 18:

The pharmaceutical dosage form of claim 8 wherein, said cellulose derivative is cellulose acetate.

Claim 19:

The pharmaceutical dosage form of claim 8, wherein said coating further comprising a water soluble polymer having an average molecular weight between 2000 and 100,000 daltons.

Claim 20:

The pharmaceutical dosage form of claim 19, wherein said water soluble polymer is selected from the group consisting of water soluble cellulose derivatives, acacia, dextrin, guar gum,

maltodextrin, sodium alginate, starch, polyacrylates, and polyvinyl alcohols.

Claim 21:

The pharmaceutical dosage form of claim 20, wherein said water soluble cellulose derivatives comprises hydroxypropylcellulose, hydroxypropylmethylcellulose or hydroxyethylcellulose.

Claim 22:

The pharmaceutical dosage forms of claim 8, wherein the osmagen is a sugar.

Claim 23:

The pharmaceutical dosage form of claim 22, wherein the sugar is sorbitol.

Claim 24:

The once daily pharmaceutical dosage form of claim 8 wherein the subject has a mean steady-state minimum plasma concentration (Cmin) less than about 0.3 ng/mL per mg of tofacitinib dosed.

Claim 25:

The once daily pharmaceutical dosage form of claim 8, wherein when administered orally to the subject has a mean fed/fasted ratio of the area under the plasma concentration versus time curve from about 0.7 to about 1.4 and a mean fed/fasted ratio of the maximum plasma concentration (Cmax) from about 0.7 to about 1.4.

5. It is submitted that a perusal of the aforesaid claims reveals that monopoly is being sought by the

Applicant/Respondent qua oral sustained release pharmaceutical dosage form of 3-((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile (having the INN name tofacitinib). It is submitted that the formulations described therein allegedly have desirable pharmacokinetic characteristics. It is submitted that Tofacitinib, its crystalline or amorphous form, salts thereof, methods of synthesizing Tofacitinib and in fact the polymorphs of tofacitinib are already known and used in the art for treatment of rheumatoid arthritis by inhibition of Janus Kinases (JAKs). Therefore, it is most respectfully submitted that the present patent intends to claim merely a new form of the already known and claimed compound, tofacitinib, the formulations of which are also already known and used in the art.

6. It is submitted that the impugned patent fails to provide any new or novel compound that is not merely a derivative or new form of the compound, tofacitinib, already known in the art and is clearly barred under Section 3(d) of the Patents Act, 1970 (hereinafter referred to as the 'Act') as the same is not an invention as per the provisions of the Act. By way of the impugned application, the Patentee/Respondent is indulging in evergreening, and attempting to circumvent the very intent of the Legislature which is to prevent grant of patents that result in repeated and extended monopolies being granted in respect of the same compounds with known activity and use in different forms.

7. The impugned patent application was published by the Patent Office on 31st August, 2016. As per Section 25(1) of the Act, any "person" may give a notice of Opposition to the Ld. Controller of Patents with respect to a patent, at any time after the publication but before the grant of patent. Therefore, the Opponent submits its opposition by way of representation under Section 25(1) of the Indian Patents Act, 1970 (hereinafter the Act) in respect of the Patent Application IN 8222/DELNP/2015. The present Opposition is being filed within the stipulated time period. Further, locus standi is not a condition precedent for an opposition under Section 25(1). The grounds of the opposition under Section 25(1) of the Act are as follow:

GROUND I

A. Section 25(1)(b): that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim:

- i. in any specification filed in pursuance of an application for a patent made in India on or after 1st day of January, 1912; or**
- ii. in India or elsewhere, in any other document:
Provided that the ground specified in sub-clause (ii) shall not be available where such publication does not constitute an anticipation of the invention by virtue of sub-section (2) or sub-section (3) of section 29**

8. It is most respectfully submitted that the claims of impugned application lack novelty in view of following prior art document:
9. It is submitted that the International Application no. **WO 2012/100949 (D1)** titled "Oral dosage forms for modified release comprising tasocitinib" (a copy whereof is being filed with the present representation and marked as Annexure A) claiming priority from January 27, 2011 and published on August 02, 2012 covers an oral dosage forms comprising a JAK3 inhibitor, preferably tasocitinib (tofacitinib), suitable for modified release, and the processes of preparation thereof.
10. It is submitted that the invention as disclosed in D1 essentially relates to oral dosage forms comprising a pharmaceutically active substance, preferably 3-{{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}}3-oxo-propionitrile i.e. tasocitinib (tofacitinib) which are suitable for modified release and the processes of preparing such oral dosage forms.
11. It is submitted that the present prior art addressed and met the need in the art for the once daily dosage form of administration of tofacitinib. The invention as taught in D1 found that the dosage forms of the present invention despite the high solubility of tofacitinib have the advantage that it is gradually released over a relatively long period such that the drug is maintained in the blood stream for a

long time and at a uniform concentration which allows administration to be only once daily.

12. It is submitted that the oral dosage form as contained in the present prior art overcomes the problems of the art by providing a dosage form for modified release comprising:
 - a. Tasocitinib (being tofacitinib)
 - b. A non-erodible material
13. It is submitted D1 teaches that the oral dosage forms of tasocitinib (tofacitinib) may contain it in amorphous form, preferably as amorphous tofacitinib citrate, in crystalline form or as a mixture of both forms. And the examples of non-erodible material, as taught, specifically include cellulose derivatives/polymers such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, etc.
14. It is submitted that a plain reading of D1 establishes that the said prior art discloses all the claimed elements of the impugned application, specially the claim 1. It is submitted that line no. 3, page 6 of D1, gives for oral dosage forms comprising 4 to 12 mg of Tofacitinib, line nos. 16 - 20 disclose the components of osmotic formulation being Osmogen and semi-permeable membrane.
15. It is submitted that the present prior art D1 discloses and enables various modified release formulations of Tofacitinib, including delayed release, prolonged release, sustained release, extended release and/or controlled

release formulations. It is submitted that the sustained release formulation, as contained in the prior art, squarely covers the claimed dissolution profile of the impugned application. It is submitted that as per the complete specification of D1, "Sustained release" usually indicates an initial release of drug (i.e., Tofacitinib), sufficient to provide a therapeutic dose soon after administration, preferably within two hours after administration, and then a gradual release after an extended period of time, preferably for about 3 to 18 hours, in particular for 4 to 8 hours".

16. It is submitted that the present prior art D1 already provides all the components and features of the sustained release dosage form of tofacitinib as sought to be claimed in the impugned application. Therefore, it is amply clear that each and every element of the claims of the impugned application were anticipated and taught by D1, much before the priority of the impugned application.
17. It is submitted that the claims 2 and 8 of the impugned application, and all other dependent claims thereof, are directed towards the pharmacokinetic profile of the dosage form contained in the Claim 1 of the impugned application, which is fully anticipated by document D1. Therefore, the mentioned prior art anticipates all the claims of the invention. It is submitted that the pharmacokinetic profile as recited by claims 2, 8 and other dependent claims thereof, are inherent features of the broad disclosure of D1.

18. It is submitted that D1, discloses an extended release formulation of tofacitinib having the purported advantage that tofacitinib is gradually released over a relatively long period at a uniform concentration, thereby, teaching toward the "once daily" dosage form of tofacitinib.
19. Therefore, it is most respectfully submitted that the prior art document D1 discloses and anticipates all the inventive features of the alleged invention as contained in the impugned application. Further, the present prior art D1 also entails all the components and their respective concentrations as claimed in the impugned application and renders the impugned application completely anticipated. It is submitted that the impugned application is, hence, liable to be rejected on this ground alone that it lacks novelty as mandated by Section 2(1) (j) of the Act.

GROUND II

B. Section 25(1)(e): that the invention so far as claimed in any claim of the complete specification is obvious and does not involve any inventive step, having regard to the matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant's claim:

20. It is humbly submitted that the impugned application relates to oral dosage formulations which are used as inhibitors of Janus Kinases. It is submitted that the formulations of tofacitinib are known to be used in the treatment of rheumatoid arthritis. It is most respectfully

submitted that the oral dosage form of tofacitinib were obvious to a person skilled in the art on the basis of international application no. **WO 2012/100949 (D1)** titled "Oral dosage forms for modified release comprising tasocitinib". Without prejudice to the Opponent's contention that the aforesaid prior art document renders the claimed invention anticipated in nature, it also provides sufficient teaching, suggestion and motivation to enable a person skilled in the art to prepare the sustained release once daily oral dosage form of tofacitinib as claimed in the impugned application. Reliance is being placed on the analysis of the aforesaid PCT patent application (D1) which has been done hereinabove under the ground of anticipation.

21. It is submitted that all the claims of the impugned application are directed towards the pharmacokinetic profile of the dosage form contained in the Claim 1 of the impugned application, which finds sufficient teaching in prior art document D1. Therefore, the mentioned prior art teaches towards the claims of the invention. It is submitted that D1, specially teaches towards a modified release formulation of tofacitinib having the purported advantage that tofacitinib is gradually released over a relatively long period at a uniform concentration, which results in little blood level fluctuation in the patient to avoid periods of therapeutic underdosing.
22. It is submitted that the present prior art D1 also teaches that osmogen and semi permeable membrane can be used to sustain the release of the core containing tofacitinib.

23. It is submitted that the compounds as claimed in the impugned patent along with their pharmaceutically acceptable salts were obvious to a person skilled in the art on the basis of the prior arts as detailed hereinbelow, in addition to prior art D1.
24. **Indian Patent No. 241773 titled as "PYRROLO[2,3-d]PYRIMIDINE COMPOUNDS" granted on 24 July, 2010 (D2)** *(a copy whereof is being filed with the present representation and marked as Annexure B)*
25. It is submitted that the present prior art D2 is directed to pyrrolo[2,3-d]pyrimidine compounds which are inhibitors of Janus Kinase 3 (JAK3) and as such are useful in therapy as immunosuppressive agent. The compounds of the present prior art relate to a method for the treatment of rheumatoid arthritis.
26. It is submitted that D1 teaches that JAK inhibitor is preferably -((3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile being tofacitinib or a pharmaceutically acceptable salt thereof.
27. It is submitted that D2 also discloses the schemes of manufacture of tofacitinib. Further, as per the present prior art D2, the dosage forms containing the active compound of the invention may be developed for sustained delivery.

28. Therefore, D2 teaches towards the development of oral dosage forms containing tofacitinib for sustained delivery using methods that were already known in the art.

29. **Indian Patent No. 218212 (D3) titled as ""CRYSTALLINE 3-{(3R,4R)-4-METHYL-3-[METHYL-[7H-PYRROLO[2,3-D]PYRIMIDIN-4-YL)-AMINO]-PIPERIDIN-L-YL}-3-OXO-PROPIONITRILE MONO CITRATE SALT AND ITS METHOD OF PREPARATION"**
(a copy whereof is being filed with the present representation and marked as Annexure C)

30. It is submitted that the present prior art D3 discloses specifically the crystalline 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-l-yl}-3-oxo-propionitrile mono citrate salt i.e the crystalline citrate salt of tofacitinib useful as JAK inhibitors.

31. The present prior art D3 also discloses the process for preparation of such citrate salts of tofacitinib. Further, it is submitted that a proposed dose of the active compounds of the invention as disclosed in D3 for oral, parenteral or buccal administration to the average adult human for the treatment of rheumatoid arthritis is 0.1 to 1000 mg of the active ingredient per unit dose which could be administered.

32. It is submitted that the dosage forms as contained in D3, may be administered 1 to 4 times per day and therefore

the present prior art provides sufficient motivation towards once daily dosage form of tofacitinib.

33. Therefore, it is submitted that the present prior art D3 teaches towards oral dosage forms containing 11mg of tofacitinib for sustained release.

34. **Indian Application no. 991/MUMNP/2003 titled "CHIRAL SALT RESOLUTION" (D4)** *(a copy whereof is being filed with the present representation and marked as Annexure D)*

35. The present prior art D4 related to methods for effecting chiral salt resolution from racemic mixtures of enantiomers and particularly the precursor enantiomers used in making pyrrolo[2,3-d] pyrimidine compounds, which are inhibitors of JAK3.

36. It is submitted that the mentioned prior art D4 was an application refused by the Ld. Controller under Section 15 of the Act and therefore is pertinent of note here to highlight the mala fide attempts of the Applicant to indulge in ever greening of the invention containing Tofacitinib.

37. **FDA guidance referred as Guidance for industry, (May 1998, clinical 6), (D5)** *(a copy whereof is being filed with the present representation and marked as Annexure E)*

38. It is submitted that Tofacitinib was approved by US FDA on Nov 6, 2012 as an immediate release dosage form. It is submitted that it was already known from D5, and otherwise also available to a person of ordinary skill in the art, that evidence of bioequivalence of a modified release formulation against the approved immediate release formulation is a simple and effective tool to establish effectiveness of a drug and its regulatory approval.
39. The relevant portion of D5, page no.7, is reproduced herein below for ready reference:
- "In some cases, modified release dosage forms may be approved on the basis of pharmacokinetic data linking the new dosage form to a previously studied immediate-release dosage form."*
40. It is submitted that determining relationship and linking the data of pharmacokinetic profile of an already approved immediate release formulation to a modified release dosage form as recited in the independent claim 2 and further the dependent claims (claims 3 to 7) of the impugned application is a general practice which is usually adopted by a person of ordinary skilled in art. Therefore, it is submitted that the claimed AUC range of 80% to 125% of the AUC of 5 mg of tofacitinib administered as an immediate release formulation BID and hence the ratio of geometric mean plasma C_{max} to C_{min} from about 10 to about 100 is obvious to a person skilled in the art in light of D5.

41. It is submitted that the combined reading of prior arts D1, D2 and D3 along with D5 will provide sufficient motivation to a person skilled in the art to arrive at the dosage formulations as contained in the impugned application. Therefore, it is submitted that the present prior art has no technical advancement over what was already known in the art and is a regular development as a result of routine experimentation in the field.
42. Therefore, it is submitted that in view of the above-mentioned prior art, any person skilled in the art will be motivated to form modified release oral dosage form of tofacitinib for use as JAK inhibitor and in treatment of rheumatoid arthritis.

CONCLUSION:

43. On the basis of the teachings and disclosures contained in the various prior art documents as discussed by the Opponent, it would be obvious for a person skilled in the art to develop the compounds as disclosed and claimed in the impugned patent since it was already known that:
- JAK inhibitors can be used for treatment of arthritis;
 - Tofacitinib can be used in modified release form as JAK inhibitors respectively for the treatment of arthritis;
 - Tofacitinib in immediate release dosage form;
 - Tofacitinib should be administered in once daily dosage form;

- Osmogen and Semi permeable membrane can be used to sustain the release of the core containing tofacitinib;

44. Moreover, it is submitted that all the features of the present alleged invention as claimed in the impugned patent find sufficient motivation/ teachings in the art. As a result, it was obvious for a person skilled in the art to arrive at the compounds as claimed in the impugned patent.

45. It is most respectfully submitted that every new form cannot be rewarded with a patent unless there is a genuine and enforceable development (which was not obvious to a person skilled in the art in view of what was already known/prevalent/used in the art). In the present case, based on the disclosures contained in the prior art documents cited hereinabove, it was worthwhile for a person skilled in the art to study the efficacy of the different dosage forms by trial and error method which does not warrant the grant of a patented monopoly. Thus, the impugned patent application is liable to be dismissed on this ground alone.

GROUND III

C. SECTION 25(2)(f): that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act

Claims not patentable under Section 3(d):

46. It is most respectfully submitted that the impugned patent application does not constitute an invention and is not patentable in view of the Section 3(d) of the Act. It is submitted that the compounds claimed in the impugned patent application fall within the purview of Section 3(d) of the Act as the same are nothing but new forms of previously known and claimed compound, tofacitinib. Section 3(d) of the Act provides that:

"Section 3: -

What are not inventions:

.....

(d) the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.

Explanation.—For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy;

....."

(emphasis added)

47. It is submitted that the alleged invention as claimed and disclosed in the impugned patent application is nothing but an alleged new dosage form, i.e. oral modified release solid dosage form of the already known compound, tofacitinib,

and composition thereof as claimed and enabled in D1 to D5 which has been discussed hereinabove.

48. It is most respectfully submitted that the dosage forms claimed in the impugned patent application fall within the mischief of Section 3(d) which states that "the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant" is not patentable under this Act.
49. It is submitted that the impugned application does not provide any experimental data or clinical trial results demonstrating "enhanced therapeutic efficacy" of the claimed osmotic composition over the already known immediate release composition.
50. It is submitted that the mere descriptive features and inherent characteristics of the dosage forms cannot be deemed to enhance the efficacy of the already known compositions and their dosage forms.
51. It is submitted that the alleged invention claimed in the impugned patent application is a merely an attempt to evergreen and extend the undue patent monopoly.

52. It is submitted that as per Section 3(d) of Indian Patents Act, 1970 and the settled law, a new form is deemed to be patentable in India only when the new form of the compound shows enhanced therapeutic efficacy over its individual components i.e. the dosage form as disclosed in the impugned application ought to have enhanced efficacy over the dosage form as known from D1.
53. It is submitted that the subject matter of the impugned application is not patentable in view of section 3(d) of Indian Patents Act, 1970 until and unless the same shows better therapeutic efficacy in comparison with the oral dosage form of tofacitinib as already known in D1 and D2. The explanation of Section 3(d) clearly and unambiguously points out to the fact that a new form of the known substance attracts 3(d).
54. It is submitted that this is nothing but a mala fide attempt on the part of the Applicant to mislead the IPO. It is submitted that the impugned patent does not constitute an invention and is not patentable in view of the Section 3(d) of the Act. It is humbly stated that the impugned application discloses and claims merely an oral dosage form of tofacitinib for use as inhibitor of JAK3 in the treatment of rheumatoid arthritis. As evident from the above analysis, the claimed dosage form of tofacitinib was already known and subject matter of sufficient patent applications, research and were within public domain. In such circumstances, the Applicant had the responsibility to

show the improvement in the properties with regard to therapeutic efficacy.

55. It is most respectfully submitted that if any patent which includes subject matter specifically excluded under Section 3(d) is inadvertently granted by the Indian Patent Office, it shall not only lead to an illegal monopoly over a known substance in favor of the Patentee, but shall also be counterproductive to the intention of the Legislature in including the said provision in order to ensure that after a substance has been used exclusively by a patentee for the full term, it must necessarily fall into public domain. Thereafter, no exclusivity can be granted to a person/entity to claim monopoly over that which is already public domain.

Claims not patentable under Section 3(e):

56. It is most respectfully submitted that Section 3(e) of the Act prohibits from patenting a substance which has been obtained by mere admixture resulting only in aggregation of properties of the components. The aforesaid section has been reproduced herein below for the sake convenience.

Section 3(e) of the Act provides that:

"Section 3: -

What are not inventions:

.....

(e) a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance

.....”

57. It is submitted that the present invention is mere admixture of known components being tofacitinib, cellulose and semipermeable membrane and is barred under Section 3(e) of the Act. It is submitted that the complete specification makes no disclosure with respect to the synergistic effect in order to be deemed patentable. It is further submitted that the synergistic effect should be clearly brought out in the description by way of comparison at the time of filing of the Application itself. However, for the present invention no such documents or details were made available either at the time of filing of the application or at the time of filing the response to examination report. Thus, the objection under section 3(e) stands and in view of the same the impugned patent is liable to be revoked.

58. It is most respectfully submitted that the dosage forms claimed in the impugned patent application fall within the purview of Section 3(e) which clearly states that a substance obtained by a mere admixture resulting only in the aggregation of properties of components thereof is not patentable.

59. It is submitted that the applicant has failed to show any data to establish the synergistic effect of the unit dose composition as contained in the impugned application. It is

submitted that absence of any data establishing synergistic effect, renders the claims non patentable under Section 3(e) of the Act.

60. Further, it is submitted that the weight independent dose is inherent property of the drug tofacitinib and same is evident from the US FDA approval label (*attached hereto as Annexure F*) which suggests that "No Dose Adjustment" is required based on age, weight, gender and race and therefore "weight independent dose" cannot be used as an evidence of synergism.
61. Thus, all the Claims of the impugned application are liable to be rejected under Section 3(e) of the Act, as the said claims define a mere admixture resulting only in aggregation of the properties of components thereof.
62. Further it is submitted that it is not clear if the combined agents act together to provide a technical effect that is greater than just the sum of the two or more agents alone, or whether the combination is in fact a mere juxtaposition with no interaction of the agents.
63. Thus, no patent can be legally granted *qua* the claims in the impugned patent and the impugned application stands liable to be rejected and not be granted a patent under the Indian Patent Law.
64. It is of importance to note that in the light of the aforesaid discussion and submissions, it is clearly evident that the

impugned patent does not possess any inventive step and is obvious to a person skilled in the art. Additionally, it also fails to meet the requirement of section 3(d) of the Act as the Patentee has not provided any details in the complete specification to establish significant enhancement in therapeutic efficacy of the oral dosage forms derived therefrom claimed and disclosed in the impugned application. Further, impugned patent also fails to meet the requirement of section 3(e) of the Act as the claimed invention is mere admixture of the known components. Further, the same also does not involve any technical advancement over what was already known in the art as the Patentee has merely conducted substitutions in the already known compounds to arrive at the impugned patent. As a result, the impugned patent cannot be regarded as an invention within the meaning of the Act and is thus liable to be revoked on the present ground alone.

GROUND IV

Section 25(1)(g) that complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed

65. It is submitted that the complete specification of the impugned patent does not sufficiently and fairly describe the invention and the method by which it is to be performed, that is to say, that the description of the method or the instructions for the working of the invention as contained in the complete specification are not themselves sufficient to enable a person possessing

average skill in, and average knowledge of, the art to which the invention relates, to work the invention, or that it does not disclose the best method of performing it which was known to the Patentee and for which he was entitled to claim protection and in light of the same the impugned patent is not patentable.

66. It is submitted that Section 10(4) of the Act states that
"Every complete specification shall—

- (a) fully and particularly describe the invention and its operation or use and the method by which it is to be performed;*
- (b) disclose the best method of performing the invention which is known to the applicant and for which he is entitled to claim protection; and*
- (c) end with a claim or claims defining the scope of the invention for which protection is claimed.*
- (d) be accompanied by an abstract to provide technical information on the invention."*

67. It is respectfully submitted that the independent claims 1, 2 and 8, and thereby their dependent claims (the claims of the impugned application in their entirety), do not clearly and sufficiently define the scope of the alleged invention in the absence of mention of all significant elements/components of composition, like constituents and their properties, percentage etc. that reflects technological contribution to establish the novelty and/or inventive step and define the scope of alleged invention.

68. It is submitted that the claims of the impugned application attempt to define the subject matter in terms of result to be achieved vis a vis the dissolution profile, C_{max}, AUC and mean area under the plasma concentration versus time

curve values. It is submitted that the claims cannot be defined by just specifying the results to be achieved without any direction of structure limited with significant elements of composition, like constituents and their properties, percentage etc. that are required to achieve these results.

69. It is submitted that the claims of the impugned application entail broad structural elements such as osmogen, semi-permeable membrane and water insoluble cellulose polymer and hence provide multiple possibilities which may or may not provide the claimed results. It is submitted that, the overlapping scope, different features, and the varied outcome makes the exact nature and scope of the alleged invention ambiguous, for which protection is sought. Therefore, it is submitted that the matter for which protection is sought is not clearly defined and hence claims does not meet the requirements of Section 10(5) of the Act, which makes it mandatory that the claims of a complete specification shall be clear and succinct and shall be fairly based on the matter disclosed in the specification.
70. It is of importance to note that the Patentee has failed to describe and disclose sufficiently in the complete specification any structural element of the dosage form which would enable a person of ordinary skill in art to distinguish between any osmotic formulations versus the osmotic formulation having the claimed release profile.

71. It is of pertinence to note here that the independent claims 1, 2 and 8 (and thus the dependent claims) attempt to define the subject matter in terms of the result to be achieved but does not provide any technical features that is necessary to achieve the desired release profile, its mechanism and control.
72. It is submitted that the specification does not teach any known general correlation between the structure of controlled release tofacitinib compositions and the ability to obtain a composition that achieves the claimed pharmacokinetic parameters, other than the specific compositions that are exemplified and tested. It is submitted that the disclosure is not sufficient to determine which design, structural configurations, ingredient and amount (properties, percentage etc.) could be used to formulate a composition which falls within the ambit of the claims.
73. Further, it is submitted that the reading of the complete specification is directed to multiple embodiments with different dosage form structures, however, the pharmacokinetic profile of all the embodiments has not been disclosed in the complete specification. It is submitted that there is no disclosure or study of the PK parameters of the formulations as contained in examples 5, 6, 7, 8 and 9. Further, the dissolution profile of formulation of example 9 has also not been disclosed in the description of the alleged invention.

74. It is submitted that a reading of the complete specification of the impugned application makes it amply clear that multiple examples disclosed in the specification, have very different structural elements in the formulation and dosage form design, thus providing wide possible range of dissolution profiles and PK parameters which render the nature of the invention ambiguous.
75. It is submitted that it is unclear from the examples/embodiments of the impugned application as to how the difference between each of the composition, its structure, ingredients and design would result into the claimed dissolution and PK profile. This creates unpredictability for the skilled artisan to determine which design, structure and ingredient could be used to formulate a composition which falls within the preview of the claims. Thus, there exists lack of clarity, sufficiency and enablement for one of ordinary skill to make or use the invention without undue experimentation.
76. The Opponent submits that a complete specification should sufficiently and clearly describe the invention and not leave a person skill in the art in a state where he has to conduct undue experimentation to perform the invention. There is no data and examples in the complete specification of the impugned application to show the best mode of working of the invention. Accordingly, it is not known as to what is the exact and actual workable method of arriving at the claimed dosage forms, and the workable and effective dosage forms claimed in the impugned application.

77. Therefore, it is submitted that the impugned patent does not meet with the requirements of Section 10(4) and Section 10(5) of the Act and hence is not patentable on this ground under Section 25(1)(g) of the Act, for lacking sufficient description and also being vague and ambiguous.

GROUND V

Section 25(1)(h) that the applicant has failed to disclose to the Controller the information required by Section 8 or has furnished the information which in any material particular was false to his knowledge;

It is most respectfully submitted that Section 8 of the Act specifically provides that:

Section 8: Information and undertaking regarding foreign applications

(1) Where an applicant for a patent under this Act is prosecuting either alone or jointly with any other person an application for a patent in any country outside India in respect of the same or substantially the same invention, or where to his knowledge such an application is being prosecuted by some person through whom he claims or by some person deriving title from him, he shall file along with his application [or subsequently [within the prescribed period as the Controller may allow]]—

[(a) a statement setting out detailed particulars or such application; and]

(b) an undertaking that, [up to the date of grant of patent in India,] he would keep the Controller informed in writing, from time to time, of [detailed particulars as required under] clause

(a) in respect of every other application relating to the same or substantially the same invention, if any, filed in any country outside India subsequently to the filing of the statement referred to in the aforesaid clause, within the prescribed time.

[(2) At any time after an application for patent is filed in India and till the grant of a patent or refusal to grant of a patent made thereon, the Controller may also require the applicant to furnish details, as may be prescribed, relating to the processing of the application in a country outside India, and in that event the applicant shall furnish to the Controller information available to him within such period as may be prescribed.]

78. As per the aforesaid provision, an applicant for a patent bears a continuing and mandatory duty to keep the Indian Patent Office informed of the status of all corresponding foreign applications (filed in respect of the same or substantially the same invention in respect of which a patent is being sought) including details regarding their grant, refusal, abandonment etc. It is of importance to note that the Patentee has failed to disclose to the Indian Patent Office, the details of the entire prosecution history of the impugned patent in other countries where a corresponding patent application has been filed, thereby deliberately hiding 'material facts' which are important to determine the patentability merits of the impugned application.

79. It is submitted that Sec 25(1)(h) mentions that a patent may be rejected if the applicant has failed to disclose

information required by Section 8 of Indian Patent Act. It is pertinent of note here that the Applicant has deliberately concealed the status of corresponding South Korean Application, being Application No. 10-2015-7029051. It is submitted that the Application has been "refused" and holds the said status since September 24, 2017. However, the Applicant has not placed the development before the Indian Patent Office even as late as August 29, 2018 when the Form 3 for the impugned application was filed before the Indian Patent Office. The current legal status and the refusal letter dated 21.08.2017 of the corresponding Korean application (*attached hereto as Annexure G.*)

80. It is submitted that the non-compliance of Section 8 by the Applicant is not merely an administrative miss. It is pertinent of note that in the present case the requirements of Section 8 was violated by failing to clearly specifying the refusal status and documents of patent application of Korea South which was withheld with an intent to deceive and mislead the examiner. The Applicant should have submitted the above details to the examiners as its duty of candor and good faith as also to comply with the requirements imposed on the Applicant by Section 8 of the Act.
81. It is relevant to note that concealment of the said facts, thus violates the mandatory provision of Section 8. Thus, the Applicant has failed to comply with the provisions of Section 8 of the Act and the impugned application is liable to be rejected on this ground alone.

PRAYER

82. In the facts and circumstances of the case the Opponent prays as follows:

- a) That the present pre-grant opposition allowed, and the Application No. IN 8222/DELNP/2015 and claims thereof be rejected under Section 25(1) of the Indian Patent Act, 1970;
- b) The Opponent may be allowed to file further documents as evidence if necessary to support their averments;
- c) The Opponent may be granted an opportunity of being heard in the matter before any orders are passed;
- d) Any other reliefs considering the facts and circumstances may be granted in favor of the Opponent in the interest of justice.

SINGH AND SINGH LAW FIRM LLP
ATTORNEYS FOR THE OPPONENT

Dated:27.06.2019

New Delhi

To,
The Controller of Patents
The Patents Office, Delhi

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(54) Title: ORAL DOSAGE FORMS FOR MODIFIED RELEASE COMPRISING TASOCITINIB

(57) Abstract: The invention essentially relates to oral dosage forms comprising a JAK3 inhibitor, preferably tasocitinib, suitable for modified release, and processes of preparing such oral dosage forms.

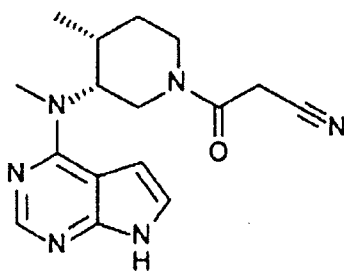
WO 2012/100949 A1

ORAL DOSAGE FORMS FOR MODIFIED RELEASE COMPRISING TASOCITINIB

Background

The invention essentially relates to oral dosage forms comprising a pharmaceutically active substance, preferably 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)3-oxo-propionitrile, suitable for modified release, and processes of preparing such oral dosage forms.

3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)3-oxo-propionitrile apparently has the chemical formula $C_{16}H_{20}N_6O$ and is reported in WO 03/048126 as an inhibitor of protein kinases, such as the enzyme Janus Kinase 3 (hereinafter also referred to as "JAK3") and as such it has been asserted that it is useful in therapy as immunosuppressive agents for organ transplants, xeno transplantation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia and other indications, where immunosuppression would be desirable (see WO 03/048126), and is known under the INN tasocitinib, which has recently changed to tofacitinib. The 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)3-oxo-propionitrile apparently has the chemical structure of formula (I):



formula (I).

In this regard it is noted that the compound according to formula (I) would seem to refer to 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)3-oxo propionitrile (= tasocitinib) or its solvates or hydrates as well as pharmaceutical acceptable salts thereof are said to be obtained according to the

procedures as outlined in WO 02/096909. The mono citrate form has apparently been described in WO 03/048162.

Whereas the prior art (WO 03/048162, WO 02/096909) mentions that tasocitinib might
5 be formulated into pharmaceutical compositions, no specific formulations have been disclosed.

When formulating tasocitinib, various physiological factors such as gastrointestinal pH, enzyme activities, gastric and intestinal transit rates apparently negatively influenced
10 important parameters of tasocitinib. As a solution for this problem an immediate release formulation, prepared by dry-compaction, was suggested, since the known pharmacokinetic parameters of tasocitinib taught the skilled person that an immediate release dosage form would be beneficial. In addition it was reported that especially low dose tasocitinib formulations generally suffered from the difficulty of providing a
15 sufficient content uniformity.

Hence, there is a need for the provision of pharmaceutical dosage forms and processes for the manufacture of these pharmaceutical dosage forms comprising tasocitinib, which do not suffer from the above mentioned draw-backs. Preferably, an
20 oral dosage form should be provided having improved properties like content-uniformity, solubility, dissolution profile, well defined, predictable and reproducible dissolution rates, stability and bioavailability. Such an oral dosage form should be producible in a large scale in an economic beneficial way.

25 Summary of the Invention

The present invention provides an oral dosage form for modified release that can overcome the above drawbacks, the oral dosage form for modified release comprising

- (a) tasocitinib (= tofacitinib), and
- 30 (b) a non-erodible material.

It was found that the dosage forms of the present invention despite the high solubility of tasocitinib have the advantage that the tasocitinib is gradually released over a relatively long period so that the drug is maintained in the blood stream for a long time and at a
35 uniform concentration. This allows administration, e.g., only once daily. Administration

of the oral dosage forms of the present invention result in little blood level fluctuation, that means periods of transient therapeutic overdose, followed by a period of therapeutic underdosing can be avoided. Consequently, the dosage forms of the present invention, particularly provide a constant release of tasocitinib, preferably over
5 a prolonged period of time, which avoids blood level fluctuations of the drug in the patient.

Moreover, the dosage form of the present invention is released in the gastrointestinal tract of the patient but not in the stomach, in order to avoid a "nervous stomach" or
10 nausea.

A further subject of the present invention is a process for manufacturing the oral dosage forms of the present invention, preferably in form of a modified release tablet.

15 Detailed Description of the Invention

In the following, explanations regarding the pharmaceutical dosage form of the present invention are given. However, these explanations also apply to the processes for manufacturing the pharmaceutical dosage form, such as the modified release tablet of
20 the present invention, and to the use of the present invention.

Within the present application generally the term "modified release" is used as defined by the USP. Preferably, modified release dosage forms are those whose drug release characteristics accomplish therapeutic or convenience objectives not offered by
25 immediate release forms. Generally, immediate release (IR) forms release at least 70 % of the drug within 1 hour or less. The term "modified release" can comprise delayed release, prolonged release, sustained release, extended release and/or controlled release.

30 Delayed release usually indicates that the drug (i.e., tasocitinib) is not being released immediately after administration but at a later time, preferably less than 10 % are released within two hours after administration.

Prolonged release usually indicates that the drug (i.e., tasocitinib) is provided for absorption over a longer period of time than IR forms, preferably for about 2 to 24 hours, in particular for 3 to 12 hours.

- 5 Sustained release usually indicates an initial release of drug (i.e., tasocitinib), sufficient to provide a therapeutic dose soon after administration, preferably within two hours after administration, and then a gradual release after an extended period of time, preferably for about 3 to 18 hours, in particular for 4 to 8 hours.
- 10 Extended release usually indicates a slow drug (i.e., tasocitinib) release, so that plasma concentrations are maintained at a therapeutic level for a time period of between 6 and 36 hours, preferably between 8 and 24 hours.

- 15 Controlled release dosage forms usually release the drug (i.e., tasocitinib) at a constant rate and provide plasma concentrations that remain essentially invariant with time.

In a preferred embodiment, the oral dosage form of the present invention is an extended release dosage form.

20

In particular, the oral dosage form of the present invention shows a drug release of less than 10 % within 2.0 hours. Further, the oral dosage form of the present invention shows a drug release of more than 80 % within 3.0 to 12.0 hours, preferably between 4.0 and 8.0 hours.

25

Generally, within this application the release profile is determined according to USP 31-NF26 release method, apparatus II (paddle). The measurements are carried out in preferably 900 ml 0.1 n HCl at 37 °C, wherein the stirring speed was 75 rpm, and re-buffering after 2 hours to pH 6.8.

30

In a preferred embodiment, the oral dosage form of the present invention is a solid oral dosage form, in particular a solid peroral dosage form.

- 35 The term tasocitinib (component (a)) as used in the present invention relates to the compound as shown in formula I (free base) or to its acid form or its basic form. That

means, "tasocitinib" as used in the present invention also relates to the pharmaceutically acceptable salts, preferably pharmaceutically acceptable acid addition salts, e.g., as described in WO 02/096909. The acids, which are used to prepare the pharmaceutically acceptable acid addition salts, are preferably those which

5 form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate (preferably monotartrate and bitartrate), succinate, malate (preferably monomalate), maleate, oxalate (preferably monooxalate), fumarate, gluconate, saccharate, benzoate,

10 methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

The term "tasocitinib" also relates to stereospecific base addition salts of formula (I). The chemical bases that may be used as reagents to prepare pharmaceutically

15 acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to, those derived from such pharmacologically acceptable cations, such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water soluble amine

20 addition salts, such as N-methylglucamine-(meglumine), and the lower alkanol ammonium and other base salts of pharmaceutically acceptable organic amines.

In the oral dosage form of the present invention, tasocitinib as the active ingredient (component (a)) can be provided in amorphous form, preferably as amorphous

25 tasocitinib citrate, in crystalline form or as a mixture of both forms. Preferably, tasocitinib is present in crystalline form, wherein the crystalline modification is as described in WO 03/048162. In a particularly preferred embodiment of the present invention tasocitinib is provided as the citrate or hemi citrate. Most preferred is the crystalline form of the citrate or hemi citrate of tasocitinib.

30 In a preferred embodiment, the oral dosage form of the present invention comprises 1.0 to 60 wt.%, more preferably 2.0 to 30 wt.-%, still more preferably 3.0 to 20 wt.%, in particular 4.0 to 15 wt.% tasocitinib, based upon the total weight of the oral dosage form and based on the weight of tasocitinib in form of the free base, i.e. as shown in

35 formula (I) above.

In a preferred embodiment, the oral dosage form of the present invention comprises 1.0 to 100 mg, more preferably 2.0 to 50 mg, still more preferably 3.0 to 20 mg, in particular 4.0 to 12 mg tasocitinib, based upon the total weight of the oral dosage form and based on the weight of tasocitinib in form of the free base, i.e. as shown in formula (I) above.

In a preferred embodiment, the pharmaceutical composition of the invention can comprise only tasocitinib as pharmaceutical active agent.

10 In another preferred embodiment the pharmaceutical composition of the invention can comprise tasocitinib in combination with further pharmaceutical active agent(s).

15 It is preferred that the pharmaceutical composition of the invention comprises only tasocitinib as pharmaceutical active agent.

The modified release tablet of the present invention further contains a non-erodible material (b). Generally, the non-erodible material is suitable as release controlling agent.

20

In a first embodiment, the non-erodible material can be described as providing a scaffold (matrix) for embedding the active ingredient and to form a physical barrier, which hinders the active ingredient from being released immediately from the dosage form. Thus, the non-erodible material has the effect that the active ingredient can be released from the scaffold in continuous manner. Release of the drug from the matrix can further be by dissolution controlled as well as diffusion controlled mechanisms. In this first embodiment the non-erodible material functions as matrix forming material.

25

In a second embodiment, the non-erodible material can be described as a shell-forming material. Preferably, in that embodiment the oral dosage form is a tablet. The release modifying shell preferably encompasses the drug containing tablet core.

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In a third embodiment, the non-erodible material can be described as a release modifying coating in a multiple unit pellet system (MUPS).

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Generally, (i.e. for all three above described embodiments) the oral dosage form of the present invention further comprises a non-erodible material (b). Non-erodible materials are materials, which are able to provide modified release properties, preferably due to their limited solubility, more preferably due to their limited solubility in aqueous conditions at pH 5.0. Preferably, the non-erodible polymer has a water solubility of less than 33 mg/l at a temperature of 25 °C at a pH of 5.0, more preferably of less than 22 mg/l, still more preferably of less than 11 mg/l, especially from 0.01 to 5 mg/l. The water-solubility is determined according to the column elution method of the Dangerous Substances Directive (67/548/EEC), Annex V, Chapter A6. The pH value is determined according to Ph.Eur. 6.0, 2.2.3. The pH value of the aqueous medium usually is achieved by addition of HCl (or NaOH), if necessary.

The solubility of the non-erodible material can be pH independent or pH dependent. Both embodiments are preferred. If the non-erodible material is pH dependent, it is preferred that the non-erodible material has a solubility in water at 25 °C at a pH of 7.0 of more than 33 g/l, more preferably of 50 g/l to 10,000 g/l, still more preferably from 100 g/l to 5,000 g/l, in particular from 200 g/l to 2,000 g/l.

The non-erodible material can comprise an inert non-erodible material, a lipid non-erodible material and/or a hydrophilic non-erodible material. Examples for an inert non-erodible material are ethylcellulose, methacrylate copolymer, polyamide, polyethylene, and polyvinyl acetate; examples for lipid non-erodible materials are carnauba wax, cetyl alcohol, hydrogenated vegetable oils, microcrystalline waxes, monoglycerides, triglycerides and PEG monostearate; examples for hydrophilic non-erodible materials are alginates, carbopol, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, xanthan gum and polyethylene oxide as well as mixtures thereof..

In a preferred embodiment, the non-erodible material is a non-erodible polymer. The non-erodible polymer usually has a weight average molecular weight ranging from 30,000 to 3,000,000 g/mol, preferably from more than 50,000 to 2,500,000 g/mol, more preferably from more than 125,000 to 2,000,000 g/mol, still more preferably from 250,000 to 2,200,000 g/mol, particularly preferred from 400,000 to 1,500,000 g/mol. Furthermore, a 2 % w/w solution of the non-erodible polymer in water at pH 7.0 preferably has a viscosity of more than 2 mPas, more preferably of more than 5 mPas,

particularly more than 8 mPas and up to 850 mPas, when measured at 25 °C. The viscosity is determined according to Ph. Eur., 6th edition, Chapter 2.2.10. In the above definition the term "solution" may also refer to a partial solution (in case that the polymer does not dissolve completely in the solution). The weight average molecular weight is preferably determined by gel electrophoresis.

It is further preferred that the non-erodible polymer has a melting temperature of below 220 °C, more preferably of between 25 °C and 200 °C. In a particularly preferred embodiment the melting temperature is between 35 °C and 190 °C. The determination of the melting temperature is carried out according to Ph. Eur., 6th edition, Chapter 2.2.15.

If the non-erodible material (b) is a polymeric material, it preferably can be selected from acrylic polymers or acrylic copolymers such as polymers obtained from acrylic acid and/or methacrylic acid monomers. Other preferred polymers include, but are not limited to, cellulose and cellulose derivatives such as cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl methyl cellulose acetate (HPMCA), hydroxypropyl methyl cellulose phthalate (HPMCP) and cellulose acetate succinate (CAS), polyvinyl polymers such as polyvinyl alcohol phthalate, polyvinyl acetate phthalate and polyvinyl butyl phthalate, and mixtures of one or more of these polymers.

In particular, the following kinds of non-erodible polymers are particularly preferred.

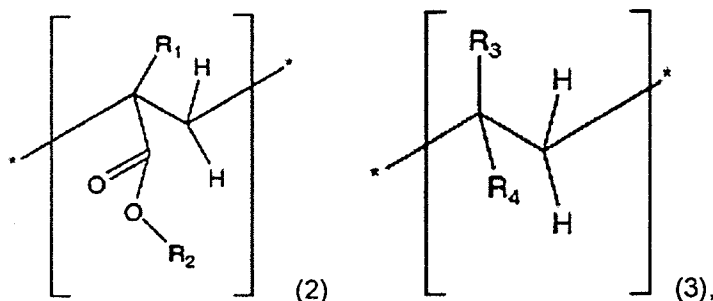
1. Cellulose ether, preferably ethyl cellulose, preferably ethyl cellulose having an average molecular weight of 150,000 to 300,000 g/mol and/or an average degree of substitution, ranging from 1.8 to 3.0, preferably from 2.2 to 2.6. This embodiment preferably is used for MUPS or core/shell-tablets;
2. Cellulose ester, preferably cellulose acetate phthalate, carboxymethyl ethyl cellulose, hydroxypropyl methylcellulose phthalate. This embodiment is preferably used for core/shell tablets;
3. Copolymers of methacrylic acid or methacrylic acid esters, preferably ethylacrylate-methyl methacrylate and methacrylic acid-methyl methacrylate. Particularly preferred is

ethylacrylate-methylmethacrylate-trimethylammonioethylmethacrylate-chloride, for example Eudragit® RL PO (Röhm) and Eudragit® RS PO (Röhm).

4. Polyvinyl acetate or polyvinyl acetate copolymers, preferably polyvinyl acetate
5 phthalate; and mixtures thereof.

Preferred acrylic polymers are, for example, polyacrylate, polymethacrylate as well as derivatives and mixtures or copolymers thereof. The polyacrylates used in the invention preferably show the above indicated parameters (e.g. weight average molecular
10 weight, solubility, etc).

In a preferred embodiment the non-erodible acrylic polymer (b) is a polymer consisting of the structures according to the general formulae (2) and (3).



wherein in formulae (2) and (3)

R_1 is a hydrogen atom or an alkyl group, preferably a hydrogen atom or a methyl group or an ethyl group, particularly preferred a methyl group;

- 20 R_2 is a hydrogen atom or an alkyl group, preferably a hydrogen atom or a C_1 - C_4 alkyl group, particularly preferred a methyl group, ethyl group or butyl;

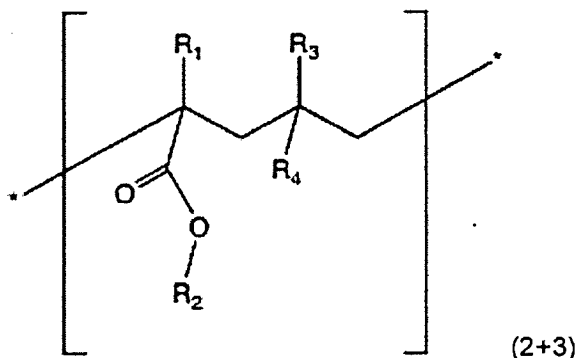
R_3 is a hydrogen atom or an alkyl group, preferably a hydrogen atom or a methyl group;

- 25 R_4 is an organic group, preferably a carboxylic acid or a derivative thereof, particularly preferred a group according to the formula $-COOH$, $-COOR_5$,

R_5 is an alkyl group or a substituted alkyl group, preferably a methyl, ethyl, propyl or butyl group, or $-CH_2-CH_2-N(CH_3)_2$ or $-CH_2-CH_2-N(CH_3)_3^+$ halogen⁻ (in particular Cl^-) as substituted alkyl group.

The acrylic polymer (b) according to formulae (2) and (3) is usually comprised of structures with a molar ratio of from 1 : 40 to 40 : 1. The preferred ratio of the structures of formula (2) to structures of formula (3) is from 2 : 1 to 1 : 1, particularly 1 : 1. When R_4 is $-\text{COO}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_3^+\text{Cl}^-$, the ratio of structures according to formula (2) to structures of formula (3) preferably is 20 : 1 to 40 : 1.

In case of an alternating copolymerization with a ratio of 1 : 1, this results in a preferred polymer according to formula (2+3)



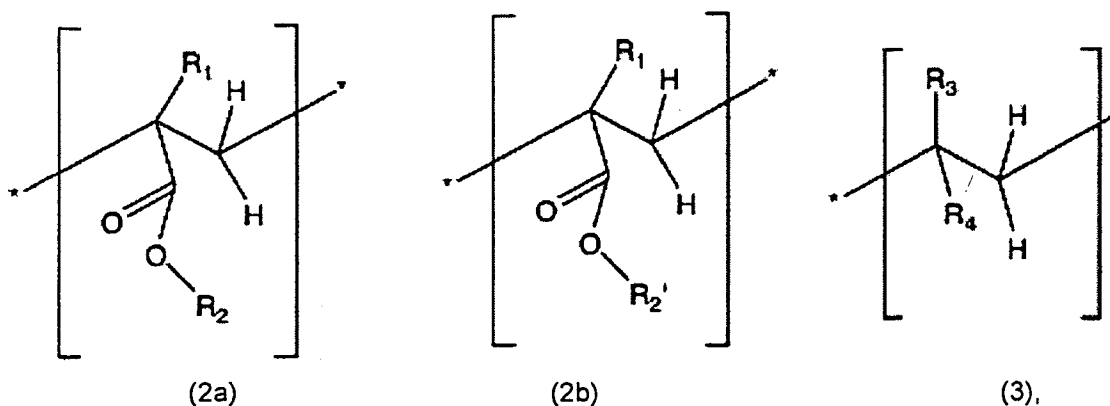
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Polyacrylates according to the formulae (2) and (3) as mentioned above are particularly preferred, wherein R_1 and R_3 are alkyl, particularly methyl, R_2 is methyl and/or ethyl and R_4 is hydrogen or $-\text{COO}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_3^+\text{Cl}^-$. A particularly preferred ratio of the structures according to formula (2) to the structures according to formula (3) is 1 : 1 or 1 : 20. A corresponding polymer preferably has a weight average molecular weight of from 20,000 to 250,000 g/mol, more preferred of from 30,000 to 180,000 g/mol.

In a particularly preferred embodiment in formula (2) (or in formula (2+3) as well), as indicated above, R_2 is both a methyl and a butyl group, whereby the ratio methyl to butyl group preferably is 1 : 1.

20

Further, the acrylic polymer preferably can be a ternary polymer comprising the structures according to the general formulae (2a), (2b) and (3)



wherein R_1 and R_3 are hydrogen or alkyl, particularly methyl, R_2 is methyl, R_2' is ethyl
 5 and R_4 is $-\text{COO}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_3^+\text{Cl}^-$.

Further, a preferred non-erodible polymer is a blend of lactose and hydroxypropylmethylcellulose (hypromellose), more preferably a spray agglomerated blend, in particular of 50 parts lactosemonohydrate and 50 parts hypromellose.

10

The non-erodible material (b) is contained in the tablet in an amount of 5 to 80 wt.%, preferably from 10 to 50 wt.%, most preferably from 15 to 40 wt.%, based upon the total weight of the oral dosage form. If too little non-erodible material is used, the formulations may break up during the passage down the gastrointestinal tract and this,
 15 in turn, may lead to a premature release of a large portion of the content of the drug. If too much matrix former is used, there is a risk that some of the drug will be encapsulated and not released from the tablet.

The oral dosage form of the invention further optionally comprises a pore-forming material (c). The term "channelling agent" is in the art often synonymously used for the pore-forming material of the present invention. Since the pore-forming material is generally soluble in the gastrointestinal tract and leaches out from the oral dosage form, the pore-forming material can be described as having the effect of forming pores, such as small holes within the tablet, through which the active ingredient can be
 20 released from the tablet matrix in a controlled manner. Thus, release of the active ingredient generally depends on dissolving the pore forming material and thereby forming a porous matrix of capillaries such that the drug can leach out of the matrix.

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The pore-forming substance usually has a water solubility of more than 50 mg/l, preferably more than 100 mg/l, at a temperature of 25 °C and pH 5.0, more preferred of more than 250 mg/l and particularly preferred of more than 25 g/l. The water-solubility of the pore-forming substance may range up to 2.5 kg/l. The water-solubility
5 is determined according to the column elution method of the Dangerous Substances Directive (67/548/EEC), Annex V, Chapter A6.

The pore-forming substances can be selected from inorganic substances, preferably from inorganic salts such as NaCl, KCl, Na₂SO₄. Furthermore, the pore-forming
10 substances can be selected from organic substances, in particular from organic substances being solid at 30 °C and having the above-mentioned water solubility. Suitable examples are PEG, particularly PEG, having a weight average molecular weight of from 2,000 to 10,000 g/mol.

15 Furthermore, polyvinylpyrrolidone, preferably having a weight average molecular weight of from 5,000 to 29,000 g/mol, PEG with a weight average molecular weight of 380 – 4800, polyethylene oxide with a weight average molecular weight of less than 100,000 and a viscosity of less than 20 mPa·s, sugar alcohols like mannitol, sorbitol, xylitol, isomalt, and mono or disaccharides, like lactose, are also suitable as pore-
20 forming substances.

The pore forming material is usually contained in the tablet in an amount of 1 to 50 wt.%, preferably from 2 to 40 wt.%, most preferably from 5 to 30 wt.%, based upon the total weight of the oral dosage form.

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The tablet of the present invention can further comprise at least one excipient (d) selected from solubilizers (d1), fillers (d2), disintegrants (d3), lubricants (d4), surfactants (d5), glidants (d6), anti-sticking agents (d7), plasticizers (d8) and mixtures thereof.

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The composition of the subject invention preferably comprises one or more solubilizers, preferably hydrophilic solubilizers. Generally, the term "solubilizer" means any organic excipient, which is capable of improving the solubility and/or dissolution of the active pharmaceutical ingredient. Generally, the term "hydrophilic solubilizer" means any
35 organic excipient, which possesses hydrophilic groups and is capable of improving the

solubility and/or dissolution of the active pharmaceutical ingredient. Preferably, the hydrophilic solubilizer is capable of reducing the dissolution time of a pharmaceutical composition by 5 %, more preferably by 20 %, according to USP 31-NF26 release method, using apparatus 2 (paddle), compared to the same pharmaceutical composition comprising calcium hydrogen phosphate instead of the hydrophilic solubilizer.

The solubilizers are selected, for example, from the group of known inorganic or organic excipients. Such excipients preferably include polymers, low molecular weight oligomers and natural products.

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Preferably, the hydrophilic solubilizer is a water-soluble compound, having a water solubility of more than 10 mg/l, more preferably of more than 20 mg/l, still more preferably of more than 50 mg/l at a temperature of 25 °C. The solubility of the hydrophilic solubilizer might be e.g. up to 1,000 mg/l or up to 300 mg/ml at a temperature of 25 °C. The water-solubility is determined according to the column elution method of the Dangerous Substances Directive (67/548/EEC), Annex V, Chapter A6.

15

In a preferred embodiment the solubilizer is a hydrophilic polymer, preferably having the above-mentioned water-solubility. Generally, the term "hydrophilic polymer" encompasses polymers comprising polar groups. Examples for polar groups are hydroxy, amino, amido, carboxy, carbonyl, ether, ester and sulfonate. Amido groups are particularly preferred.

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The hydrophilic polymer usually has a weight average molecular weight, ranging from 1,000 to 250,000 g/mol, preferably from 2,000 to 100,000 g/mol, particularly from 4,000 to 75,000 g/mol. Furthermore, a 2 % w/w solution of the hydrophilic polymer in pure water preferably has a viscosity of from 1 to 20 mPa·s, more preferably from 2 to 8 mPa·s at 25 °C. The viscosity is determined according to the European Pharmacopoeia (hereinafter referred to as Ph. Eur.), 6th edition, Chapter 2.2.10.

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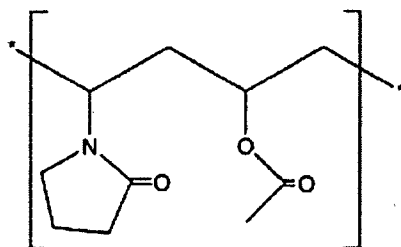
Furthermore, the hydrophilic polymer used as hydrophilic solubilizer preferably has a glass transition temperature (T_g) or a melting point of 25 °C to 200 °C, more preferably of 90 °C to 170 °C. The glass transition temperature, T_g , is the temperature, at which the hydrophilic polymer becomes brittle on cooling and soft on heating. That means,

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above T_g , the hydrophilic polymers become soft and capable of plastic deformation without fracture. The glass transition temperature or the melting point are determined with a Mettler-Toledo® DSC 1, wherein a heating rate of 10 °C per minute and a cooling rate of 15 °C per minute is applied. The determination method essentially is based on Ph. Eur. 6.1, section 2.2.34. For the determination of T_g , the polymer is heated twice (i.e. heated, cooled, heated).

More preferably, derivatives of cellulose (e.g. hydroxypropyl methyl cellulose (HPMC), preferably having a weight average molecular weight from 20,000 to 90,000 g/mol, and/or preferably a ratio of methyl groups from 10 to 35 %, and preferably a ratio of hydroxypropyl groups from 1 to 35 %; hydroxypropyl cellulose (HPC), preferably having a weight average molecular weight of from 40,000 to 100,000 g/mol), polyvinylpyrrolidone, preferably having a weight average molecular weight of from 10,000 to 60,000 g/mol, copolymers of polyvinylpyrrolidones, preferably copolymers comprising vinylpyrrolidone and vinylacetate units (e.g. Povidon® VA 64; BASF), preferably having a weight average molecular weight of 40,000 to 75,000 g/mol, polyoxyethylene alkyl ethers, co-blockpolymers of ethylene oxide and propylene oxide, preferably having a polyethylene content of 70 to 90 wt.% and/or preferably having a weight average molecular weight from 1,000 to 50,000 g/mol, in particular from 3,000 to 25,000 g/mol, polyvinyl alcohol, polyethylene glycol, preferably having a weight average molecular weight ranging from 1,000 to 50,000 g/mol, are used as hydrophilic solubilizers. The weight average molecular weight is preferably determined by gel electrophoresis.

In particular, polyvinylpyrrolidone and copolymers of polyvinylpyrrolidone, in particular copolymers comprising vinylpyrrolidone and vinylacetate units, having the structure



can be used as hydrophilic solubilizers.

It is particularly preferred that the above-mentioned kinds of hydrophilic polymers fulfill the functional requirements (molecular weight, viscosity, T_g , melting point, non-semi-permeable properties), as illustrated above.

- 5 In the pharmaceutical composition of the present invention, at least one of the above-mentioned hydrophilic solubilizers is present. Alternatively, a combination of two or more hydrophilic solubilizers can be employed.

10 Usually, solubilizers can be used in an amount of 0.1 to 20 wt.%, preferably of 1 to 15 wt.% based on the total weight of the oral dosage form.

Generally, fillers are used to top up the volume for an appropriate oral deliverable dose, when low concentrations of the active pharmaceutical ingredients (about 30 wt.% or lower) are present. Preferred fillers of the invention are calcium phosphate, saccharose, calcium carbonate, calcium silicate, magnesium carbonate, magnesium
15 oxide, maltodextrin, glucopyranosyl mannitol, calcium sulfate, dextrate, dextrin, dextrose, hydrogenated vegetable oil and/or cellulose derivatives, such as microcrystalline cellulose. A pharmaceutical composition according to the invention may comprise an inorganic salt as a filler. Preferably, this inorganic salt is dicalcium
20 phosphate, preferably in form of the dihydrate (dicafos).

Dicalcium phosphate dihydrate is insoluble in water, non-hygroscopic, but still hydrophilic. Surprisingly, this behavior contributes to a high storage stability of the composition.

25 Usually, fillers can be used in an amount of 0 to 60 wt.%, preferably of 5 to 40 wt.%, based on the total weight of the composition.

The oral composition of the present invention can further comprise one or more of a disintegrant. In a preferred embodiment of the invention, the tablet does not contain a disintegrant.

30 Generally, disintegrants are compounds, capable of promoting the break up of a solid composition into smaller pieces when the composition gets in contact with a liquid, preferably water.

Preferred disintegrants are sodium carboxymethyl starch, cross-linked polyvinylpyrrolidone (crospovidone), sodium carboxymethyl glycolate (e.g. Explotab®), swelling polysaccharide, e.g. soya polysaccharide, carrageenan, agar, pectin, starch and derivatives thereof, protein, e.g. formaldehyde - casein, sodium bicarbonate or mixtures thereof. Crospovidone is particularly preferred as disintegrant. Furthermore, a combination of crospovidone and agar is particularly preferred.

Usually, disintegrants can be used in an amount of 0 to 20 wt.%, preferably of 1 to 10 wt.%, based on the total weight of the composition.

In a preferred embodiment of the present invention the oral dosage form is free of any disintegrants.

The oral dosage form of the present invention might further comprise one or more of a surfactant (d4). Preferably, sodium lauryl sulfate is used as surfactant.

Usually, surfactants can be used in an amount of 0.05 to 2 wt.%, preferably of 0.1 to 1.5 wt.%, based on the total weight of the oral dosage form.

Additionally, the oral dosage form of the present invention may comprise a lubricant (d5), a glidant (d6) and/or an anti-sticking agent (d7).

In a preferred embodiment of this invention, a lubricant may be used. Lubricants are generally employed to reduce dynamic friction. The lubricant preferably is a stearate, talcum powder or fatty acid, more preferably, hexanedioic acid or an earth alkali metal stearate, such as magnesium stearate. The lubricant is suitably present in an amount of 0.1 to 3 wt.%, preferably about 0.5 to 1.5 wt.% of the total weight of the composition. Preferably, the lubricant is applied in a final lubrication step during the powder preparation. The lubricant generally increases the powder flowability.

The glidant can for example be colloidal silicone dioxide (e.g. Aerosil®). Preferably, the glidant agent is present in an amount of 0 to 8 wt.%, more preferably at 0.1 to 3 wt.% of the total weight of the composition. Preferably, the silicone dioxide has a specific surface area of 50 to 400 m²/g, measured by gas adsorption according to Ph. Eur., 6th edition, Chapter 2.9.26. multipoint method, volumetric determination

The anti-sticking agent is for example talcum and may be present in amounts of 0.05 to 5 wt.%, more preferably in an amount of 0.5 to 3 wt.% of the total weight of the composition.

- 5 Furthermore, in a preferred embodiment the pharmaceutical composition of the present invention further comprises one or more plasticizers (d8). The "plasticizers" usually are compounds capable of lowering the glass transition temperature (T_g) of the non-erodible material, preferably the non-erodible polymer, preferably of lowering T_g from 1 to 50 °C, especially from 5 to 30 °C. Plasticizers (d8) usually are low molecular weight
10 compounds (having a molecular weight from 50 to 500 g/mol) and comprise at least one hydrophilic group.

Examples of suitable plasticizers are dibutyl sebacetate (DBS), Myvacet® (acetylated monoglycerides), triacetin (GTA), citric acid esters, like acetyltriethyl citrate (ATEC) or
15 triethyl citrate (TEC), propylene glycol, dibutyl phthalate, diethyl phthalate, or mixtures thereof.

The combined use of the non-erodible polymer (b) and the pore-forming substance (c) and optionally the plasticizer (d8) preferably is capable of modifying the drug release
20 rate. The use of plasticizers is particularly preferred in the third embodiment concerning MUPS.

Regarding the above mentioned pharmaceutically acceptable excipients, the application generally refers to "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und
25 angrenzende Gebiete", edited by H. P. Fiedler, 5th Edition, Editio Cantor Verlag, Aulendorf and earlier editions, and "Handbook of Pharmaceutical Excipients", third edition, edited by Arthur H. Kibbe, American Pharmaceutical Association, Washington, USA, and Pharmaceutical Press, London.

30 In the tablet according to the present invention the non-erodible material (b), the pore forming material (c) and/or the at least one excipient (d) preferably have a surface of 0.2 to 10 m²/g, preferably of 0.3 to 8 m²/g, most preferably of 0.4 to 5 m²/g, as measured by gas adsorption according to Ph. Eur., 6th edition, Chapter 2.9.26, multipoint method, volumetric determination.

In the tablet of the invention the at least one non-erodible material (b), the pore forming material (c) and/or the excipient(s) generally show a plastic behavior, such as a ductile behaviour. This behavior can be described by the yield pressure of the material. The materials of components (a), (b) and/or (c) generally have a yield pressure of less than 150 MPa, preferably less than 100 MPa, most preferably of less than 75 MPa. If the yield pressure is above 150 MPa, the material is too brittle and causes difficulties in being compressed into a tablet, bearing the risk that the tablet breaks or crumbles. The yield pressure can be determined from a Heckel plot. According to Heckel, there is a linear relationship between the relative porosity (inverse density) of a powder and the applied pressure. The slope of the linear regression is the Heckel constant, a material dependent parameter inversely proportional to the mean yield pressure (the minimum pressure required to cause deformation of the material undergoing compression). Thus, the yield pressure is obtained by measuring the reciprocal value from the slope of the Heckel plot.

In this context it is generally noted that, due to the nature of pharmaceutical excipients, it cannot be excluded that a certain compound meets the functional requirements of more than one of the above mentioned excipient classes. However, in order to enable an unambiguous distinction and terminology in the present application, the same pharmaceutical compound can only be subsumed as one of the functional excipient classes presented above. For example, if microcrystalline cellulose is used as a filler, it cannot additionally classify as a disintegrant (although microcrystalline cellulose has some disintegrating properties).

As explained above, the present invention concerns three preferred embodiments of the solid oral dosage form. Hence, the present invention further relates to three preferred embodiments of a process for producing said oral dosage forms.

In the first preferred embodiment, the present invention concerns a matrix dosage form, preferably a matrix tablet. The matrix tablet preferably is produced by a process, comprising the steps of

(1-I) providing (and optionally blending) components (a), (b), optionally c), and optionally (d),

(1-II) optionally agglomerating the components of step (I) to yield granules,

- (1-III) compressing the mixture resulting from step (I) or (II) into tablets; and
- (1-IV) optionally coating the tablets, preferably with a suitable film (e).

In this first preferred embodiment of the invention, the dosage form preferably
5 comprises tasocitinib, a non-erodible material, a pore-forming material, a filler, a glidant
and a lubricant. In a further preferred embodiment, the composition comprises from 5
to 20 wt.% of tasocitinib, from 25 to 60 wt.% of non-erodible material, from 10 to
40 wt.% of a pore-forming material, from 10 to 40 wt.% of a filler, from 1 to 10 wt.% of a
glidant and from 1 to 10 wt.% of a lubricant, based upon the total weight of the dosage
10 form.

In a second preferred embodiment of the invention, the oral dosage form is in form of a
tablet, comprising a core and a shell, wherein the core comprises components (a) and
optionally (c) and/or (d), and wherein the shell comprises components (b) and
15 optionally (c) and/or (d).

The tablet of the invention preferably is produced by a process, comprising the steps of

- (2-I) mixing components (a) and optionally (c) and/or (d),
- 20 (2-II) optionally agglomerating the components of step (I) to yield granules,
- (2-III) compressing the mixture into tablets, and
- (2-IV) coating the tablets with a coating comprising components (b) and
optionally (c) and/or (d).
- (2-V) Optionally, the resulting tablets can be film-coated with a suitable film (e).

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The preferred processes of the first and second embodiment are described below in
more detail.

In step (1-I) or (2-I) components (a), (b), (c) and/or (d) can be provided in micronized
30 form. Micronization can be carried out by milling, such as in a air jet mill. Preferably,
the mean particle size (D50) of tasocitinib (a) is from 20 to 120 μm , and from
components (b), (c) and/or (d) it is from 30 to 150 μm .

Optionally, the ingredients of the tablet of the invention are blended in order to provide
35 a formulation having a homogenous distribution of tasocitinib (a) within the formulation.

Blending can be carried out with conventional mixing devices, e.g. in a free-fall mixer like Turbula® T10B (Bachofen AG, Switzerland). Blending can be carried out e.g. for 1 minute to 30 minutes, preferably for 2 minutes to less than 10 minutes.

- 5 Generally, the step (1-II) or (2-II) of "agglomerating" components (a) to (d) (components (c) and (d) optional) refers to a process, wherein particles are attached to each other, thereby giving larger particles. The attachments may occur through physical forces, preferably van der Waals forces. The attachment of particles preferably does not occur through chemical reactions.

10

Agglomeration (II) can be carried out in different devices. For example, agglomeration can be carried out by a granulation device, preferably by a dry granulation device. More preferably, agglomeration can be carried out by intensive blending. For example, agglomeration can be carried out by blending in a free-fall mixer or a container mixer.

- 15 An example for a suitable free fall mixer is Turbula® T10B (Bachofen AG, Switzerland). Generally, the blending is carried out for a time, being long enough for agglomeration to occur. Usually, blending is carried out for 10 minutes to 2 hours, preferably for 15 minutes to 60 minutes, more preferably from 20 minutes to 45 minutes.

- 20 In a possible embodiment the agglomeration step can be carried out as a dry-compaction step. In a preferred embodiment the dry-compaction step is carried out by roller compaction. Alternatively, e.g. slugging can be used. If roller compaction is applied, the compaction force usually ranges from 1 to 30 kN/cm, preferably from 2 to 20 kN/cm, more preferably from 2 to 10 kN/cm. The gap width of the roller compactor
- 25 usually is 0.8 to 5 mm, preferably 1 to 4 mm, more preferably 1.5 to 3.2 mm, especially 1.8 to 3.0 mm. After the compaction step, the received comprimate preferably is granulated. Preferably, the granulation step is carried out by an elevated sieving equipment, e.g. Comil® U5 (Quadro Engineering, USA). Alternatively, compaction and granulation can be carried out within one device.

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In a preferred embodiment, the agglomeration step is carried as melt processing, in particular melt granulation. For this, the mixture of components (a), (b), optionally (c) and optionally (d) are molten. In a preferred embodiment the melting conditions can be preferably chosen such that they assure that tasocitinib is obtained in a non-crystalline

35 form.

The specific melting conditions can depend on compounds (a), (b), optionally (c) and optionally (d). Usually, temperatures from 40 °C to 200 °C, preferably from 60 °C to 180 °C are used. Preferably, tasocitinib (a), the non-erodible material (b) and the optional components (c) and (d) in their respective ratios may be chosen to achieve an eutectic mixture. In this way, the need of high temperatures for melting can be decreased.

In another embodiment, the cooling off step can be conducted under cooling conditions chosen such that non-crystalline tasocitinib remains in a non-crystalline form. Non-crystalline tasocitinib can be detected by XRD or DSC.

Further, the above molten mixture can be granulated, either in molten state or after having cooled off.

The melt processing can be carried out, for example, by an extrusion process. Hence, the melting step and the granulating step preferably can be regarded as melt-extrusion processes. Generally, the extrusion process should be capable of providing essentially spherical particles. Suitable extruders are, for example, screw-feed extruders (axial or endplate, dome and radial) or gravity extruders (cylinder roll, gear roll or radial). Screw-feed extruders are preferred.

The granulation can also, for example, be carried out by a - preferably heatable - High-Shear-Mixer (e.g. Diosna® P1/6). In this case, the providing step, the melting step and the granulating step can be regarded as one process with different sequences of special parameters. The first sequence can be the providing step without heating, the second sequence can be a mixture of providing step and melting step with heating, sequence three can include parts of melting step and granulating step. Preferred parameters of the sequences can be dependent on the chosen components (a), (b) and optionally (c) and (d).

In a preferred embodiment, the granulation can be carried out with a melt screw extruder (e.g. ThermoFisher® Eurolab 16), wherein the providing step and the granulating step can be unified in one continuous process. Generally, a temperature gradient can be applied, preferably between 70 °C to 200 °C.

In another possible embodiment, the agglomeration step is carried as wet granulation. In this embodiment the mixture of components (a), (b), optionally (c) and optionally (d) is wetted with a granulation liquid or suspended in a granulation liquid. The granulation liquid preferably further comprises a binder. Preferably, the granulation liquid, containing a binder, is a solution or a suspension, preferably a solution. Suitable liquids for preparing the granulation liquid are, for example, water, alcohols and mixtures thereof. A mixture of water and ethanol is preferred.

The providing and the agglomerating step can be carried out in known granulation apparatuses, for example in a Diosna® P1/6. or in a Glatt® GPCG 3.

In a preferred embodiment, the agglomeration conditions in step (1-II) or (2-II) are chosen such that the resulting agglomerated pharmaceutical composition comprises a volume mean particle size (D50) of 5 to 500 µm, more preferably of 20 to 250 µm, further more preferably of 50 to 200 µm.

The bulk density of the agglomerated pharmaceutical composition made by the process of the present invention generally ranges from of 0.1 to 0.85 g/ml, preferably of from 0.25 to 0.85 g/ml, more preferably of from 0.3 to 0.75 g/ml.

In a preferred embodiment the composition has a bulk density of 0.5 to 0.8 g/ml when used for direct compressing and 0.1 to 0.5 when used for dry compaction.

The Hausner factor of the agglomerated (or granulated) composition is less than 1.3, preferably less than 1.2 and most preferably less than 1.15. The agglomerated pharmaceutical composition resulting from step (iii) of the invention preferably possesses Hausner ratios in the range of 1.02 to 1.5, preferably of 1.05 to 1.4, more preferably between 1.08 to 1.3. The Hausner ratio is the ratio of tapped density to bulk density. Bulk density and tapped density are determined according to USP 24, Test 616 "Bulk Density and Tapped Density".

The compression step (1-III) or (2-III), can be carried out on a rotary press, e.g. on a Fette® 102i (Fette GmbH, Germany) or a Riva® piccola (Riva, Argentina). If a rotary press is applied, the main compaction force usually ranges from 1 to 50 kN, preferably

from 2 to 40 kN, more preferably from 3.5 to 30 kN. The resulting tablets usually have a hardness of 30 to 100N, preferably of 50 to 85 N.

5 The shell of the tablets of the second preferred embodiment of the present invention is applied in process step (2-IV). Said step comprises coating the tablet core with a coating comprising preferably components (b) and optionally (c) and/or (d). Preferably, the coating comprises components (b), (c) and a plasticizer.

10 The coating process is generally carried out in a continuously process in a pan coater or a fluid bed dryer. The coating process is preferably carried out on a pan coater, e.g. on a Lödige LHC 25 (Lödige GmbH, Germany). If a pan coater is applied, the spray pressure usually ranges from 0,8 - 2 bar, preferably from 1 - 1.5 bar. The product temperature varies according to the applied polymer. Usually the product temperature is adjusted by 20 - 40 °C, preferably from 32 - 38 °C.

15 The coating usually has a thickness of 0.01 to 2 mm, preferably from 0.1 to 1.5 mm, more preferably from 0.2 to 1 mm.

20 After having received the compressed tablets, in both preferred processes the compressed tablet could be film-coated (step 1-IV or 2-V).

In the present invention, the following three types of film-coatings are possible:

- 25 e1) film-coating without effecting the release of the active ingredient (preferred),
e2) gastric juice resistant film-coatings,
e3) retard coatings.

30 Film-coatings without effecting the release of the active ingredient are preferred. Generally, said coating can be water-soluble (preferably having a water solubility at 25 °C of more than 250 mg/ml). With gastric juice resistant coatings, the solubility depends on the pH of the surroundings. Retard coatings are usually non-soluble (preferably having a water solubility at 25 °C of less than 10 mg/ml).

Generally, film-coatings e1) were prepared using cellulose derivatives, poly(meth)acrylate, polyvinyl pyrrolidone, polyvinyl acetate phthalate, and/or shellac or natural rubbers such as carrageenan.

- 5 Preferred examples of coatings, which do not effect the release of the active ingredient, include methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), polyvinyl pyrrolidone (PVP) and mixtures thereof. These polymers generally have a median molecular weight of 10,000 to 150,000 g/mol.

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A preferred polymer is HPMC, most preferably a HPMC having a median molecular weight of 10,000 to 150,000 g/mol and a median level of substitution of -OCH₃-residues of 1.2 to 2.

- 15 Examples of gastric juice resistant coatings e2) are cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP and polyvinyl acetate phthalate (PVAP). Examples of retard coatings e3) are ethyl cellulose (EC, commercially available e.g. as Surelease®) and poly(meth)acrylate (commercially available e.g. as Eudragit® RL or RS and L/S).

20

The coating e) can be free of active ingredient. However, it is also possible that the coating contains active ingredient (tasocitinib). In such a case, that amount of active ingredient would function as an initial dose. In such a case the coating e) preferably comprises 1 to 45 wt.%, preferably 5 to 35 wt.%, most preferably 10 to 30 wt.% of

25 tasocitinib, based on the total amount of tasocitinib contained in the tablet. In this embodiment, the coating preferably is a coating, which does not effect the release of tasocitinib.

- 30 In case the film coating does not contain tasocitinib (which is preferred), it usually has a thickness of 2 µm to 100 µm, preferably from 20 to 60 µm. In case of a coating containing tasocitinib, the thickness of the coating is usually 10 µm to 2 mm, more preferably from 50 to 500 µm.

- Accordingly, in a further embodiment the subject invention relates to a tablet in which
- 35 1 to 45 wt.%, preferably 5 to 35 wt.%, most preferably 10 to 30 wt.% of the total amount

of the tasocitinib contained in the tablet, are present as initial doses having immediate release, and 55 to 99 wt.%, preferably 65 to 95 wt.%, most preferably 70 to 90 wt.% of the active ingredient are present in the tablet as a modified release formulation.

- 5 The third preferred embodiment of the present invention relates to a multiple unit pellet system (MUPS). As the name implies, this type of dosage form comprises more than one discrete unit. Typically, such systems comprise 2 to 50, preferably 3 to 30 discrete units. Typically, such discrete units are coated spheroids. Preferably, such coated spheroids are filled into capsules, preferably hard gelatin capsules. Alternatively, such
10 coated spheroids are compressed into tablets.

Hence, a further subject of the present invention is a process for manufacturing an oral modified release dosage form comprising tasocitinib, comprising the steps of

- 15 (3-I) providing a pellet core,
(3-II) spraying a solution or suspension comprising component (a) and optionally (d) onto the pellet core,
(3-III) spraying a solution or suspension comprising component (b) and optionally (c) and/or (d) onto the pellet, preferably onto the pellet
20 resulting from step (3-II),
(3-IV) optionally blending the pellets with components (b) and (c) and/or (d);
and
(3-V) further processing the resulting mixture into a final oral dosage form.

- 25 In this pellet layering embodiment, the present invention provides a process for the manufacture of a modified release dosage form comprising tasocitinib, employing a pellet layering process.

- In step (3-I) a pellet core is provided. Preferably, the pellet core is a so-called neutral
30 pellet core, that means it does not comprise an active ingredient. Such pellet cores are known in the art as non-pareils. The pellet core can be made of suitable materials, e.g. cellulose, sucrose, starch or mannitol or combinations thereof.

- Suitable pellet cores are commercially available under the trade name Cellets® and
35 preferably comprise a mixture of lactose and microcrystalline cellulose.

Furthermore, in a preferred embodiment, pellet cores commercially available as Suglets® are used. Those preferred pellet cores comprise a mixture of corn starch and sucrose. The mixture usually comprises 1 to 20 wt.% corn starch and 80 to 99 wt.% sucrose, in particular, about 8 wt.% corn starch and 92 % sucrose.

- 5 In step (3-II) the tasocitinib is dissolved or suspended in a solvent. The solvent can be water, a pharmaceutically acceptable organic solvent or mixtures thereof. Preferably, the solvent is water or an alcohol. Most preferably, the solvent is methanol.

- 10 The solution or dispersion of tasocitinib can comprise further excipients (d). It preferably comprises a solubilizer (d1) and/or a plasticizer (d8). Generally, it is noted that all comments made above regarding the excipients (d) used in the present invention also apply for the processes of the present invention. In addition, the solution or dispersion may comprise anti-sticking agents and lubricants.

- 15 The resulting emulsion or suspension is sprayed onto the pellet core, preferably by a fluid bed dryer, e.g. Glatt GPCG 3 (Glatt GmbH, Germany).

- 20 Subsequently, the spraying step is repeated. In step (3-III) a solution or suspension comprising component (b) and optionally (c) and/or (d) is sprayed onto the pellet resulting from step (3-II). In the spraying step (3-III), preferably solubilizer (d1) and/or plasticizer (d8) are used as excipients.

- 25 Alternatively, the spraying steps (3-II) and (3-III) can be combined. In such a case, the solution or dispersion of tasocitinib further comprises components (b) and optionally (c) and/or excipients (d).

- 30 In a preferred embodiment, the spraying conditions are chosen such that the resulting coated spheroids have a mean particle size (D50) of 10 to 1000 µm, more preferably of 50 to 800 µm, further more preferably of 100 to 750 µm, most preferably of 250 to 650 µm.

The coated spheroids of the present invention (i.e. the primary pharmaceutical composition) may be used to prepare suitable solid oral dosage forms with modified released properties. That means, the primary pharmaceutical composition can be

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further processed to give a "final pharmaceutical composition", i.e. to give a final oral dosage form.

Hence, the present invention encompasses a process for producing oral dosage forms comprising a pharmaceutical composition as received by the above-described pellet layering process, comprising the steps of

- (3-V-i) optionally mixing the granulates as received by the above-described pellet layering process with further excipients,
- 10 (3-V-ii) further processing the resulting mixture into a final oral dosage form.

Preferably, step (ii) comprises

- 15 (3-V-ii- α) filling the resulting mixture into capsules,
- (3-V-ii- β) filling the resulting mixture into sachets, or
- (3-V-ii- γ) compressing the resulting mixture into tablets. The tablets can be film-coated (e), as described above.

20 Generally, it is noted that all comments made above with respect to the tablets of the present invention also apply for the process of manufacturing such a tablet and the use of the tablet of the present invention.

Consequently, further subjects of the present invention are tablets obtainable by any of
25 the processes as described above.

All explanations above given for the process of the present invention also apply for the tablet of the present invention.

30 The release profile of a non-coated tablet or a coated tablet, wherein the coating is free of drug, usually shows a constant release as determined by method USP (paddle). Preferably, the slope of the initial drug release is less than 0.6 to 0.8 % per minute.

In a further aspect the present invention is related to an osmotic controlled release
35 device comprising tofacitinib, preferably in form of a tablet.

The controlled release device comprises:

- (A) a core comprising tofacitinib and an osmotic agent, and
- (B) a water-permeable coating comprising a non-erodible polymer.

5

It is noted that all explanations made above for preferred embodiments (e.g. preferred tofacitinib salts, preferred non-erodible polymers, preferred excipients, preferred ratios and amounts) apply as well for the below described second aspect.

- 10 In a preferred embodiment of the osmotic controlled release devices the water-permeable, non-dissolving coating, which comprises the non-erodible material surrounding the core, controls the influx of water to the core from an aqueous environment, so as to cause drug release by extrusion of some or all of the core to the environment of use.

15

The osmotic agent contained in the core of this device may be an aqueous-swelling hydrophilic polymer or it may be an osmogen. The coating is preferably polymeric, aqueous-permeable and has at least one delivery port. Examples of such devices are disclosed more fully in U.S. Patent No. 6,706,283, the disclosure of which is hereby
20 incorporated by reference.

- Preferably, the osmotic agent creates a driving force for the transport of water from the environment of use into the core of the device. Exemplary osmotic agents are water-swelling hydrophilic polymers. The amount of water-swelling hydrophilic polymers
25 present in the core may range from about 5 to about 80 wt.%, preferably 10 to 50 wt.%, based on the total weight of the core. Exemplary materials include hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic acid), poly(methacrylic acid), polyvinylpyrrolidone (PVP) and
30 cross-linked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers and PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate, vinyl acetate, and the like, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and
35 carboxyethyl cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum

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and sodium starch glycolate. Typical classes of suitable osmotic agents are water-soluble organic acids, salts and sugars that are capable of imbibing water, to thereby effect an osmotic pressure gradient across the barrier of the surrounding coating. Typical useful osmogens include magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, sodium sulfate, mannitol, xylitol, urea, sorbitol, sucrose, glucose, fructose, lactose, and mixtures thereof. The core may include a wide variety of additives and excipients that enhance the performance of the dosage form or that promote stability, tableting or processing.

Such osmotic delivery devices may be fabricated in various geometries including bilayer, wherein the core comprises a drug layer and a sweller layer adjacent to each other; including trilayer, wherein the core comprises a sweller layer "sandwiched" between two drug layers; and including concentric, wherein the core comprises a central sweller composition surrounded by the drug layer.

The coating of the device comprises a non-erodible coating (B), which preferably is insoluble in water but permeable to water and substantially impermeable to drug and excipients contained therein. The coating preferably contains one or more exit passageways or ports in communication with the drug-containing layer(s) for delivering the drug composition. Preferably, the drug-containing layer(s) of the core contains the drug composition, while the sweller layer consists of an expandable hydrogel, with or without additional osmotic agents. When placed in an aqueous medium, the device imbibes water through the membrane, causing the composition to form a dispensable aqueous composition and causing the hydrogel layer to expand and push against the drug-containing composition, forcing the composition out of the exit passageway. The composition can swell, aiding by forcing the drug out of the passageway. A drug can be delivered from this type of delivery system either dissolved or dispersed in the composition that is expelled from the exit passageway.

In the case of a bilayer geometry, the delivery port(s) or exit passageway(s) may be located on the side of the tablet containing the drug composition or may be located on both sides of the tablet or even on the edge of the tablet so as to connect both the drug layer and the sweller layer with the exterior of the device. The exit passageway(s) may be produced by mechanical means or by laser drilling or by creating a difficult-to-coat

region on the tablet by use of special tooling during tablet compression or by other means.

A particularly useful embodiment of an osmotic device comprises: (A) a single-layer
5 compressed core comprising: (i) tofacitinib (ii) a modified cellulose, in particular
hydroxyethylcellulose, and (iii) an osmotic agent, wherein the modified cellulose is
present in the core from about 2.0% to about 35% by weight and the osmotic agent is
present from about 15% to about 70% by weight; (B) a water-permeable layer
10 surrounding the core; and at least one passageway within the layer for delivering the
drug to a fluid environment surrounding the tablet.

Several disintegrants tend to form gels as they swell with water, thus hindering the
drug delivery from the device. Non-gelling, non-swelling disintegrants provide a more
rapid dispersion of the drug particles within the core as water enters the core. Preferred
15 non-gelling, non-swelling disintegrants are resins, preferably ion-exchange resins. A
preferred resin is Amberlite™ IRP 88 (available from Rohm and Haas, Philadelphia,
PA). When used, the disintegrant is present in amounts ranging from about 1% - 25%
of the core composition.

20 Another example for an osmotic device is an osmotic capsule. The capsule shell or
portion of the capsule shell can be semi-permeable.

Coating is conducted in conventional fashion, typically by dissolving or suspending the
coating material in a solvent and then coating by dipping, spray coating or preferably
25 by pan-coating. A preferred coating solution contains 5 to 15 wt.% polymer. Typical
solvents, useful with the cellulosic polymers mentioned above, include acetone, methyl
acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone,
methyl propyl ketone, ethylene glycol monoethyl ether, ethylene glycol monoethyl
acetate, methylene dichloride, ethylene dichloride, propylene dichloride, nitroethane,
30 nitropropane, tetrachloroethane, 1,4-dioxane, tetrahydrofurane, diglyme, water, and
mixtures thereof. Pore-formers and non-solvents (such as water, glycerol and ethanol)
or plasticizers (such as diethyl phthalate) may also be added in any amount as long as
the polymer remains soluble at the spray temperature. Pore-formers and their use in
fabricating coatings are described in U.S. Patent No. 5,612,059, the pertinent
35 disclosures of which are incorporated herein by reference.

Coatings may also be hydrophobic microporous layers, wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed in U.S. Patent No. 5,798,119, the pertinent disclosures of which are incorporated herein by reference. Such hydrophobic but

5 water-vapor permeable coatings are typically composed of hydrophobic polymers such as polyalkenes, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes and synthetic waxes. Especially preferred hydrophobic microporous coating materials include polystyrene, polysulfones, polyethersulfones, polyethylene,

10 polypropylene, polyvinyl chloride, polyvinylidene fluoride and polytetrafluoroethylene. Such hydrophobic coatings can be made by known phase inversion methods, using any of vapor-quench, liquid quench, thermal processes, leaching soluble material from the coating or by sintering coating particles. In thermal processes, a solution of polymer in a latent solvent is brought to liquid-liquid phase separation in a cooling step. When

15 evaporation of the solvent is not prevented, the resulting membrane will typically be porous. Such coating processes may be conducted by the processes disclosed in U.S. Patent Nos. 4,247,498, 4,490,431 and 4,744,906, the disclosures of which are also incorporated herein by reference.

20 In a preferred embodiment, the oral dosage form of the present invention is suitable for administration once or twice per day, most preferably once per day. Alternatively, the oral dosage form of the present invention can be administered every second day, thrice a week, twice a week or once a week.

25 The present invention also provides the use of the modified release tablet of the present invention as an immunosuppressive agent for organ transplants, xeno transplantation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease,

30 leukemia. The pharmaceutical composition or the oral dosage form of the present invention can be used as an immunosuppressive agent in a method for organ transplants or xenotransplantation, or for treating lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease,

35 Alzheimer's disease, leukemia, said method comprising administering an effective

amount of the pharmaceutical composition or the oral dosage form in a subject in need thereof.

The present invention is illustrated by the following examples.

5

EXAMPLES

The following commercially available compounds were used in the Examples below:

- | | | |
|----|-----------------------------|---|
| 10 | Eudragit® L100-55 (Röhm): | anionic copolymer of methacrylic acid and acrylic acid ethylester |
| | Eudragit® RL PO (Röhm): | copolymer of acrylic and methacrylic acid esters containing quaternary ammonium groups |
| | Eudragit® RS PO (Röhm): | copolymer of ethyl acrylate, methyl methacrylate and a |
| 15 | | low content of methacrylic acid ester with quaternary ammonium groups |
| | Kollicoat® MAE 100P (BASF): | methacrylic acid copolymer |
| | Kollidon® SR (BASF): | mixture of 80 % hydrophobic polyvinyl acetate, 19 % hydrophilic polyvinyl pyrrolidone, 0.8 % sodium lauryl sulfate and 0.2 % colloidal silicate |
| 20 | Aerosil® 200 (Degussa): | highly dispersed silicium dioxide |
| | Avicel® PH102 (FMC): | microcrystalline cellulose, with D50 particle size of about 100 µm |
| | Lubritab® | hydrogenated vegetable oil |
| 25 | Opadry® | film-coating |
| | Retalac® (Meggle) | spray agglomerated blend of 50 parts lactosemonohydrate and 50 parts hypromellose |

Examples 1 – 3: Formulations Containing a Pore-Forming Material with pH Dependent Solubility

Example 1: Matrix tablet, direct compression

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Tablet formulation 1:

	Tasocitinib citrate	10 mg (based on the free base)
	Eudragit® L100-55	40 mg
10	Lactose monohydrate	30 mg
	Dicalcium phosphate anhydrate	30 mg
	Aerosil® 200	1 mg
	Magnesium stearate	1 mg

- 15 All ingredients except magnesium stearate were blended in a free fall mixer for 15 min. Then, sieved (500 µm) magnesium stearate was added and the mixture was blended for further 5 min. The final blend was compressed into tablets.

Example 2: Matrix tablet, wet granulation

20 Tablet formulation 2:

	Tasocitinib citrate	10 mg (based on the free base)
	Kollicoat® MAE 100P	45 mg
	Lactose monohydrate	25 mg
25	Avicel® PH102	17 mg
	Aerosil® 200	2 mg
	Magnesium stearate	1 mg

- 30 Tasocitinib, Kollicoat® and lactose were sieved (1.25 mm mesh) into the pot of a Diosna® P1-6 wet granulator and blended for 2 min. This pre-mixture was granulated, adding a suitable amount of water to gain a mixture having a "snow ball" consistency. The wet granulate was sieved (2 mm mesh) and dried for 2 h at 40 °C in a cabinet drier. The dried granulate was sieved (1.25 mm mesh) and Avicel® and Aerosil® (both sieved with 1.25 mm mesh) were added and the resulting mixture was blended for
- 35 further 15 min in a free fall mixer. Sieved (500 µm mesh) magnesium stearate was

added and the resulting mixture was blended in a free fall mixer for 5 min. The final blend was compressed into tablets.

Example 3: Dry granulation

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Tablet formulation 3:

	Tasocitinib	10 mg (based on the free base)
	Eudragit L 100-55	40 mg
10	GalenIQ 800	30 mg
	Dicalciumphosphat anhydrate	30 mg
	Aerosil® 200	1 mg
	Magnesium stearate	1 mg

- 15 All ingredients, except Aerosil 200 and magnesium stearate, were sieved (1mm mesh) and blended in a free fall mixer for 15 min. The premixture was compacted and the resulting slug was sieved (1mm mesh). Subsequently, Aerosil 200 was added over a sieve (2mm mesh) and blended for further 10 minutes. Then, sieved (500 µm) magnesium stearate was added and the mixture was blended for further 5 min. The
- 20 final blend was compressed into tablets.

Examples 4 – 5: Formulations Containing a Pore-Forming Material with pH Independent Solubility

25 Example 4: Direct compression

Tablet formulation 4:

	Tasocitinib hemi citrate	10 mg (based on the free base)
30	Kollidon® SR	40 mg
	Lactose monohydrate	30 mg
	Dicalcium phosphate anhydrate	30 mg
	Aerosil® 200	1 mg
	Magnesium stearate	1 mg

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All ingredients, except magnesium stearate, were sieved (1mm mesh) and blended in a free fall mixer for 15 min. Then, sieved (500 µm) magnesium stearate was added and the mixture blended for further 5 min. The final blend was compressed into tablets.

5 Example 5: Wet granulation

Tablet formulation 5:

	Tasocitinib citrate	10 mg (based on the free base)
10	Eudragit® RL PO	45 mg
	Lactose monohydrate	25 mg
	Avicel® PH102	17 mg
	Aerosil® 200	2 mg
	Magnesium stearate	1 mg

15

Tasocitinib, Eudragit® and lactose were sieved (1.25 mm mesh) into the pot of a Diosna® P1-6 wet granulator and blended for 2 min. This pre-mixture was granulated, adding a suitable amount of water to gain a mixture having a "snow ball" consistency. The wet granulate was sieved (2 mm mesh) and dried for 2 h at 40 °C in a cabinet drier. The dried granulate was sieved (1.25 mm mesh) and Avicel® and Aerosil® (both sieved with 1.25 mm mesh) were added and the resulting mixture was blended for further 15 min in a free fall mixer. Sieved (500 µm mesh) magnesium stearate was added and the resulting mixture was blended in a free fall mixer for 5 min. The final blend was compressed into tablets.

25

Example 6: Coated tablet

Tablet formulation 6:

30	Tablet core	
	Tasocitinib	10 mg (based on the free base)
	StarLac®	80 mg
	Dicalciumphosphat anhydrate	10 mg
	Aerosil 200	1 mg
35	Magnesiumstearate	1 mg

All excipients, excluding magnesium stearate, were sieved (800µm) and mixed together for 15 min in a free fall mixer. Sieved (500 µm mesh) magnesium stearate was added and the resulting mixture was blended in a free fall mixer for 5 min. The final blend was compressed into tablets.

5

Tablet coating

	Ethylcellulose	20 mg
	PEG 6000	1 mg
10	TEC	5 mg

The coating process was carried out on a pan coater, e.g. on a Lödige LHC 25 (Lödige GmbH, Germany). The spray pressure usually ranges from 1 - 1.5 bar. The product temperature varies according to the applied polymer from 32 – 38 °C.

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Example 7: MUPSTablet formulation 7:

20	Tasocitinib, micronized	10 mg
	Polyoxyethylenepropylene copolymer	4 mg
	Ethylcellulose:	15 mg
	PEG 4000	4 mg
	Nonpareils	40 mg
25	MCC	200 mg
	Polyvinylpyrrolidone	10 mg
	Lubritab	5 mg
	Aerosil	2 mg
	Opadry	2.5 mg

30

Procedure:

Tasocitinib was suspended together with ethyl cellulose in an aqueous solution of polyoxyethylene propylene copolymer and PEG. The placebo pellets were pre-heated

to 38 °C in a fluid bed dryer. Subsequently the pellets were coated with the suspension, using the following parameter:

	Inlet temperature:	40-80°C
5	Product temperature:	35-40°C
	Spray nozzle:	1 - 2 mm
	Spray pressure:	1 – 2 bar

After sintering at elevated temperature the pellets were blended with MCC and Aerosil® and polyvinylpyrrolidone for 25 min in a tumble blender. Afterwards, Lubritab® was added and the blend was mixed for additional 3 minutes.

The final blend was compressed on a Fette® 102 rotary press, characterized by following parameters:

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Hardness: 80 -110 N
Friability: less than 1 %.

The tablets were film-coated in order to achieve a better compliance with an aqueous solution of Opadry® (Colorcon®):

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	Product temperature:	37 - 40°C
	Supply air temperature:	40 - 80°C
	Nozzle diameter:	1,2 mm
25	Spray pressure:	1 -3 bar

Afterwards, the tablets were sintered at 60 °C for 0.5 hour.

Example 8:

30

Tasocitinib citrate	10.0 g (based on free base)
Eudragit® RS PO	84.0 g

API and Eudragit were sieved over a 1000 µm sieve and blended for 15 minutes in a Turbula blender. The resulting blend was extruded in a ThermoFisher extruder. 11.78 g

35

of the resulting extrudate was milled in a Comil, sieved over 800 µm and blended together with 3.5 g RetaLac®, 1.2 g Tablettose 80, 0.1g Aerosil and 0.2 g magnesium stearate. The resulting blend was compressed to tablets on a Korsch tablet press, each tablet containing 10 mg tasocitinib (based on free base).

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Example 9:

	Tasocitinib citrate	1.0 g (based on free base)
	Eudragit® RS PO	8.4 g
10	Granulac® 200	3.0 g
	Aerosil 200	0.2 g
	Magnesiumstearate	0.2 g

API, Eudragit and Granulac 200 were sieved over a 1000 µm sieve, blended, granulated with water/ 2-propanol (1:1) and dried at 40°C. The resulting granulate was sieved over 1000 µm sieve, blended with Aerosil and magnesiumstearate. The resulting mixture was compressed to tablets on a Korsch press, each tablet containing 10.0 mg of tasocitinib (based on free base).

20 **Example 10: Osmotic-controlled tablet**Tablet core:

	Tasocitinib citrate	10 mg (based on the free base)
25	PolyOx® WSR-N80 (Dow)	193 mg
	Xylitol (trade name XYLITAB® 200)	93 mg
	Magnesiumstearate	2 x 2 mg

PolyOx and xylitol are combined and blended in a free fall mixer. The blended material is passed through a sieve (800 µm). The resulting material is added to a blender, the tasocitinib citrate is added and the resulting mixture is mixed for 15 minutes. Magnesiumstearate (2 mg) is added and the resulting blend is mixed for another 5 minutes. The blend is roller-compacted. The resulting granules are transferred to a free fall mixer. Magnesiumstearate (2 mg) is added and the final blend is mixed for another 15 minutes.

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	PEO WSR Coagulant (Dow)	129 mg
	Avicel® PH 200 (FMC)	51.6 mg
	Sodium chloride	17.2 mg
	FD&C #2 Blue Lake	0.6 mg
5	Magnesiumstearate	1 mg

Coagulant, Avicel, sodium chloride and FD&C are mixed in a free fall mixer for 15 minutes. Magnesiumstearate is added and the final blend for the swellable layer is mixed for 15 minutes.

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Tablet cores are formed by compressing 600 mg (400 mg tofacitinib-containing layer; 200 mg swellable layer, using a rotary tri-layer press (e.g. Elizabeth-HATA AP-55). Feed hopper #1 is filled with the tofacitinib-containing layer, feed hopper #2 is empty and feed hopper #3 is filled with the swellable layer. A tamp force of 50 - 65 kg is used for the tofacitinib-containing layer and the tamp force of 500 - 600 kg is used after hopper #3 and the final compression force is approximately 14 kN, resulting in tablets of approximately 15 kP hardness.

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Coating

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Polyethylene glycol	8.0 mg
Water	40 mg
Acetone	920 mg
Cellulose acetate	32 mg

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Polyethylene glycol (PEG 3350) is dissolved in water and acetone is added to the solution. The cellulose acetate (CA 398-10 from Eastman Fine Chemical) is added to the solution and the resulting solution is mixed until homogeneous. The coating solution is applied to the tablet cores by using a pan coater, e.g. on a Lödige LHC 25 (Lödige GmbH, Germany). The spray pressure usually ranges from 1 - 1.5 bar. The product temperature varies according to the applied polymer from 32 °C – 38 °C. The so-coated tablets are dried in a convection oven. One 1200 µm diameter hole is then laser-drilled in the coating on the drug-containing composition side of the tablet to provide one delivery port per tablet.

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Claims

1. Oral dosage form for modified release comprising
 - (a) tasocitinib, and
 - (b) a non-erodible material.
2. Oral dosage form according to claim 1, wherein tasocitinib is contained in an amount of 1 to 60 wt.%, based upon the total weight of the oral dosage form.
3. Oral dosage form according to claim 1 or 2, wherein the non-erodible material has a solubility in water at 25 °C at a pH of 5.0 of less than 33 g/l.
4. Oral dosage form according to anyone of the previous claims, wherein the non-erodible material has a solubility in water at 25 °C at a pH of 7.0 of more than 33 g/l.
5. Oral dosage form according to anyone of the previous claims, wherein the non-erodible material is a non-erodible polymer, preferably having a weight average molecular weight from 30,000 to 3,000,000 g/mol.
6. Oral dosage form according to anyone of the previous claims, wherein the non-erodible material is contained in an amount of 5 to 80 wt.%, based upon the total weight of the oral dosage form.
7. Oral dosage form according to any of the previous claims, further comprising a pore-forming material (c).
8. Oral dosage form according to claim 7, wherein the pore-forming material has a solubility in water at 25 °C and at a pH of 5.0 of more than 50 g/l.
9. Oral dosage form according claims 7 or 8, wherein the pore-forming material is contained in an amount of 1 to 50 wt.%, preferably from 5 to 40 wt.%, based upon the total weight of the oral dosage form.
10. Oral dosage form according to anyone of the previous claims, further comprising at least one further excipient (d) selected from solubilizers, fillers,

lubricants, disintegrants, glidants, anti-sticking agents, plasticizers and mixtures thereof.

11. Oral dosage form according to anyone of the previous claims in form of a matrix
5 tablet.

12. Oral dosage form according to anyone of claims 1 to 10 in form of a tablet
comprising a core and a shell, wherein the core comprises components (a) and
optionally (c) and/or (d) and wherein the shell comprises components (b) and optionally
10 (c) and/or (d).

13. Oral dosage form according to anyone of claims 1 to 10 in form of a multiple
unit pellet system.

15 14. Process for manufacturing a tablet according to anyone of claims 1 to 11
comprising the steps of

- (1-I) providing components (a), (b), optionally (c), and optionally (d),
- (1-II) optionally agglomerating the components of step (I) to yield granules,
- (1-III) compressing the mixture resulting from step (I) or (II) into tablets; and
- 20 (1-IV) optionally film-coating the tablets.

15. Process for manufacturing a tablet according to anyone of claims 1 to 10 or 12
comprising the steps of

- (2-I) mixing components (a) and optionally (c) and/or (d),
- 25 (2-II) optionally agglomerating the components of step (I) to yield granules,
- (2-III) compressing the mixture into tablets, and
- (2-IV) coating the tablets with a coating comprising components (b) and
optionally (c) and/or (d).

30 16. Process for manufacturing an oral dosage form according to anyone of claims 1
to 10 or 13 comprising the steps of

- (3-I) providing a pellet core,
- (3-II) spraying a solution or suspension comprising component (a) and
optionally (d) onto the pellet core,

- (3-III) spraying a solution or suspension comprising component (b) and optionally (c) and/or (d) onto the pellet, preferably onto the pellet resulting from step (3-II),
- (3-IV) optionally blending the pellets with components (b) and (c) and/or (d);
- 5 and
- (3-V) further processing the resulting mixture into a final oral dosage form.

INTERNATIONAL SEARCH REPORT

83

International application No

PCT/EP2012/000353

A. CLASSIFICATION OF SUBJECT MATTER		
INV. A61K31/515	A61K9/20	A61K9/28 A61K9/22
ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
EPO-Internal, WPI Data, BIOSIS, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"TASOCITINIB ORAL TABLET COMPOSITION", IP.COM JOURNAL, IP.COM INC., WEST HENRIETTA, NY, US, 4 January 2011 (2011-01-04), XP013141896, ISSN: 1533-0001 the whole document	1-16
X	----- WO 03/048162 A1 (PFIZER PROD INC [US]; FLANAGAN MARK EDWARD [US]; LI ZHENG JANE [US]) 12 June 2003 (2003-06-12) cited in the application page 7, lines 9-15 claims -----	1-16
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
4 May 2012		14/05/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Herrera, Suzanne

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/000353

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03048162	A1	12-06-2003	AR 037635 A1	17-11-2004
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			WO 03048162 A1	12-06-2003
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FORM 2

THE PATENTS ACT, 1970
(39 of 1970)
&
The Patent Rules, 2003
COMPLETE SPECIFICATION
(See section 10 and rule 13)

TITLE OF THE INVENTION

"PYRROLO[2,3-d]PYRIMIDINE COMPOUNDS"

We, **PFIZER PRODUCTS INC.**, a corporation organized under the laws of the State of Connecticut, United States of America, of Eastern Point Road, Groton, CT 06340, United States of America.

The following specification particularly describes the nature of the invention and the manner in which it is to be performed:

2-2- 86

PYRROLO[2,3-d]PYRIMIDINE COMPOUNDS

Background of the Invention

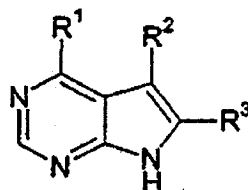
The present invention relates to pyrrolo[2,3-d]pyrimidine compounds which are inhibitors of protein kinases, such as the enzyme Janus Kinase 3 (hereinafter also referred to as JAK3) and as such are useful therapy as immunosuppressive agents for organ transplants, xeno transplantation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia and other indications where immunosuppression would be desirable.

This invention also relates to a method of using such compounds in the treatment of the above indications in mammals, especially humans, and the pharmaceutical compositions useful therefor.

JAK3 is a member of the Janus family of protein kinases. Although the other members of this family are expressed by essentially all tissues, JAK3 expression is limited to hematopoietic cells. This is consistent with its essential role in signaling through the receptors for IL-2, IL-4, IL-7, IL-9 and IL-15 by non-covalent association of JAK3 with the gamma chain common to these multichain receptors. XSCID patient populations have been identified with severely reduced levels of JAK3 protein or with genetic defects to the common gamma chain, suggesting that immunosuppression should result from blocking signaling through the JAK3 pathway. Animal studies have suggested that JAK3 not only plays a critical role in B and T lymphocyte maturation, but that JAK3 is constitutively required to maintain T cell function. Modulation of immune activity through this novel mechanism can prove useful in the treatment of T cell proliferative disorders such as transplant rejection and autoimmune diseases.

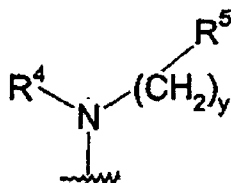
Summary of the Invention

The present invention relates to a compound of the formula



or the pharmaceutically acceptable salt thereof; wherein

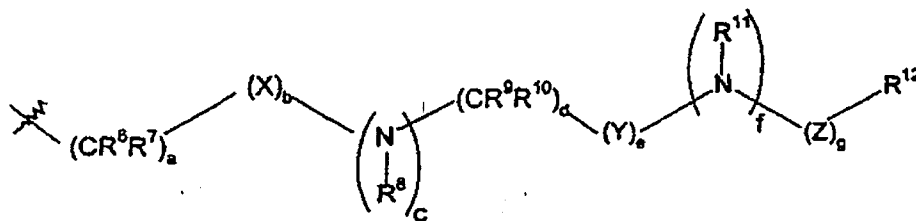
R¹ is a group of the formula



wherein y is 0, 1 or 2;

R^4 is selected from the group consisting of hydrogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{alkylsulfonyl}$, $(\text{C}_2\text{-C}_6)\text{alkenyl}$, $(\text{C}_2\text{-C}_6)\text{alkynyl}$ wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, $(\text{C}_1\text{-C}_6)\text{alkoxy}$, $(\text{C}_1\text{-C}_6)\text{acyloxy}$, $(\text{C}_1\text{-C}_6)\text{alkylamino}$, $((\text{C}_1\text{-C}_6)\text{alkyl})_2\text{amino}$, cyano, nitro, $(\text{C}_2\text{-C}_6)\text{alkenyl}$, $(\text{C}_2\text{-C}_6)\text{alkynyl}$ or $(\text{C}_1\text{-C}_6)\text{acylamino}$; or R^4 is $(\text{C}_3\text{-C}_{10})\text{cycloalkyl}$ wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, $(\text{C}_1\text{-C}_6)\text{alkoxy}$, $(\text{C}_1\text{-C}_6)\text{acylamino}$, $(\text{C}_1\text{-C}_6)\text{alkylamino}$, $((\text{C}_1\text{-C}_6)\text{alkyl})_2\text{amino}$, cyano, cyano $(\text{C}_1\text{-C}_6)\text{alkyl}$, trifluoromethyl $(\text{C}_1\text{-C}_6)\text{alkyl}$, nitro, nitro $(\text{C}_1\text{-C}_6)\text{alkyl}$ or $(\text{C}_1\text{-C}_6)\text{acylamino}$;

R^5 is $(\text{C}_2\text{-C}_6)\text{heterocycloalkyl}$ wherein the heterocycloalkyl groups must be substituted by one to five carboxy, cyano, amino, deuterium, hydroxy, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}$, halo, $(\text{C}_1\text{-C}_6)\text{acyl}$, $(\text{C}_1\text{-C}_6)\text{alkylamino}$, amino $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{alkoxy-CO-NH}$, $(\text{C}_1\text{-C}_6)\text{alkylamino-CO-}$, $(\text{C}_2\text{-C}_6)\text{alkenyl}$, $(\text{C}_2\text{-C}_6)\text{alkynyl}$, $(\text{C}_1\text{-C}_6)\text{alkylamino}$, amino $(\text{C}_1\text{-C}_6)\text{alkyl}$, hydroxy $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{acyloxy}(\text{C}_1\text{-C}_6)\text{alkyl}$, nitro, cyano $(\text{C}_1\text{-C}_6)\text{alkyl}$, halo $(\text{C}_1\text{-C}_6)\text{alkyl}$, nitro $(\text{C}_1\text{-C}_6)\text{alkyl}$, trifluoromethyl, trifluoromethyl $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{acylamino}$, $(\text{C}_1\text{-C}_6)\text{acylamino}(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}(\text{C}_1\text{-C}_6)\text{acylamino}$, amino $(\text{C}_1\text{-C}_6)\text{acyl}$, amino $(\text{C}_1\text{-C}_6)\text{acyl}(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{alkylamino}(\text{C}_1\text{-C}_6)\text{acyl}$, $((\text{C}_1\text{-C}_6)\text{alkyl})_2\text{amino}(\text{C}_1\text{-C}_6)\text{acyl}$, $\text{R}^{15}\text{R}^{16}\text{N-CO-O-}$, $\text{R}^{15}\text{R}^{16}\text{N-CO-}(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{alkyl-S(O)}_m$, $\text{R}^{15}\text{R}^{16}\text{NS(O)}_m$, $\text{R}^{15}\text{R}^{16}\text{NS(O)}_m(\text{C}_1\text{-C}_6)\text{alkyl}$, $\text{R}^{15}\text{S(O)}_m$, R^{16}N , $\text{R}^{15}\text{S(O)}_m\text{R}^{16}\text{N}(\text{C}_1\text{-C}_6)\text{alkyl}$ wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or $(\text{C}_1\text{-C}_6)\text{alkyl}$; or a group of the formula



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wherein a is 0, 1, 2, 3 or 4;

b, c, e, f and g are each independently 0 or 1;

d is 0, 1, 2, or 3;

X is $S(O)_n$ wherein n is 0, 1 or 2; oxygen, carbonyl or $-C(=N\text{-cyano})-$;

Y is $S(O)_n$ wherein n is 0, 1 or 2; or carbonyl; and

Z is carbonyl, $C(O)O-$, $C(O)NR-$ or $S(O)_n$ wherein n is 0, 1 or 2;

R^6 , R^7 , R^8 , R^9 , R^{10} and R^{11} are each independently selected from the group consisting of hydrogen or (C_1-C_6) alkyl optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C_1-C_6) acyloxy, (C_1-C_6) acylamino, (C_1-C_6) alkylamino, $((C_1-C_6)alkyl)_2$ amino, cyano, cyano $(C_1-C_6)alkyl$, trifluoromethyl $(C_1-C_6)alkyl$, nitro, nitro $(C_1-C_6)alkyl$ or $(C_1-C_6)acylamino$;

R^{12} is carboxy, cyano, amino, oxo, deuterium, hydroxy, trifluoromethyl, $(C_1-C_6)alkyl$, trifluoromethyl $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, halo, $(C_1-C_6)acyl$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2$ amino, amino $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy-CO-NH$, $(C_1-C_6)alkylamino-CO-$, $(C_2-C_6)alkenyl$, $(C_2-C_6)alkynyl$, $(C_1-C_6)alkylamino$, hydroxy $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)alkyl$, $(C_1-C_6)acyloxy(C_1-C_6)alkyl$, nitro, cyano $(C_1-C_6)alkyl$, halo $(C_1-C_6)alkyl$, nitro $(C_1-C_6)alkyl$, trifluoromethyl, trifluoromethyl $(C_1-C_6)alkyl$, $(C_1-C_6)acylamino$, $(C_1-C_6)acylamino(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)acylamino$, amino $(C_1-C_6)acyl$, amino $(C_1-C_6)acyl(C_1-C_6)alkyl$, $(C_1-C_6)alkylamino(C_1-C_6)acyl$, $((C_1-C_6)alkyl)_2$ amino $(C_1-C_6)acyl$, $R^{15}R^{16}N-CO-O-$, $R^{15}R^{16}N-CO-(C_1-C_6)alkyl$, $R^{15}C(O)NH$, $R^{15}OC(O)NH$, $R^{15}NHC(O)NH$, $(C_1-C_6)alkyl-S(O)_m$, $(C_1-C_6)alkyl-S(O)_m-(C_1-C_6)alkyl$, $R^{15}R^{16}NS(O)_m$, $R^{15}R^{16}NS(O)_m(C_1-C_6)alkyl$, $R^{15}S(O)_m$, $R^{15}N$, $R^{15}S(O)_mR^{16}N(C_1-C_6)alkyl$ wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or $(C_1-C_6)alkyl$;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, deuterium, amino, halo, hydroxy, nitro, carboxy, $(C_2-C_6)alkenyl$, $(C_2-C_6)alkynyl$, trifluoromethyl, trifluoromethoxy, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, $(C_3-C_{10})cycloalkyl$ wherein the alkyl, alkoxy or cycloalkyl groups are optionally substituted by one to three groups selected from halo, hydroxy, carboxy, amino $(C_1-C_6)alkylthio$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2$ amino, $(C_5-C_9)heteroaryl$, $(C_2-C_9)heterocycloalkyl$, $(C_3-C_9)cycloalkyl$ or $(C_6-C_{10})aryl$; or R^2 and R^3 are each independently $(C_3-C_{10})cycloalkyl$, $(C_3-C_{10})cycloalkoxy$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2$ amino, $(C_6-C_{10})arylamino$, $(C_1-C_6)alkylthio$, $(C_6-C_{10})arylthio$, $(C_1-C_6)alkylsulfinyl$, $(C_6-C_{10})arylsulfinyl$, $(C_1-C_6)alkylsulfonyl$, $(C_6-C_{10})arylsulfonyl$, $(C_1-C_6)acyl$, $(C_1-C_6)alkoxy-CO-NH-$, $(C_1-C_6)alkylamino-CO-$, $(C_5-C_9)heteroaryl$, $(C_2-C_9)heterocycloalkyl$ or $(C_6-C_{10})aryl$ wherein the heteroaryl, heterocycloalkyl and aryl groups are optionally substituted by one to three halo, $(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-CO-NH-$, $(C_1-C_6)alkoxy-CO-NH-$, $(C_1-C_6)alkyl-CO-NH-(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy-CO-NH-(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy-CO-NH-(C_1-C_6)alkoxy$, carboxy, carboxy $(C_1-C_6)alkyl$, carboxy $(C_1-C_6)alkoxy$, benzyloxycarbonyl $(C_1-C_6)alkoxy$, $(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy$, $(C_6-C_{10})aryl$, amino, amino $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxycarbonylamino$, $(C_6-C_{10})aryl(C_1-C_6)alkoxycarbonylamino$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2$ amino, $(C_1-$

C_6)alkylamino(C_1 - C_6)alkyl, ((C_1 - C_6)alkyl)₂amino(C_1 - C_6)alkyl, hydroxy, (C_1 - C_6)alkoxy, carboxy, carboxy(C_1 - C_6)alkyl, (C_1 - C_6)alkoxycarbonyl, (C_1 - C_6)alkoxycarbonyl(C_1 - C_6)alkyl, (C_1 - C_6)alkoxy-CO-NH-, (C_1 - C_6)alkyl-CO-NH-, cyano, (C_5 - C_9)heterocycloalkyl, amino-CO-NH-, (C_1 - C_6)alkylamino-CO-NH-, ((C_1 - C_6)alkyl)₂amino-CO-NH-, (C_6 - C_{10})arylamino-CO-NH-, (C_5 - C_9)heteroarylamino-CO-NH-, (C_1 - C_6)alkylamino-CO-NH-(C_1 - C_6)alkyl, ((C_1 - C_6)alkyl)₂amino-CO-NH-(C_1 - C_6)alkyl, (C_6 - C_{10})arylamino-CO-NH-(C_1 - C_6)alkyl, (C_5 - C_9)heteroarylamino-CO-NH-(C_1 - C_6)alkyl, (C_1 - C_6)alkylsulfonyl, (C_1 - C_6)alkylsulfonylamino, (C_1 - C_6)alkylsulfonylamino(C_1 - C_6)alkyl, (C_6 - C_{10})arylsulfonyl, (C_6 - C_{10})arylsulfonylamino, (C_6 - C_{10})arylsulfonylamino(C_1 - C_6)alkyl, (C_1 - C_6)alkylsulfonylamino, (C_1 - C_6)alkylsulfonylamino(C_1 - C_6)alkyl, (C_5 - C_9)heteroaryl or (C_5 - C_9)heterocycloalkyl.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

The invention also relates to base addition salts of formula I. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched moieties or combinations thereof.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

The term "halo", as used herein, unless otherwise indicated, includes fluoro, chloro, bromo or iodo.

The compounds of this invention may contain double bonds. When such bonds are present, the compounds of the invention exist as *cis* and *trans* configurations and as mixtures thereof.

Unless otherwise indicated, the alkyl and alkenyl groups referred to herein, as well as the alkyl moieties of other groups referred to herein (e.g., alkoxy), may be linear or branched, and they may also be cyclic (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl) or be linear or branched and contain cyclic moieties. Unless otherwise indicated, halogen includes fluorine, chlorine, bromine, and iodine.

(C₂-C₉)Heterocycloalkyl when used herein refers to pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydropyranyl, pyranal, thiopyranal, aziridinyl, oxiranyl, methylenedioxy, chromenyl, isoxazolidinyl, 1,3-oxazolidin-3-yl, isothiazolidinyl, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, piperidinyl, thiomorpholinyl, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazinyl, morpholinyl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, tetrahydroazepinyl, piperazinyl, chromanyl, etc. One of ordinary skill in the art will understand that the connection of said (C₂-C₉)heterocycloalkyl rings is through a carbon or a sp³ hybridized nitrogen heteroatom.

(C₂-C₉)Heteroaryl when used herein refers to furyl, thienyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, pyrazolo[3,4-b]pyridinyl, cinnolinyl, pteridinyl, purinyl, 6,7-dihydro-5H-[1]pyrindinyl, benzo[b]thiophenyl, 5, 6, 7, 8-tetrahydro-quinolin-3-yl, benzoxazolyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, isoindolyl, indolyl, indolizyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalyl, quinazolinyl, benzoxazinyl; etc. One of ordinary skill in the art will understand that the connection of said (C₂-C₉)heterocycloalkyl rings is through a carbon atom or a sp³ hybridized nitrogen heteroatom.

(C₆-C₁₀)aryl when used herein refers to phenyl or naphthyl.

Compounds of formula (I) may be administered in a pharmaceutically acceptable form either alone or in combination with one or more additional agents which modulate a mammalian immune system or with antiinflammatory agents. These agents may include but are not limited to cyclosporin A (e.g. Sandimmune® or Neoral®, rapamycin, FK-506 (tacrolimus), leflunomide, deoxyspergualin, mycophenolate (e.g. Cellcept®), azathioprine (e.g. Imuran®), daclizumab (e.g. Zenapax®), OKT3 (e.g. Orthoclone®), AlGam, aspirin, acetaminophen, ibuprofen, naproxen, piroxicam, and antiinflammatory steroids (e.g. prednisolone or dexamethasone). These agents may be administered as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice.

The compounds of this invention include all conformational isomers (e.g., cis and trans isomers). The compounds of the present invention have asymmetric centers and

therefore exist in different enantiomeric and diastereomeric forms. This invention relates to the use of all optical isomers and stereoisomers of the compounds of the present invention, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment that may employ or contain them. In this regard, the invention includes both the E and Z configurations. The compounds of formula I may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

This invention also encompasses pharmaceutical compositions containing prodrugs of compounds of the formula I. This invention also encompasses methods of treating or preventing disorders that can be treated or prevented by the inhibition of protein kinases, such as the enzyme Janus Kinase 3 comprising administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy or carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvlin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain.

Preferred compounds of formula I include those wherein a is 0; b is 1; X is carbonyl; c is 0; d is 0; e is 0; f is 0; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is carbonyl; c is 0; d is 1; e is 0; f is 0, and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is carbonyl; c is 1; d is 0; e is 0; f is 0; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is $-C(=N=\text{cyano})-$; c is 1; d is 0; e is 0; f is 0; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 0; c is 0; d is 0; e is 0; f is 0; g is 1; and Z is $-C(O)-O-$.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is $S(O)_n$; n is 2; c is 0; d is 0; e is 0; f is 0; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is $S(O)_n$; n is 2; c is 0; d is 2; e is 0; f is 1; g is 1; and Z is carbonyl.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is $S(O)_n$; n is 2; c is 0; d is 2; e is 0; f is 1; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is carbonyl; c is 1; d is 0; e is 1; Y is $S(O)_n$; n is 2; f is 0; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is $S(O)_n$; n is 2; c is 1; d is 0; e is 0; f is 0; and g is 0.

Other preferred compounds of formula I include those wherein a is 1; b is 1; X is carbonyl; c is 1; d is 0; e is 0; f is 0; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is $S(O)_n$; c is 0; d is 1; e is 1; Y is $S(O)_n$; n is 2; f is 0; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is $S(O)_n$; c is 0; d is 1; e is 1; Y is $S(O)_n$; n is 2; f is 1; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is oxygen; c is 0; d is 1; e is 1; Y is $S(O)_n$; n is 2; f is 1; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is oxygen; c is 0; d is 1; e is 1; Y is $S(O)_n$; n is 2; f is 0; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is carbonyl; c is 1; d is 1; e is 1; Y is $S(O)_n$; f is 0; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is carbonyl; c is 1; d is 1; e is 1; Y is $S(O)_n$; n is 2; f is 1; and g is 0.

Other preferred compounds of formula I include those wherein R^{12} is cyano, trifluoromethyl, (C_1-C_6) alkyl, trifluoromethyl (C_1-C_6) alkyl, (C_1-C_6) alkylamino, $((C_1-C_6)alkyl)_2$ amino, (C_2-C_6) alkynyl, cyano (C_1-C_6) alkyl, $(C_1-C_6)alkyl-S(O)_m$ wherein m is 0, 1 or 2.

Specific preferred compounds of formula I include those wherein said compound is selected from the group consisting of:

Methyl-[4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;

4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid methyl ester;

3,3,3-Trifluoro-1-[4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-propan-1-one;

4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid dimethylamide;

[(4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carbonyl)-amino]-acetic acid ethyl ester;

3-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile;

3,3,3-Trifluoro-1-{4-methyl-3-[methyl-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-propan-1-one;

1-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-but-3-yn-1-one;

1-{3-[(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one;

1-{3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one;

N-cyano-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-N'-propyl-piperidine-1-carboxamidine; and

N-cyano-4,N',N'-Trimethyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxamidine.

The present invention also relates to a pharmaceutical composition for (a) treating or preventing a disorder or condition selected from organ transplant rejection, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia, and other autoimmune diseases or (b) the inhibition of protein kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, effective in such disorders or conditions and a pharmaceutically acceptable carrier.

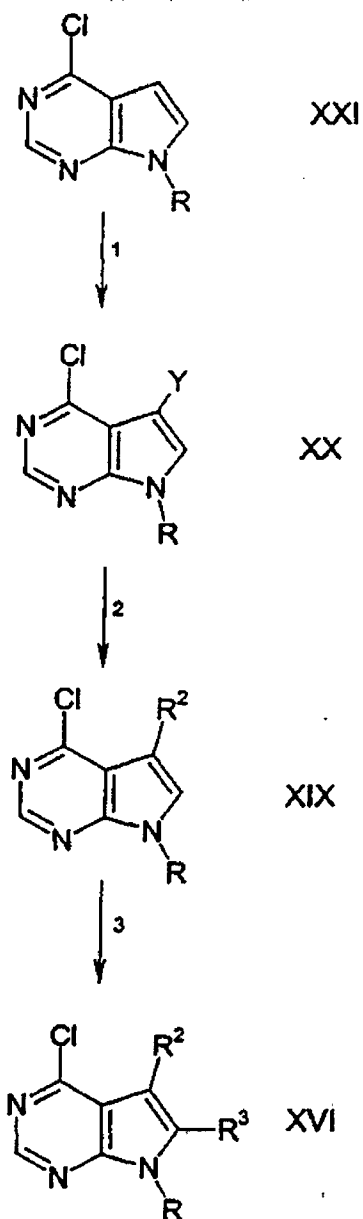
The present invention also relates to a method for the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method for treating or preventing a disorder or condition selected from organ transplant rejection, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia, and other autoimmune diseases in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, effective in treating such a condition.

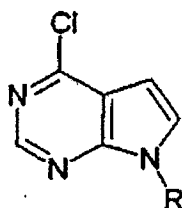
Detailed Description of the Invention

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated R^2 , R^3 , R^4 and R^5 in the reaction Schemes and the discussion that follow are defined as above.

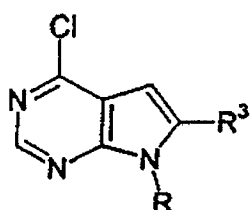
PREPARATION A



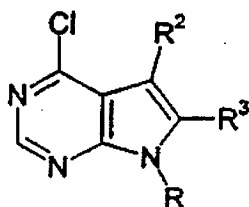
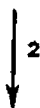
PREPARATION B



XXI

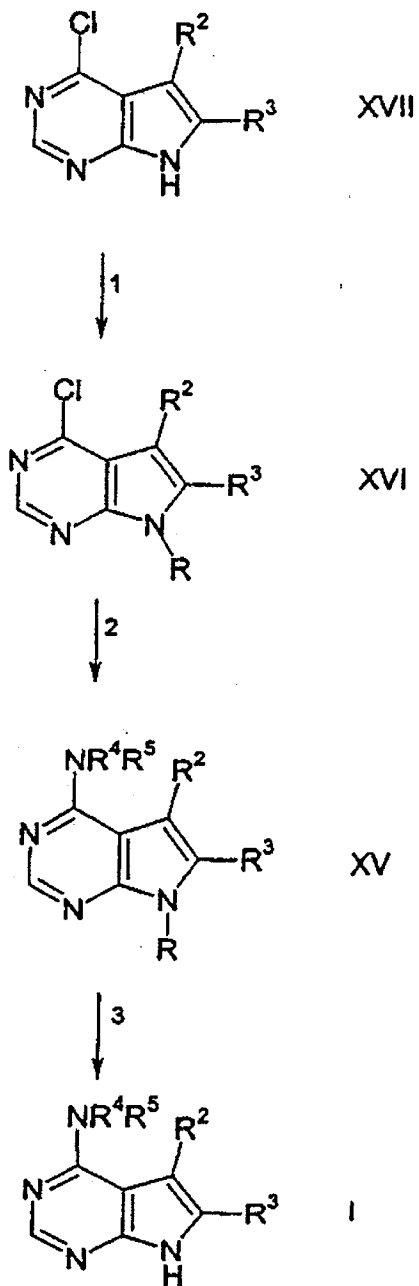


XXII

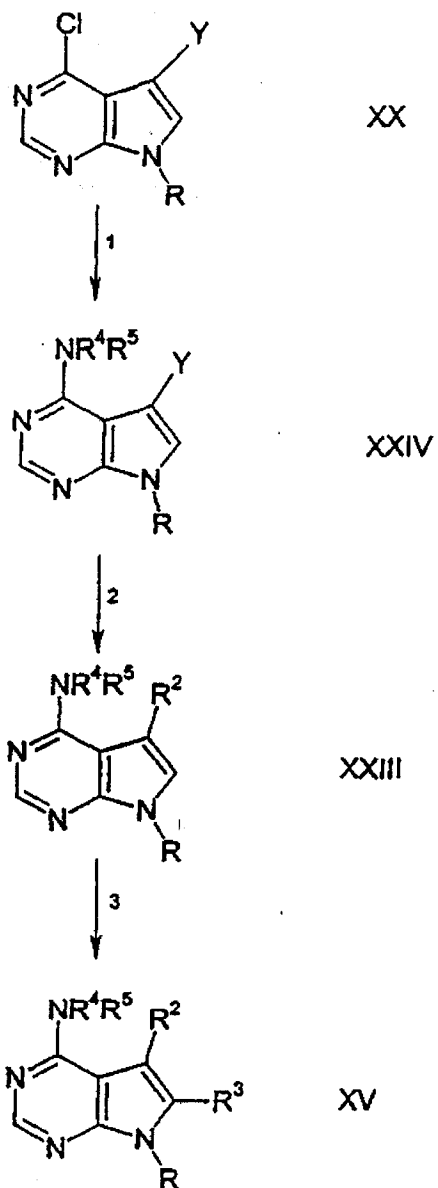


XVI

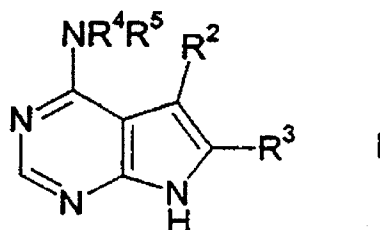
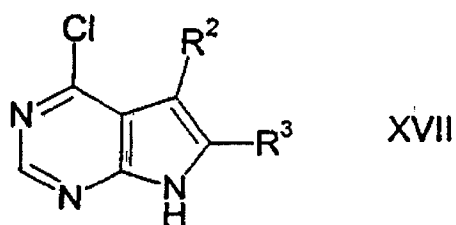
SCHEME 1



SCHEME 2



SCHEME 3



In reaction 1 of Preparation A, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula XXI, wherein R is hydrogen or a protecting group such as benzenesulfonyl or benzyl, is converted to the 4-chloro-5-halopyrrolo[2,3-d]pyrimidine compound of formula XX, wherein Y is chloro, bromo or iodo, by reacting XXI with N-chlorosuccinimide, N-bromosuccinimide or N-iodosuccinimide. The reaction mixture is heated to reflux, in chloroform, for a time period between about 1 hour to about 3 hours, preferably about 1 hour. Alternatively, in reaction 1 of Preparation A, the 4-chloropyrrolo[2,3-d]pyrimidine of formula XXI, wherein R is hydrogen, is converted to the corresponding 4-chloro-5-nitropyrrolo[2,3-d]pyrimidine of formula XX, wherein Y is nitro, by reacting XXI with nitric acid in sulfuric acid at a temperature between about -10°C to about 10°C, preferably about 0°C, for a time period between about 5 minutes to about 15 minutes, preferably about 10 minutes. The compound of formula XXI, wherein Y is nitro, is converted to the corresponding 4-chloro-5-aminopyrrolo[2,3-d]pyrimidine of the formula XX, wherein Y is amino, by reacting XXI under a variety of conditions known to one skilled in the art such as palladium hydrogenolysis or tin(IV)chloride and hydrochloric acid.

In reaction 2 of Preparation A, the 4-chloro-5-halopyrrolo[2,3-d]pyrimidine compound of formula XX, wherein R is hydrogen, is converted to the corresponding compound of formula XIX, wherein R² is (C₁-C₆)alkyl or benzyl, by treating XX with N-butyllithium, at a temperature of about -78°C, and reacting the dianion intermediate so formed with an alkylhalide or benzylhalide at a temperature between about -78°C to room temperature, preferably room temperature. Alternatively, the dianion so formed is reacted with molecular oxygen to form the corresponding 4-chloro-5-hydroxypyrrolo[2,3-d]pyrimidine compound of formula XIX, wherein R² is hydroxy. The compound of formula XX, wherein Y is bromine or iodine and R is benzenesulfonate, is converted to the compound of formula XIX, wherein R² is (C₆-C₁₂)aryl or vinyl, by treating XX with N-butyllithium, at a temperature of about -78°C, followed by the addition of zinc chloride, at a temperature of about -78°C. The corresponding organo zinc intermediate so formed is then reacted with aryl iodide or vinyl iodide in the presence of a catalytic quantity of palladium. The reaction mixture is stirred at a temperature between about 50°C to about 80°C, preferably about 70°C, for a time period between about 1 hour to about 3 hours, preferably about 1 hour.

In reaction 3 of Preparation A, the compound of formula XIX is converted to the corresponding compound of formula XVI by treating XIX with N-butyllithium, lithium diisopropylamine or sodium hydride, at a temperature of about -78°C, in the presence of a polar aprotic solvent, such as tetrahydrofuran. The anionic intermediate so formed is further reacted with (a) alkylhalide or benzylhalide, at a temperature between about -78°C to room temperature, preferably -78 °C, when R³ is alkyl or benzyl; (b) an aldehyde or ketone, at a temperature between about -78°C to room temperature, preferably -78°C, when R³ is alkoxy;

and (c) zinc chloride, at a temperature between about -78°C to room temperature, preferably -78°C , and the corresponding organozinc intermediate so formed is then reacted with aryl iodide or vinyl iodide in the presence of a catalytic quantity of palladium. The resulting reaction mixture is stirred at a temperature between about 50°C to about 80°C , preferably about 70°C , for a time period between about 1 hour to about 3 hours, preferably about 1 hour. Alternatively, the anion so formed is reacted with molecular oxygen to form the corresponding 4-chloro-6-hydroxypyrrolo[2,3-d]pyrimidine compound of formula XVI, wherein R^3 is hydroxy.

In reaction 1 of Preparation B, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula XXI is converted to the corresponding compound of formula XXII, according to the procedure described above in reaction 3 of Preparation A.

In reaction 2 of Preparation B, the compound of formula XXII is converted to the corresponding compound of formula XVI, according to the procedures described above in reactions 1 and 2 of Preparation A.

In reaction 1 of Scheme 1, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula XVII is converted to the corresponding compound of formula XVI, wherein R is benzenesulfonyl or benzyl, by treating XVII with benzenesulfonyl chloride, benzylchloride or benzylbromide in the presence of a base, such as sodium hydride or potassium carbonate, and a polar aprotic solvent, such as dimethylformamide or tetrahydrofuran. The reaction mixture is stirred at a temperature between about 0°C to about 70°C , preferably about 30°C , for a time period between about 1 hour to about 3 hours, preferably about 2 hours.

In reaction 2 of Scheme 1, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula XVI is converted to the corresponding 4-aminopyrrolo[2,3-d]pyrimidine compound of formula XV by coupling XVI with an amine of the formula HNR^4R^5 . The reaction is carried out in an alcohol solvent, such as tert-butanol, methanol or ethanol, or other high boiling organic solvents, such as dimethylformamide, triethylamine, 1,4-dioxane or 1,2-dichloroethane, at a temperature between about 60°C to about 120°C , preferably about 80°C . Typical reaction times are between about 2 hours to about 48 hours, preferably about 16 hours. When R^5 is a nitrogen containing heterocycloalkyl group, each nitrogen must be protected by a protecting group, such a benzyl. Removal of the R^5 protecting group is carried out under conditions appropriate for that particular protecting group in use which will not affect the R protecting group on the pyrrolo[2,3-d]pyrimidine ring. Removal of the R^5 protecting group, when benzyl, is carried out in an alcohol solvent, such as ethanol, in the present of hydrogen and a catalyst, such as palladium hydroxide on carbon. The R^5 nitrogen containing heterocycloalkyl group so formed may be further reacted with a variety of different electrophiles of formula II. For urea formation, electrophiles of formula II such as isocyanates, carbamates and carbamoyl chlorides are reacted with the R^5 nitrogen of the heteroalkyl group in a solvent, such as

acetonitrile or dimethylformamide, in the presence of a base, such as sodium or potassium carbonate, at a temperature between about 20°C to about 100 °C for a time period between about 24 hours to about 72 hours. For amide and sulfonamide formation, electrophiles of formula II, such as acylchlorides and sulfonyl chlorides, are reacted with the R⁵ nitrogen of the heteroalkyl group in a solvent such as methylene chloride in the presence of a base such as pyridine at ambient temperatures for a time period between about 12 hours to about 24 hours. Amide formation may also be carried out by reacting a carboxylic acid with the heteroalkyl group in the presence of a carbodiimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide in a solvent such as methylene chloride at ambient temperatures for 12-24 hours. For alkyl formation, electrophiles of formula II, such as α,β -unsaturated amides, acids, nitriles, esters, and α -halo amides, are reacted with the R⁵ nitrogen of the heteroalkyl group in a solvent such as methanol at ambient temperatures for a time period between about 12 hours to about 18 hours. Alkyl formation may also be carried out by reacting aldehydes with the heteroalkyl group in the presence of a reducing agent, such as sodium cyanoborohydride, in a solvent, such as methanol, at ambient temperature for a time period between about 12 hours to about 18 hours.

In reaction 3 of Scheme 1, removal of the protecting group from the compound of formula XV, wherein R is benzenesulfonyl, to give the corresponding compound of formula I, is carried out by treating XV with an alkali base, such as sodium hydroxide or potassium hydroxide, in an alcohol solvent, such as methanol or ethanol, or mixed solvents, such as alcohol/tetrahydrofuran or alcohol/water. The reaction is carried out at room temperature for a time period between about 15 minutes to about 1 hour, preferably 30 minutes. Removal of the protecting group from the compound of formula XV, wherein R is benzyl, is conducted by treating XV with sodium in ammonia at a temperature of about -78°C for a time period between about 15 minutes to about 1 hour.

In reaction 1 of Scheme 2, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula XX is converted to the corresponding 4-aminopyrrolo[2,3-d]pyrimidine compound of formula XXIV, according to the procedure described above in reaction 2 of Scheme 1.

In reaction 2 of Scheme 2, the 4-amino-5-halopyrrolo[2,3-d]pyrimidine compound of formula XXIV, wherein R is benzenesulfonate and Z is bromine or iodine, is converted to the corresponding compound of formula XXIII by reacting XXIV with (a) arylboronic acid, when R² is aryl, in an aprotic solvent, such tetrahydrofuran or dioxane, in the presence of a catalytic quantity of palladium (0) at a temperature between about 50°C to about 100°C, preferably about 70°C, for a time period between about 2 hours to about 48 hours, preferably about 12 hours; (b) alkynes, when R² is alkynyl, in the presence of a catalytic quantity of copper (I) iodide and palladium (0), and a polar solvent, such as dimethylformamide, at room

temperature, for a time period between about 1 hour to about 5 hours, preferably about 3 hours; and (c) alkenes or styrenes, when R^2 is vinyl or styrenyl, in the presence of a catalytic quantity of palladium in dimethylformamide, dioxane or tetrahydrofuran, at a temperature between about 80°C to about 100°C, preferably about 100°C, for a time period between about 2 hours to about 48 hours, preferably about 48 hours.

In reaction 3 of Scheme 2, the compound of formula XXIII is converted to the corresponding compound of formula XV, according to the procedure described above in reaction 3 of Preparation A.

In reaction 1 of Scheme 3, the compound of formula XVII is converted to the corresponding compound of formula I, according to the procedure described above in reaction 2 of Scheme 1.

The compounds of the present invention that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid.

Those compounds of the present invention that are acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of the present invention. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and

then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or in a form suitable for administration by inhalation or insufflation. The active compounds of the invention may also be formulated for sustained delivery.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (e.g., rheumatoid arthritis) is 0.1 to 1000 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

Aerosol formulations for treatment of the conditions referred to above (e.g., asthma) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20 µg to 1000 µg of the compound of the invention. The overall daily dose with an aerosol will be within the range 0.1 mg to 1000 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times; giving for example, 1, 2 or 3 doses each time.

A compound of formula (I) administered in a pharmaceutically acceptable form either alone or in combination with one or more additional agents which modulate a mammalian immune system or with antiinflammatory agents, agents which may include but are not limited to cyclosporin A (e.g. Sandimmune® or Neoral®, rapamycin, FK-506 (tacrolimus), leflunomide, deoxyspergualin, mycophenolate (e.g. Cellcept®, azathioprine (e.g. Imuran®), daclizumab (e.g. Zenapax®), OKT3 (e.g. Orthoclone®), AtGam, aspirin, acetaminophen, ibuprofen, naproxen, piroxicam, and antiinflammatory steroids (e.g. prednisolone or dexamethasone); and such agents may be administered as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice.

FK506 (Tacrolimus) is given orally at 0.10-0.15 mg/kg body weight, every 12 hours, within first 48 hours postoperative. Dose is monitored by serum Tacrolimus trough levels.

Cyclosporin A (Sandimmune oral or intravenous formulation, or Neoral®, oral solution or capsules) is given orally at 5 mg/kg body weight, every 12 hours within 48 hours postoperative. Dose is monitored by blood Cyclosporin A trough levels.

The active agents can be formulated for sustained delivery according to methods well known to those of ordinary skill in the art. Examples of such formulations can be found in United States Patents 3,538,214, 4,060,598, 4,173,626, 3,119,742, and 3,492,397.

The ability of the compounds of formula I or their pharmaceutically acceptable salts to inhibit Janus Kinase 3 and, consequently, demonstrate their effectiveness for treating disorders or conditions characterized by Janus Kinase 3 is shown by the following in vitro assay tests.

Biological Assay

JAK3 (JH1:GST) Enzymatic Assay

The JAK3 kinase assay utilizes a protein expressed in baculovirus-infected SF9 cells (a fusion protein of GST and the catalytic domain of human JAK3) purified by affinity chromatography on glutathione-Sepharose. The substrate for the reaction is poly-Glutamic acid-Tyrosine (PGT (4:1), Sigma catalog # P0275), coated onto Nunc Maxi Sorp plates at 100 µg/ml overnight at 37°C. The morning after coating, the plates are washed three times and JAK3 is added to the wells containing 100 µl of kinase buffer (50 mM HEPES, pH 7.3, 125 mM NaCl, 24 mM MgCl₂) + 0.2 µM ATP + 1 mM Na orthovanadate.) The reaction proceeds for 30 minutes at room temperature and the plates is washed three more times. The level of phosphorylated tyrosine in a given well is quantitated by standard ELISA assay utilizing an anti-phosphotyrosine antibody (ICN PY20, cat. #69-151-1).

Inhibition of Human IL-2 Dependent T-Cell Blast Proliferation

This screen measures the inhibitory effect of compounds on IL-2 dependent T-Cell blast proliferation *in vitro*. Since signaling through the IL-2 receptor requires JAK-3, cell active inhibitors of JAK-3 should inhibit IL-2 dependent T-Cell blast proliferation.

The cells for this assay are isolated from fresh human blood. After separation of the mononuclear cells using Accuspin System-Histopaque-1077 (Sigma # A7054), primary human T-Cells are isolated by negative selection using Lympho-Kwik T (One Lambda, Inc., Cat # LK-50T). T-Cells are cultured at $1-2 \times 10^6$ /ml in Media (RPMI + 10% heat-inactivated fetal calf serum (Hyclone Cat # A-1111-L) + 1% Penicillin/Streptomycin (Gibco)) and induce to proliferate by the addition of 10ug/ml PHA (Murex Diagnostics, Cat # HA 16). After 3 days at 37°C in 5% CO₂, cells are washed 3 times in Media, resuspended to a density of $1-2 \times 10^6$ cells/ml in Media plus 100 Units/ml of human recombinant IL-2 (R&D Systems, Cat # 202-IL). After 1 week the cells are IL-2 dependent and can be maintained for up to 3 weeks by feeding twice weekly with equal volumes of Media + 100 Units/ml of IL-2.

To assay for a test compounds ability to inhibit IL-2 dependent T-Cell proliferation, IL-2 dependent cells are washed 3 times, resuspended in media and then plated (50,000 cells/well/0.1ml) in a Flat-bottom 96-well microtiter plate (Falcon # 353075). From a 10 mM

stock of test compound in DMSO, serial 2-fold dilutions of compound are added in triplicate wells starting at 10 μ M. After one hour, 10 Units/ml of IL-2 is added to each test well. Plates are then incubated at 37°C, 5% CO₂ for 72 hours. Plates are then pulsed with ³H-thymidine (0.5 μ Ci/well) (NEN Cat # NET-027A), and incubated an additional 18 hours. Culture plates are then harvested with a 96-well plate harvester and the amount of ³H-thymidine incorporated into proliferating cells is determined by counting on a Packard Top Count scintillation counter. Data is analyzed by plotting the % inhibition of proliferation verses the concentration of test compound. An IC₅₀ value (μ M) is determined from this plot.

The following Examples illustrate the preparation of the compounds of the present invention but it is not limited to the details thereof. Melting points are uncorrected. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform unless otherwise specified). Commercial reagents were utilized without further purification. THF refers to tetrahydrofuran. DMF refers to N,N-dimethylformamide. Low Resolution Mass Spectra (LRMS) were recorded on either a Hewlett Packard 5989B, utilizing chemical ionization (ammonium), or a Fisons (or Micro Mass) Atmospheric Pressure Chemical Ionization (APCI) platform which uses a 50/50 mixture of acetonitrile/water with 0.1% formic acid as the ionizing agent. Room or ambient temperature refers to 20-25°C.

Example 1

1-(4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-ethanone

Method A

(1-Benzyl-4-methyl-piperidin-3-yl)-methyl-amine

To a stirred solution of 1-benzyl-4-methyl-piperidin-3-one (2.3 grams, 11.5 mmol), prepared by the methods of Iorio, M.A. and Damia, G., Tetrahedron, 26, 5519 (1970) and Grieco et al., Journal of the American Chemical Society, 107, 1768 (1985), (modified using 5% methanol as a co-solvent), both references are incorporated by reference in their entirety, dissolved in 23 mL of 2 M methylamine in tetrahydrofuran was added 1.4 mL (23 mmol) of acetic acid and the resulting mixture stirred in a sealed tube for 16 hours at room temperature. Triacetoxy sodium borohydride (4.9 grams, 23 mmol) was added and the new mixture stirred at room temperature in a sealed tube for 24 h, at which time, the reaction was quenched upon addition of 1 N sodium hydroxide (50 mL). The reaction mixture was then extracted 3 x 80 mL with ether, the combined ether layers dried over sodium sulfate (Na₂SO₄) and concentrated to dryness in vacuo affording 1.7 grams (69%) of the title compound as a white solid. LRMS: 219.1 (M+1).

Method B

(1-Benzyl-4-methyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

A solution of 4-chloropyrrolo[2,3-d]pyrimidine (2.4 grams, 15.9 mmol), prepared by the method of Davoll, J. Am. Chem. Soc., 82, 131 (1960), which is incorporated by reference in its entirety, and the product from Method A (1.7 grams, 7.95 mmol) dissolved in 2 equivalents of triethylamine was heated in a sealed tube at 100 °C for 3 days. Following cooling to room temperature and concentration under reduced pressure, the residue was purified by flash chromatography (silica; 3% methanol in dichloromethane) affording 1.3 grams (50%) of the title compound as a colorless oil. LRMS: 336.1 (M+1).

Method C

Methyl-(4-methyl-piperidin-3-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

To the product from Method B (0.7 grams, 2.19 mmol) dissolved in 15 mL of ethanol was added 1.5 mL of 2 N hydrochloric acid and the reaction mixture degassed by nitrogen purge. To the reaction mixture was then added 0.5 grams of 20% palladium hydroxide on carbon (50% water) (Aldrich) and the resulting mixture shaken (Parr-Shaker) under a 50 psi atmosphere of hydrogen at room temperature for 2 days. The Celite filtered reaction mixture was concentrated to dryness in vacuo and the residue purified by flash chromatography (silica; 5% methanol in dichloromethane) affording 0.48 grams (90%) of the title compound. LRMS: 246.1 (M+1).

Method D

1-(4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-ethanone

To a stirred solution of the product from Method C (0.03 grams, 0.114 mmol) dissolved in 5 mL of 10:1 dichloromethane/pyridine was added (0.018 grams, 0.228 mmol) of acetylchloride and the resulting mixture stirred at room temperature for 18 hours. The reaction mixture was then partitioned between dichloromethane and saturated sodium bicarbonate (NaHCO₃). The organic layer was washed again with saturated NaHCO₃, dried over sodium sulfate and concentrated to dryness in vacuo. The residue was purified by preparative thin layer chromatography (PTLC) (silica; 4% methanol in dichloromethane) affording 0.005 mg (15%) of the title compound as a colorless oil. LRMS: 288.1 (M+1).

The title compounds for examples 2-26 were prepared by a method analogous to that described in Example 1.

Example 2

[1-(2-Amino-ethanesulfonyl)-4-methyl-piperidin-3-yl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

[1-(2-Amino-ethanesulfonyl)-4-methyl-piperidin-3-yl]-methyl-amine. LRMS: 353.

Example 3

(1-Ethanesulfonyl-4-methyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(1-Ethanesulfonyl-4-methyl-piperidin-3-yl)-methyl-amine. LRMS: 338.

Example 4

[1-(Butane-1-sulfonyl)-4-methyl-piperidin-3-yl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

[1-(Butane-1-sulfonyl)-4-methyl-piperidin-3-yl]-methyl-amine. LRMS: 366.

Example 5

4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid isobutyl ester

4-Methyl-3-methylamino-piperidine-1-carboxylic acid isobutyl ester. LRMS: 346.

Example 6

N-[2-(4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-sulfonyl)-ethyl]-propionamide

N-[2-(4-Methyl-3-methylamino-piperidine-1-sulfonyl)-ethyl]-propionamide. LRMS: 409.

Example 7

[2-(4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-sulfonyl)-ethyl]-carbamic acid methyl ester

[2-(4-Methyl-3-methylamino-piperidine-1-sulfonyl)-ethyl]-carbamic acid methyl ester. LRMS: 411.

Example 8

N-[2-(4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-sulfonyl)-ethyl]-isobutyramide

N-[2-(4-Methyl-3-methylamino-piperidine-1-sulfonyl)-ethyl]-isobutyramide. LRMS: 423.

Example 9

(1-Methanesulfonyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(1-Methanesulfonyl-piperidin-3-yl)-methyl-amine. LRMS: 310.

Example 10(1-Ethanesulfonyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(1-Ethanesulfonyl-piperidin-3-yl)-methyl-amine. LRMS: 324.

Example 11Methyl-[1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(1-Propylsulfonyl-piperidin-3-yl)-methyl-amine. LRMS: 338.

Example 12[1-(Butane-1-sulfonyl)-piperidin-3-yl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(1-Butylsulfonyl-piperidin-3-yl)-methyl-amine. LRMS: 352.

Example 132,2-Dimethyl-N-[2-(4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-sulfonyl)-ethyl]-propionamide

2,2-Dimethyl-N-[2-(4-methyl-3-methylamino-piperidine-1-sulfonyl)-ethyl]-propionamide. LRMS: 437.

Example 143-(4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-piperidin-1-yl)-3-oxo-propionitrile

3-(4-Methyl-3-methylamino-piperidin-1-yl)-3-oxo-propionitrile. LRMS: 313.

Example 15(3-(4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propyl)-carbamic acid tert-butyl ester

[3-(4-Methyl-3-methylamino-piperidin-1-yl)-3-oxo-propyl]-carbamic acid tert-butyl ester. LRMS: 417.

Example 16Methyl-[4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-[4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-amine. LRMS: 352.

Example 173-Amino-1-(4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-propan-1-one

3-Amino-1-(4-methyl-3-methylamino-piperidin-1-yl)-propan-1-one. LRMS: 317.

Example 182-Methoxy-1-(4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-ethanone

2-Methoxy-1-(4-methyl-3-methylamino-piperidin-1-yl)-ethanone. LRMS: 318.

Example 19

2-Dimethylamino-1-(4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-ethanone

2-Dimethylamino-1-(4-methyl-3-methylamino-piperidin-1-yl)-ethanone. LRMS: 331.

Example 20

(3-(4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propyl)-carbamic acid tert-butyl ester

[3-(4-Methyl-3-methylamino-piperidin-1-yl)-3-oxo-propyl]-carbamic acid tert-butyl ester. LRMS: 417.

Example 21

3,3,3-Trifluoro-1-(4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-propan-1-one

3,3,3-Trifluoro-1-(4-methyl-3-methylamino-piperidin-1-yl)-propan-1-one.

Example 22

N-(2-(4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-2-oxo-ethyl)-acetamide

N-[2-(4-Methyl-3-methylamino-piperidin-1-yl)-2-oxo-ethyl]-acetamide. LRMS: 345.

Example 23

3-Ethoxy-1-(4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-propan-1-one

3-Ethoxy-1-(4-methyl-3-methylamino-piperidin-1-yl)-propan-1-one. LRMS: 346.

Example 24

4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid methylamide

4-Methyl-3-methylamino-piperidine-1-carboxylic acid methylamide. LRMS: 303.

Example 25

4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid diethylamide

4-Methyl-3-methylamino-piperidine-1-carboxylic acid diethylamide. LRMS: 345.

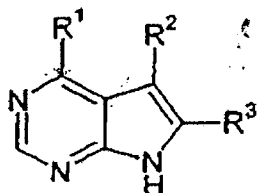
Example 26

Methyl-[4-methyl-1-(2-methylamino-ethanesulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-[4-methyl-1-(2-methylamino-ethanesulfonyl)-piperidin-3-yl]-amine. LRMS: 367.

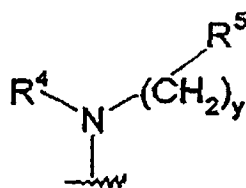
We claim :

1. A Pyrrolo (2,3-d) Pyrimidine compounds of the Formula I;



or the pharmaceutically acceptable salt thereof as herein described wherein

R¹ is a group of the formula

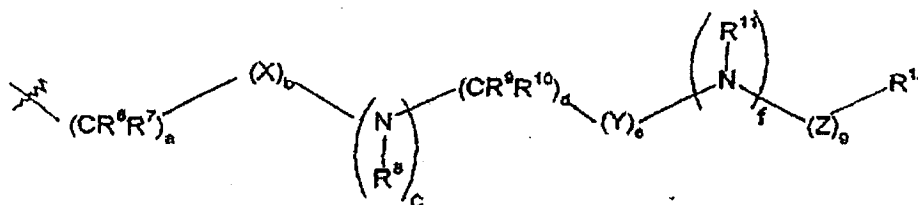


wherein y is 0, 1 or 2;

R⁴ is selected from the group consisting of hydrogen, (C₁-C₆) alkyl, (C₁-C₆) alkylsulfonyl, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₄) alkoxy, (C₁-C₆) acyloxy, (C₁-C₆) alkylamino, (C₁-C₆) alkyl)₂ amino, cyano, nitro, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl or (C₁-C₆) acylamino; or R⁴ is (C₃-C₁₀) cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₆) acyloxy, (C₁-C₆) alkylamino, ((C₁-C₆) alkyl)₂amino, cyano, cyano (C₁-C₆) alkyl, trifluoromethyl (C₁-C₆) alkyl, nitro, nitro (C₁-C₆) alkyl or (C₁-C₆) acylamino;

R⁵ is a piperidinyl substituted by one to five carboxy, cyano, amino, deuterium, hydroxy, (C₁-C₆) alkyl, (C₁-C₆)alkoxy, halo, (C₁-C₆)acyl, (C₁-C₆)alkylamino, amino (C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH, (C₁-C₆)alkylamino-CO-, (C₂-C₆)alkenyl, (C₂-C₆) alkynyl, hydroxy (C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆) acyloxy (C₁-C₆)alkyl, nitro, cyano(C₁-C₆)alkyl, halo(C₁-C₆) alkyl, nitro(C₁-C₆) alkyl, trifluoromethyl, trifluoromethyl (C₁-C₆)alkyl, (C₁-C₆) acylamino, (C₁-C₆) acylamino (C₁-C₆)alkyl,

(C₁-C₆)alkoxy (C₁-C₆)acylamino, amino (C₁-C₆)acyl, amino (C₁-C₆)acyl (C₁-C₆)alkyl, (C₁-C₆)alkylamino (C₁-C₆)acyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)acyl, R¹⁵R¹⁶N-CO-O-, R¹⁵R¹⁶N-CO-(C₁-C₆)alkyl, (C₁-C₆)alkyl-S(O)_m, R¹⁵R¹⁶NS(O)_m, R¹⁵R¹⁶NS(O)_m(C₁-C₆)alkyl, R¹⁵S(O)_mR¹⁶N, R¹⁵S(O)_mR¹⁶N(C₁-C₆)alkyl wherein m is 0, 1 or 2, and R¹⁵ and R¹⁶ are each independently selected from hydrogen or (C₁-C₆) alkyl; or a group of the formula



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wherein a is 0, 1, 2, 3 or 4;

b, c, e, f and g are each independently 0 or 1;

d is 0, 1, 2, or 3;

X is S(O)_n wherein n is 0, 1 or 2; oxygen, carbonyl or -C(=N-cyano)-;

Y is S(O)_n wherein n is 0, 1 or 2; or carbonyl; and

Z is carbonyl, C(O)O-, C(O) NR- or S(O)_n wherein n is 0, 1 or 2;

R⁶, R⁷, R⁸, R⁹, R¹⁰ and R¹¹ are each independently selected from the group consisting of hydrogen or (C₁-C₆)alkyl optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₆) acyloxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, cyano(C₁-C₆)alkyl, trifluoromethyl (C₁-C₆) alkyl, nitro, nitro (C₁-C₆) alkyl or (C₁-C₆) acylamino;

R¹² is carboxy, cyano, amino, oxo, deuterium, hydroxy, trifluoromethyl, (C₁-C₆)alkyl, trifluoromethyl (C₁-C₆)alkyl, (C₁-C₆)alkoxy, halo, (C₁-C₆)acyl, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂ amino, amino(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH, (C₁-C₆)alkylamino-CO-, (C₂-C₆)alkenyl, (C₂-C₆) alkynyl, hydroxy (C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, nitro, cyano (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, nitro(C₁-C₆) alkyl, (C₁-C₆)acylamino, (C₁-C₆)acylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆) acylamino, amino (C₁-C₆)acyl, amino (C₁-C₆)acyl (C₁-C₆)alkyl

(C₁-C₆) alkylamino (C₁-C₆) acyl, (C₁-C₆) alkyl)₂amino(C₁-C₆)acyl, R¹⁵R¹⁶N-CO-O-, R¹⁵R¹⁶N-CO-(C₁-C₆) alkyl, R¹⁵C(O)NH, R¹⁵OC(O)NH, R¹⁵NHC(O)NH, (C₁-C₆)alkyl-S(O)_m, (C₁-C₆)alkyl-S(O)_m-(C₁-C₆)alkyl, R¹⁵R¹⁶NS(O)_m, R¹⁵R¹⁶NS(O)_m (C₁-C₆) alkyl, R¹⁵S(O)_m R¹⁶N, R¹⁵S(O)_mR¹⁶N(C₁-C₆)alkyl wherein m is 0, 1 or 2 and R¹⁵ and R¹⁶ are each independently selected from hydrogen or (C₁-C₆) alkyl;

R² and R³ are each hydrogen.

2. A compound as claimed in claim 1, wherein y is 0;
3. A compound as claimed in any of the preceding claims, wherein R⁴ is (C₁-C₆)alkyl
4. A compound as claimed in any of the preceding claims, wherein a is 0; b is 1; X is carbonyl; c is 0; d is 1; e is 0; f is 0 and g is 0.
5. A compound as claimed in any of the preceding claims, wherein R¹² is cyano, trifluoromethyl, (C₁-C₆)alkyl, trifluoromethyl (C₁-C₆)alkyl, (C₁-C₆) alkylamino, ((C₁-C₆)alkyl)₂amino, (C₂-C₆) alkynyl, cyano(C₁-C₆)alkyl, (C₁-C₆)alkyl-S(O)_m wherein m is 0, 1 or 2.
6. A compound as claimed in claim 1 is selected from the group consisting of:

Methyl- [4-methyl-1- (propane - 1 - sulfonyl) - piperidin - 3 - yl] -(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;

4-Methyl-3- [methyl-(7 H - pyrrolo [2, 3 - d] pyrimidin - 4- yl)-amino]-piperidine-1-carboxylic acid methyl ester;

3,3,3 - Trifluoro- 1 -(4- methyl- 3-[methyl-(7H- pyrrolo[2,3-d] pyrimidin - 4 -yl)- amino]-piperidin-1-yl)-propan-1-one;

4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin - 4 - yl) - amino] - piperidine-1-carboxylic acid dimethylamide;

3-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-[propionitrile];

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3,3,3,-Trifluoro-1-(4- methyl - 3 -[methyl - (5 - methyl -(5 - methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-propan-1-one;

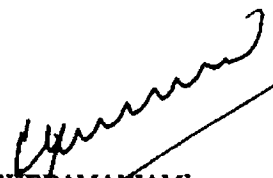
1-(4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-but-3-yn-1-one;

1-{3-[(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one;

1-{3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl- amino]- 4-methyl-piperidin-1-yl}-propan-1-one;

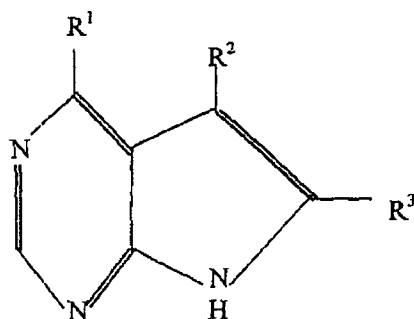
7. A compound as claimed in claim 6, wherein the said compound is 3-(4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile or a pharmaceutically acceptable salt thereof.

Dated this 10th day of June 2002.


(H. SUBRAMANIAM)
of SUBRAMANIAM, NATARAJ & ASSOCIATES
ATTORNEYS FOR THE APPLICANTS

ABSTRACT**PYRROLO(2,3-d)PYRIMIDINE COMPOUNDS**

A compound of formula (I)



(I)

wherein R1, R2 and R3 are as defined above, which are inhibitors of the enzyme protein kinases such as Janus Kinase 3 and as such are useful therapy as immunosuppressive agents for organ transplants, xeno transplantation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukaemia and other autoimmune diseases.

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Original
1095 Delup/24

FORM 2
THE PATENTS ACT 1970
[39 OF 1970]
&
THE PATENTS (AMENDMENT) RULES 2006
COMPLETE SPECIFICATION

[See Section 10; rule 13]

**"CRYSTALLINE 3-((3R,4R)-4-METHYL-3-[METHYL-(7H-PYRROLO[2,3-D]PYRIMIDIN-4-YL)-AMINO]-PIPERIDIN-L-YL)-3-
OXO-PROPIONITRILE MONO CITRATE SALT AND ITS METHOD
OF PREPARATION"**

PFIZER PRODUCTS INC., a corporation organized under the laws of the State of Connecticut, United States of America, of Eastern Point Road, Groton, Connecticut 06340, United States of America,

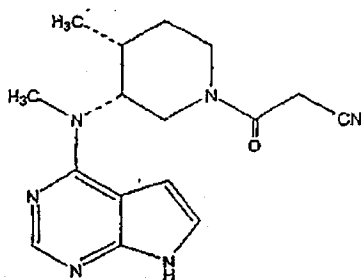
The following specification particularly describes the invention and the manner in which it is to be performed:

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Background of the Invention

This invention relates to a novel crystalline form of 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt and to its method of preparation.

3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile has the chemical formula $C_{18}H_{20}N_6O$ and the following structural formula



Its synthesis is described in co-pending United States patent application serial number 09/732,669, filed December 8, 2000 and United States provisional patent application serial number 60/294,775, filed May 31, 2001, commonly assigned to the assignee of the present invention and which are incorporated herein by reference in their entirety. ^{Indian equivalent: InIPer/2002/00588/Del} 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile, and its corresponding citrate salt, are useful as inhibitors of protein kinases, such as the enzyme Janus Kinase 3 (hereinafter also referred to as JAK3) and as such are useful therapy as immunosuppressive agents for organ transplants, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia and other indications where immunosuppression would be desirable.

The crystalline form of 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt was determined to have solid state properties which are acceptable to support tablet development.

The present invention is also directed to processes for preparing crystalline 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt.

Summary of the Invention

This invention relates to a novel crystalline form of 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt which is useful in (a) treating or preventing a disorder or condition selected from organ transplant rejection, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia and other autoimmune diseases or (b) the inhibition of protein kinases or Janus Kinase 3 (JAK3) in a mammal, including a human. The novel crystalline form melts at a temperature of about 203°C to about 210°C, and exhibits an X-ray diffraction pattern with characteristic peaks expressed in degrees 2-theta (2θ) at 5.7, 16.1, 20.2 and 20.5, as depicted in FIG 1. A discussion of the theory of X-ray power diffraction patterns can be found in Stout & Jensen, X-Ray Structure Determination: A Practical Guide, MacMillan Co., New York, N.Y. (1968), which is incorporated by reference in its entirety.

This invention also relates to the crystalline form of 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt with a differential scanning calorimetry thermogram, as depicted in Fig. 2, having a characteristic peak at a temperature between about 203°C to about 210°C, having an onset at a temperature between about 199°C to about 206°C at a scan rate of 5°C per minute.

The invention also relates to an amorphous form of 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt.

The present invention also relates to a pharmaceutical composition for (a) treating or preventing a disorder or condition selected from organ transplant rejection, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's

disease, Leukemia, and other autoimmune diseases or (b) the inhibition of protein kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising an amount of a compound of formula I, effective in such disorders or conditions and a pharmaceutically acceptable carrier.

The present invention also relates to a method for the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I.

The present invention also relates to a method for treating or preventing a disorder or condition selected from organ transplant rejection, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia, and other autoimmune diseases in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I, effective in treating such a condition.

The present invention also relates to a process for preparing 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt comprising reacting 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile with citric acid.

Brief Description of the Drawings

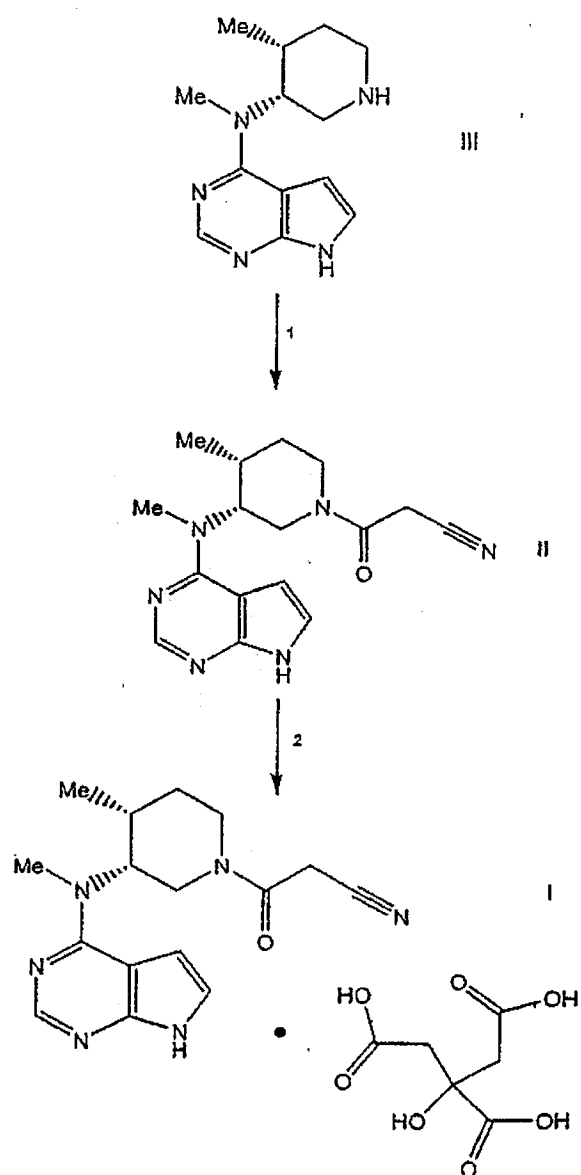
Fig. 1 is a characteristic X-ray powder diffraction pattern for 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt. (Vertical Axis: Intensity (counts); Horizontal Axis: Two Theta (Degrees)).

Fig. 2 is a characteristic differential scanning calorimetry thermogram of 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt. (Scan Rate: 5°C per minute; Vertical Axis: Heat Flow (w/g); Horizontal Axis: Temperature (°C)).

Detailed Description of the Invention

The crystalline form of the compound of this invention 3-((4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt is prepared as described below.

Scheme 1



In reaction 1 of Scheme 1, the (3R,4R)-methyl-(4-methyl-piperidin-3-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amine compound of formula III is converted to the corresponding 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile compound of formula II by reacting III with cyano-acetic acid 2,5-dioxo-pyrrolidin-1-yl ester in the presence of a base, such as triethylamine. The reaction mixture is stirred, at room temperature, for a time period between about 15 minutes to about 2 hours, preferably about 30 minutes.

In reaction 2 of Scheme 1, the 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile compound of formula II is converted to the corresponding 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt compound of formula I by reacting II with aqueous citric acid.

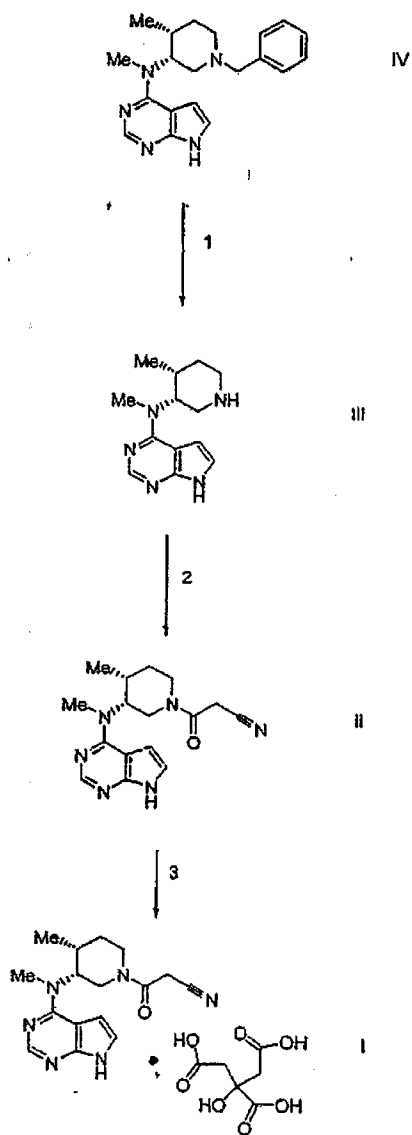
In reaction 1 of Scheme 2, the ((3R,4R)-1-benzyl-4-methyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amine compound of formula IV is converted to the corresponding the (3R,4R)-methyl-(4-methyl-piperidin-3-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amine compound of formula III by treating IV with hydrogen in the presence of 20% palladium hydroxide on carbon (50% water by weight) and a polar protic solvent, such as ethanol. The reaction mixture is stirred at a temperature between about 45°C to about 75°C, preferably about 60°C, under a pressure of about 60 psi, preferably about 50 psi, for a time period between about two days to about four days, preferably about three days.

In reaction 2 of Scheme 2, the (3R,4R)-methyl-(4-methyl-piperidin-3-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amine compound of formula III is converted to the corresponding 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile compound of formula II by reaction III with cyano-acetic acid 2,5-dioxo-pyrrolidin-1-yl ester in the presence of a polar protic solvent, such as ethanol. The reaction mixture is stirred, at room temperature, for a time period between about 30 minutes to about 3 hours, preferably about 1 hour.

In reaction 3 of Scheme 2, the 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile compound of formula II is converted to the corresponding 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt compound of formula I by reacting II with citric acid in the presence of a polar solvent, such as acetone. The reaction mixture is stirred at a temperature between about 30°C to

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Scheme 2



about 50°C, preferably about 40°C, for a time period between about 1 hour to about 3 hours, preferably about 2 hours. The resulting reaction mixture may optionally be further stirred at a temperature between about 20°C to about 40°C, preferably about 30°C, for a time period between about 3 hours to about 5 hours, preferably about 4 hours, followed by additional stirring, at room temperature, for a time period between about 16 hours to about 20 hours, preferably about 18 hours.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers.

For oral administration, the pharmaceutical compositions may take the form of tablets prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art.

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (e.g., rheumatoid arthritis) is 0.1 to 1000 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

A compound of formula I administered in a pharmaceutically acceptable form either alone or in combination with one or more additional agents which modulate a mammalian immune system or with antiinflammatory agents, agents which may include but are not limited to cyclosporin A (e.g. Sandimmune® or Neoral®, rapamycin, FK-506 (tacrolimus), leflunomide, deoxyspergualin, mycophenolate (e.g. Cellcept®, azathioprine (e.g. Imuran®), daclizumab (e.g. Zenapax®), OKT3 (e.g. Orthoclone®), AtGam, aspirin, acetaminophen, ibuprofen, naproxen, piroxicam, and antiinflammatory steroids (e.g. prednisolone or dexamethasone); and such agents may be administered as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice.

FK506 (Tacrolimus) is given orally at 0.10-0.15 mg/kg body weight, every 12 hours, within first 48 hours postoperative. Does is monitored by serum Tacrolimus trough levels.

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Cyclosporin A (Sandimmune oral or intravenous formulation, or Neoral®, oral solution or capsules) is given orally at 5 mg/kg body weight, every 12 hours within 48 hours postoperative. Dose is monitored by blood Cyclosporin A trough levels.

The active agents can be formulated for sustained delivery according to methods well known to those of ordinary skill in the art. Examples of such formulations can be found in United States Patents 3,538,214, 4,060,598, 4,173,626, 3,119,742, and 3,492,397.

The ability of the compound of formula I; to inhibit Janus Kinase 3 and, consequently, demonstrate its effectiveness for treating disorders or conditions characterized by Janus Kinase 3 is shown by the following in vitro assay tests.

Biological Assay

JAK3 (JH1:GST) Enzymatic Assay

The JAK3 kinase assay utilizes a protein expressed in baculovirus-infected SF9 cells (a fusion protein of GST and the catalytic domain of human JAK3) purified by affinity chromatography on glutathione-Sepharose. The substrate for the reaction is poly-Glutamic acid-Tyrosine (PGT (4:1), Sigma catalog # P0275), coated onto Nunc Maxi Sorp plates at 100 µg/ml overnight at 37°C. The morning after coating, the plates are washed three times and JAK3 is added to the wells containing 100 µl of kinase buffer (50 mM HEPES, pH 7.3, 125 mM NaCl, 24 mM MgCl₂) + 0.2 µM ATP + 1 mM Na orthovanadate.) The reaction proceeds for 30 minutes at room temperature and the plates is washed three more times. The level of phosphorylated tyrosine in a given well is quantitated by standard ELISA assay utilizing an anti-phosphotyrosine antibody (ICN PY20, cat. #69-151-1).

Inhibition of Human IL-2 Dependent T-Cell Blast Proliferation

This screen measures the inhibitory effect of compounds on IL-2 dependent T-Cell blast proliferation *in vitro*. Since signaling through the IL-2 receptor requires JAK-3, cell active inhibitors of JAK-3 should inhibit IL-2 dependent T-Cell blast proliferation.

The cells for this assay are isolated from fresh human blood. After separation of the mononuclear cells using Accuspin System-Histopaque-1077 (Sigma # A7054), primary human T-Cells are isolated by negative selection using Lympho-Kwik T (One Lambda, Inc., Cat # LK-50T). T-Cells are cultured at $1-2 \times 10^6$ /ml in Media (RPMI + 10% heat-inactivated fetal calf serum (Hyclone Cat # A-1111-L) + 1% Penicillin/Streptomycin (Gibco)) and induce to proliferate by the addition of 10ug/ml

PHA (Murex Diagnostics,, Cat # HA 16). After 3 days at 37°C in 5% CO₂, cells are washed 3 times in Media, resuspended to a density of 1-2 x 10⁶ cells/ml in Media plus 100 Units/ml of human recombinant IL-2 (R&D Systems, Cat # 202-IL). After 1 week the cells are IL-2 dependent and can be maintained for up to 3 weeks by feeding twice weekly with equal volumes of Media + 100 Units/ml of IL-2.

To assay for a test compounds ability to inhibit IL-2 dependent T-Cell proliferation, IL-2 dependent cells are washed 3 times, resuspended in media and then plated (50,000 cells/well/0.1ml) in a Flat-bottom 96-well microtiter plate (Falcon # 353075). From a 10 mM stock of test compound in DMSO, serial 2-fold dilutions of compound are added in triplicate wells starting at 10 uM. After one hour, 10 Units/ml of IL-2 is added to each test well. Plates are then incubated at 37°C, 5% CO₂ for 72 hours. Plates are then pulsed with ³H-thymidine (0.5 uCi/well) (NEN Cat # NET027A), and incubated an additional 18 hours. Culture plates are then harvested with a 96-well plate harvester and the amount of ³H-thymidine incorporated into proliferating cells is determined by counting on a Packard Top Count scintillation counter. Data is analyzed by plotting the % inhibition of proliferation verses the concentration of test compound. An IC₅₀ value (uM) is determined from this plot.

The present species demonstrates a more than 5-fold potency in the Jak-3 Enzyme Assay and a more than 4-fold potency in the IL-2 Blast Assay.

The following Examples illustrate the preparation of the compounds of the present invention but it is not limited to the details thereof. Melting points are uncorrected. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform unless otherwise specified).

Example I

3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt

Ethanol (13 liters), (3R, 4R)-methyl-(4-methyl-piperidin-3-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine (1.3 kg), cyano-acetic acid 2,5-dioxo-pyrrolidin-1-yl ester (1.5 kg), and triethylamine (1.5 liters) were combined and stirred at ambient temperature. Upon reaction completion (determined by High Pressure Liquid Chromotography (HPLC) analysis, approximately 30 minutes), the solution was filtered, concentrated and azeotroped with 15 liters of methylene chloride. The reaction mixture was washed sequentially with 12 liters of 0.5 N sodium hydroxide solution, 12 liters of brine and 12 liters of water. The organic layer was concentrated and azeotroped with 3 liters of acetone (final pot temperature was 42°C). The resulting solution was

cooled to 20°C to 25°C followed by addition of 10 liters of acetone. This solution was filtered and then aqueous citric acid (0.8 kg in 4 liters of water) added via in-line filter. The reaction mixture was allowed to granulate. The slurry was cooled before collecting the solids by filtration. The solids were dried to yield 1.9 kg (71%) (3R, 4R)-3-[4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-3-oxo-propionitrile mono citrate. This material was then combined with 15 liters of a 1:1 ratio of ethanol/water and the slurry was agitated overnight. The solids were filtered and dried to afford 1.7 kg (63% from (3R, 4R)-methyl-(4-methyl-piperidin-3-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine) of the title compound as a white crystalline solid. ¹H NMR (400 MHz)(D₂O) δ HOD: 0.92 (2H, d, J = 7.2 Hz), 0.96 (1H, d, J = 7.6 Hz), 1.66 (1H, m), 1.80 (1H, m), 2.37 (1H, m), 2.58 (2H, ½ ABq, J = 15.4 Hz), 2.70 (2H, ½ ABq, J = 15.4 Hz), 3.23 (2H, s), 3.25 (1H, s), 3.33 (1H, m), 3.46 (1H, m), 3.81 (4H, m), 4.55 (1H, m), 6.65 (1H, d, J = 3.2 Hz), 7.20 (1H, t, J = 3.2 Hz), 8.09 (1H, m).

Example 2

3-[(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-3-oxo-propionitrile mono citrate salt

To a solution of 79 grams of ((3R, 4R)-1-Benzyl-4-methyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine dissolved in 2 liters of ethanol was added 79 grams of 20% palladium hydroxide on carbon (50% water by weight) and the mixture agitated under an atmospheric pressure of 50 psi hydrogen for three days (conducting the hydrogenolysis at elevated temperature [50°C to 70°C] significantly decreases reaction times). After the catalyst was removed by filtration through Celite®, 51 grams of cyano-acetic acid 2,5-dioxo-pyrrolidin-1-yl ester was added to the ethanolic solution and the resulting mixture stirred at room temperature for 1 hour, at which time the ethanol was removed under reduced pressure. The residue was redissolved in 1.0 liters of dichloromethane and the solution sequentially washed with 0.6 liters of saturated aqueous sodium bicarbonate and 0.4 liters saturated sodium bicarbonate. The combined aqueous layers were backwashed with 0.4 liters of dichloromethane, the dichloromethane layers combined, dried over magnesium sulfate, filtered and concentrated in vacuo affording 61 grams of amber oil. This material was then redissolved in 2.1 liters of acetone and the solution heated to 40°C. Finely ground citric acid (37 grams) was added slowly (as a solid) to the solution. The mixture continued stirring at 40°C for two hours (granulation was complete).

After cooling to room temperature, the solids were collected by filtration, washed with acetone and dried in vacuo affording 78.5 grams (66% from ((3R, 4R)-1-Benzyl-4-methyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine) of the title compound as a slightly off-white crystalline solid.

Example 3

3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt

A stirred solution of (3R,4R)-3-(4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile (230 mg/0.74 mmol) dissolved in 23 mL of acetone was heated to 40°C. To this solution was added 155 mg (0.81 mmol) of finely ground citric acid. The resulting mixture stirred at 40°C for 2 hours, then at 30°C for 4 hours followed by stirring at room temperature for an additional 18 hours. At this point, the solids were collected by filtration, washed with acetone and dried in vacuo affording 280 mg (75%) of the title compound as a white crystalline solid.

Example 4

Method for collecting powder X-ray diffraction for 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt

Powder x-ray diffraction patterns for 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt were collected using a Bruker D5000 diffractometer (Madison, Wisconsin) equipped with copper radiation, fixed slits (1.0, 1.0, 0.6mm) and a Kevex solid state detector. Data was collected as follows: Cu anode; wavelength 1: 1.54056; wavelength 2: 1.54439 (rel. intensity: 0.500); from 3.0 to 40.0 degrees in 2 theta using a step size of 0.04 degrees and a step time of 1.0 seconds. The results are summarized in Table 1.

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Table 1
List of Powder X-ray Diffraction Peaks (± 0.2 degrees)

Angle 2-theta	d-value angstrom	Intensity* (rel.) %	Angle 2-theta	d-value angstrom	Intensity* (rel.) %
5.7	15.4	62.4	25.5	3.5	21.5
7.7	11.5	7.5	26.2	3.4	16.7
8.9	9.9	6.8	27.0	3.3	43.6
11.0	8.0	7.7	27.5	3.2	15.1
11.5	7.7	9.7	28.1	3.2	32.1
13.6	6.5	13.7	28.7	3.1	12.6
13.9	6.4	19.6	29.4	3.0	14.8
14.8	6.0	38	30.1	3.0	13.8
15.2	5.8	42.4	30.3	2.9	11
16.1	5.5	87.8	31.1	2.9	23.4
16.6	5.3	11.4	32.0	2.8	6.8
17.3	5.1	50.8	32.8	2.7	14.1
18.7	4.7	49.7	33.6	2.7	22.9
20.2	4.4	100	34.4	2.6	7.7
20.5	4.3	59.4	34.8	2.6	5.7
21.1	4.2	46.7	35.3	2.5	8.5
21.4	4.1	24	35.9	2.5	16.3
22.0	4.0	46.5	36.5	2.5	9.2
23.0	3.9	7.5	37.8	2.4	8.5
23.4	3.8	12.8	38.5	2.3	6.8
24.0	3.7	6	39.2	2.3	11.1
25.0	3.6	28.3			

* The peak intensities may change depending on the crystal size and habit.

WE CLAIM:-

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1. Crystalline 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt.
2. A crystalline form as claimed in claim 1, comprising a powder diffraction pattern having characteristic peaks expressed in degree of 2-theta at approximately:

Angle 2-theta	Angle 2-theta	Angle 2-theta	Angle 2-theta
5.7	17.3	25.5	32.8
7.7	18.7	26.2	33.6
8.9	20.2	27.0	34.4
11.0	20.5	27.5	34.8
11.5	21.1	28.1	35.3
13.6	21.4	28.7	35.9
13.9	22.0	29.4	36.5
14.8	23.0	30.1	37.8
15.2	23.4	30.3	38.5
16.1	24.0	31.1	39.2
16.6	25.0	32.0	

3. A crystalline form of 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt as claimed in claims 1 and 2, comprising an x-ray powder diffraction pattern having characteristic peaks expressed in degrees two-theta at approximately 5.7, 16.1, 20.2 and 20.5.

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4 A process for preparing crystalline 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile mono citrate salt as claimed in claim 1, comprising the steps of:

combining 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile with a solvent selected from the group consisting of acetone and ethanol to form a reaction mixture;

filtering, concentrating, and azeotroping the reaction mixture with methylene chloride;

washing and concentrating reaction mixture to form an organic layer;

concentrating and azeotroping the organic layer with acetone to form a solution;

cooling the solution to 20°C to 25°C;

adding acetone to the solution;

filtering the solution;

adding aqueous citric acid to the solution to form a slurry;

collecting the solids from the slurry;

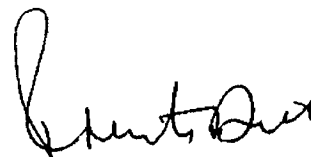
drying the solids;

combining the solids with a 1:1 mixture of ethanol:water;

agitating the solids; and

drying the solids.

Dated this 23rd Day of April, 2004.



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(15)

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FIG. 1

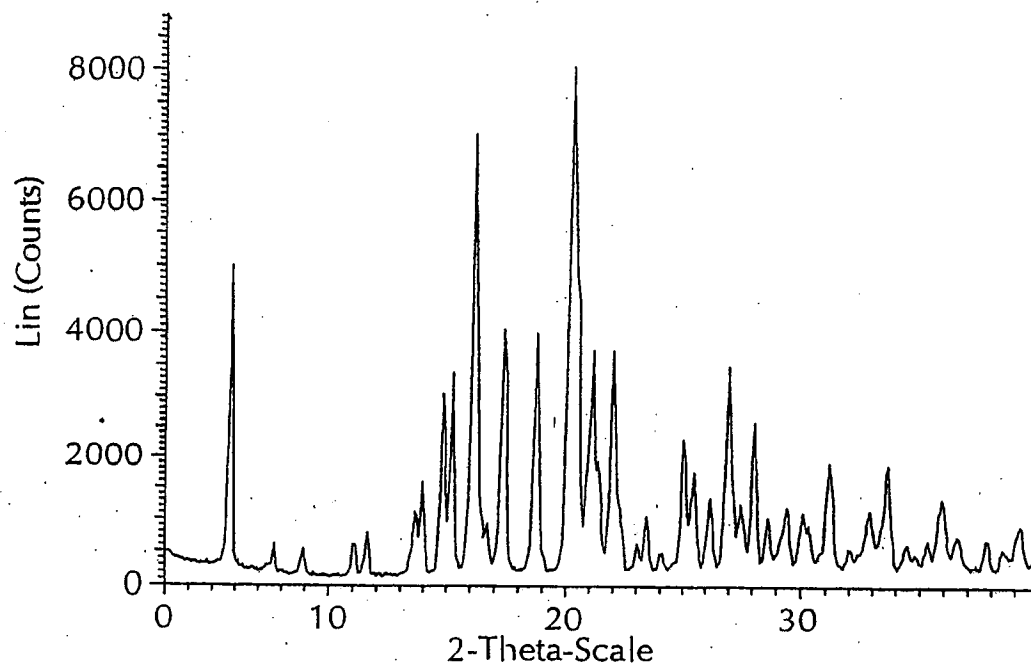
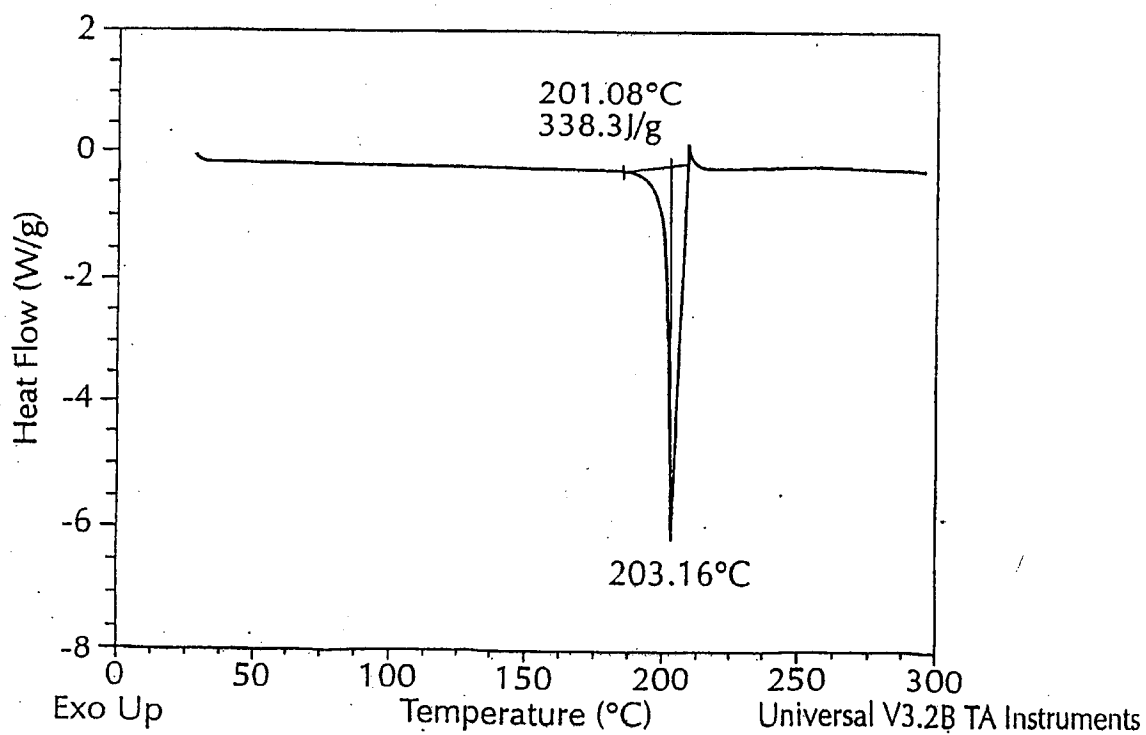


FIG. 2



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ABSTRACT

"CRYSTALLINE 3-((3R,4R)-4-METHYL-3-[METHYL-(7H-PYRROLO[2,3-D]PYRIMIDIN-4-YL)-AMINO]-PIPERIDIN-L-YL)-3-OXO-PROPIONITRILE MONO CITRATE SALT AND ITS METHOD OF PREPARATION"

The invention relates to a novel crystalline form of 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-l-yl)-3-oxo propionitrile mono citrate salt, useful as inhibitors of protein kinases, and to its method of preparation.

E-101/3405/2018

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Field of the Invention

The present invention relates to methods for effecting chiral salt resolution from racemic mixtures of enantiomers and particularly precursor enantiomers used in making pyrrolo[2,3-d] pyrimidine compounds, which are inhibitors of protein kinases. The present invention also relates to pyrrolo[2,3-d]pyrimidine compounds and methods of using such compounds as inhibitors of protein kinases, such as the enzyme Janus Kinase 3.

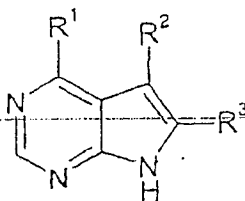
Background of the Invention

Pyrrolo[2,3-d]pyrimidine compounds are inhibitors of protein kinases, such as the enzyme Janus Kinase 3 (JAK3) and are therefore useful therapy as immunosuppressive agents for organ transplants, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia and other indications where immunosuppression would be desirable. The pyrrolo[2,3-d]pyrimidine compounds, pharmaceutical compositions thereof and methods of use are described in application serial no. IN/PCT/2002/00588/DEL, filed November 23, 2000, and assigned to the assignee of the present invention. The disclosure of said application is included in its entirety herein by reference thereto. Racemic mixtures of the pyrrolo[2,3-d]pyrimidine compounds are initially obtained whereas the individual enantiomers in substantially isolated pure form are preferred and at times required for drug use. It is possible to pre-ordain the stereochemistry of the compounds by use of stereospecific precursor compounds in the synthesis thereof. The methods of the present invention accordingly specifically relate to a method for the substantial chiral salt resolution of racemic mixtures of precursor compounds, used in the production of the separate enantiomeric forms of the pyrrolo[2,3-d]pyrimidine compounds.

Summary of the Invention

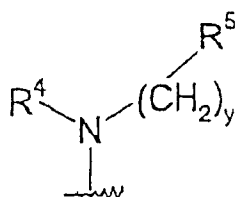
The present invention relates to methods for resolving the enantiomers of the precursors used in preparing a compound of the following formula and particularly the R¹ group thereof:

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or the pharmaceutically acceptable salt thereof; wherein

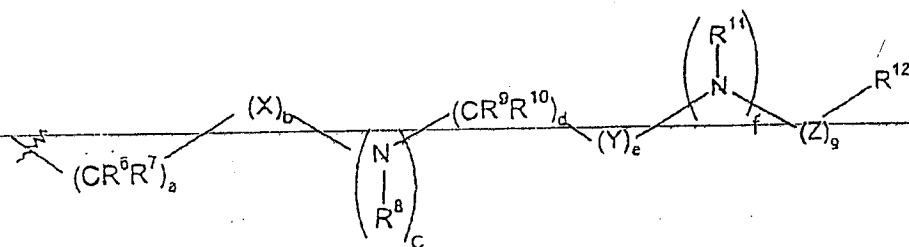
R¹ is a group of the formula



5 wherein y is 0, 1 or 2;

R⁴ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₄)alkoxy, (C₁-C₆)acyloxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, nitro, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl or (C₁-C₆)acylamino; or R⁴ is (C₃-C₁₀)cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₆)acyloxy, (C₁-C₆)acylamino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, cyano(C₁-C₆)alkyl, trifluoromethyl(C₁-C₆)alkyl, nitro, nitro(C₁-C₆)alkyl or (C₁-C₆)acylamino;

15 R⁵ is (C₁-C₆)heterocycloalkyl wherein the heterocycloalkyl groups must be substituted by one to five carboxy, cyano, amino, deuterium, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, halo, (C₁-C₆)acyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH, (C₁-C₆)alkylamino-CO-, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, nitro, cyano(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, nitro(C₁-C₆)alkyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)acylamino, (C₁-C₆)acylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)acylamino, amino(C₁-C₆)acyl, amino(C₁-C₆)acyl(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)acyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)acyl, R¹⁵R¹⁶N-CO-O-, R¹⁵R¹⁶N-CO-(C₁-C₆)alkyl, (C₁-C₆)alkyl-S(O)_m, R¹⁵R¹⁶NS(O)_m, R¹⁵R¹⁶NS(O)_m(C₁-C₆)alkyl, R¹⁵S(O)_mR¹⁶N, R¹⁵S(O)_mR¹⁶N(C₁-C₆)alkyl wherein m is 0, 1 or 2 and R¹⁵ and R¹⁶ are each independently selected from hydrogen or (C₁-C₆)alkyl; or a group of the formula II



II

wherein a is 0, 1, 2, 3 or 4;

b, c, e, f and g are each independently 0 or 1;

d is 0, 1, 2, or 3;

5 X is $S(O)_n$ wherein n is 0, 1 or 2; oxygen, carbonyl or $-C(=N\text{-cyano})-$;

Y is $S(O)_n$ wherein n is 0, 1 or 2; or carbonyl; and

Z is carbonyl, $C(O)O-$, $C(O)NR-$ or $S(O)_n$ wherein n is 0, 1 or 2;

10 R^6 , R^7 , R^8 , R^9 , R^{10} and R^{11} are each independently selected from the group consisting of hydrogen or (C_1-C_6) alkyl optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C_1-C_6) acyloxy, (C_1-C_6) acylamino, (C_1-C_6) alkylamino, $((C_1-C_6)alkyl)_2$ amino, cyano, cyano $(C_1-C_6)alkyl$, trifluoromethyl $(C_1-C_6)alkyl$, nitro, nitro $(C_1-C_6)alkyl$ or (C_1-C_6) acylamino;

15 R^{12} is carboxy, cyano, amino, oxo, deuterium, hydroxy, trifluoromethyl, $(C_1-C_6)alkyl$, trifluoromethyl $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, halo, $(C_1-C_6)acyl$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2$ amino, amino $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy-CO-NH$, $(C_1-C_6)alkylamino-CO-$, $(C_2-C_6)alkenyl$, $(C_2-C_6)alkynyl$, $(C_1-C_6)alkylamino$, hydroxy $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)alkyl$, $(C_1-C_6)acyloxy(C_1-C_6)alkyl$, nitro, cyano $(C_1-C_6)alkyl$, halo $(C_1-C_6)alkyl$, nitro $(C_1-C_6)alkyl$, trifluoromethyl, trifluoromethyl $(C_1-C_6)alkyl$, $(C_1-C_6)acylamino$, $(C_1-C_6)acylamino(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)acylamino$, amino $(C_1-C_6)acyl$, amino $(C_1-C_6)acyl(C_1-C_6)alkyl$, $(C_1-C_6)alkylamino(C_1-C_6)acyl$, $((C_1-C_6)alkyl)_2$ amino $(C_1-C_6)acyl$, $R^{15}R^{16}N-CO-O-$, $R^{15}R^{16}N-CO-(C_1-C_6)alkyl$, $R^{15}C(O)NH$, $R^{15}OC(O)NH$, $R^{15}NHC(O)NH$, $(C_1-C_6)alkyl-S(O)_m$, $(C_1-C_6)alkyl-S(O)_m-(C_1-C_6)alkyl$, $R^{15}R^{16}NS(O)_m$, $R^{15}R^{16}NS(O)_m(C_1-C_6)alkyl$, $R^{15}S(O)_mR^{16}N$, $R^{15}S(O)_mR^{16}N(C_1-C_6)alkyl$ wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from

25 hydrogen or $(C_1-C_6)alkyl$;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, deuterium, amino, halo, hydroxy, nitro, carboxy, $(C_2-C_6)alkenyl$, $(C_2-C_6)alkynyl$, trifluoromethyl, trifluoromethoxy, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, $(C_3-C_{10})cycloalkyl$

wherein the alkyl, alkoxy or cycloalkyl groups are optionally substituted by one to three groups selected from halo, hydroxy, carboxy, amino (C₁-C₆)alkylthio, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, (C₅-C₈)heteroaryl, (C₂-C₉)heterocycloalkyl, (C₃-C₉)cycloalkyl or (C₆-C₁₀)aryl; or R² and R³ are each independently (C₃-C₁₀)cycloalkyl, (C₃-C₁₀)cycloalkoxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, (C₆-C₁₀)arylamino, (C₁-C₆)alkylthio, (C₆-C₁₀)arylthio, (C₁-C₆)alkylsulfinyl, (C₆-C₁₀)arylsulfinyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl, (C₁-C₆)acyl, (C₁-C₆)alkoxy-CO-NH-, (C₁-C₆)alkylamino-CO-, (C₅-C₉)heteroaryl, (C₂-C₉)heterocycloalkyl or (C₆-C₁₀)aryl wherein the heteroaryl, heterocycloalkyl and aryl groups are optionally substituted by one to three halo, (C₁-C₆)alkyl, (C₁-C₆)alkyl-CO-NH-, (C₁-C₆)alkoxy-CO-NH-, (C₁-C₆)alkyl-CO-NH-(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH-(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH-(C₁-C₆)alkoxy, carboxy, carboxy(C₁-C₆)alkyl, carboxy(C₁-C₆)alkoxy, benzyloxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₆-C₁₀)aryl, amino, amino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonylamino, (C₆-C₁₀)aryl(C₁-C₆)alkoxycarbonylamino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, (C₁-C₆)alkylamino(C₁-C₆)alkyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, carboxy, carboxy(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH-, (C₁-C₆)alkyl-CO-NH-, cyano, (C₅-C₉)heterocycloalkyl, amino-CO-NH-, (C₁-C₆)alkylamino-CO-NH-, ((C₁-C₆)alkyl)₂amino-CO-NH-, (C₆-C₁₀)arylamino-CO-NH-, (C₅-C₉)heteroarylamino-CO-NH-, (C₁-C₆)alkylamino-CO-NH-(C₁-C₆)alkyl, ((C₁-C₆)alkyl)₂amino-CO-NH-(C₁-C₆)alkyl, (C₆-C₁₀)arylamino-CO-NH-(C₁-C₆)alkyl, (C₅-C₉)heteroarylamino-CO-NH-(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl, (C₆-C₁₀)arylsulfonylamino, (C₆-C₁₀)arylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₅-C₉)heteroaryl or (C₂-C₉)heterocycloalkyl.

The present invention also relates to the production of stereospecific pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate,

methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

The invention also relates to stereospecific base-addition salts of formula I.

The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched moieties or combinations thereof.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

The term "halo", as used herein, unless otherwise indicated, includes fluoro, chloro, bromo or iodo. The compounds of this invention may contain double bonds. When such bonds are present, the compounds of the invention exist as cis and trans configurations and as mixtures thereof. Unless otherwise indicated, the alkyl and alkenyl groups referred to herein, as well as the alkyl moieties of other groups referred to herein (e.g., alkoxy), may be linear or branched, and they may also be cyclic (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl) or be linear or branched and contain cyclic moieties. Unless otherwise indicated, halogen includes fluorine, chlorine, bromine, and iodine.

(C₂-C₉)Heterocycloalkyl when used herein refers to pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydropyranyl, pyranal, thiopyranal, aziridinyl, oxiranal, methylenedioxy, chromenyl, isoxazolidinyl, 1,3-oxazolidin-3-yl, isothiazolidinyl, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, piperidinyl, thiomorpholinyl, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazinyl, morpholinyl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, tetrahydroazepinyl, piperazinyl, chromanyl, etc. One of ordinary skill in the art will

understand that the connection of said (C₂-C₉)heterocycloalkyl rings is through a carbon or a sp³ hybridized nitrogen heteroatom.

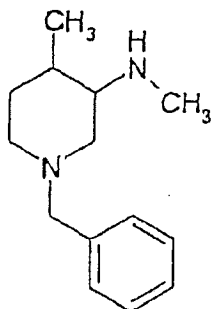
(C₂-C₉)Heteroaryl when used herein refers to furyl, thienyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, pyrazolo[3,4-b]pyridinyl, cinnolinyl, pteridinyl, purinyl, 6,7-dihydro-5H-[1]pyrindinyl, benzo[b]thiophenyl, 5, 6, 7, 8-tetrahydro-quinolin-3-yl, benzoxazolyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, isoindolyl, indolyl, indoliziny, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxaliny, quinazoliny, benzoxazinyl; etc. One of ordinary skill in the art will understand that the connection of said (C₂-C₉)heterocycloalkyl rings is through a carbon atom or a sp³ hybridized nitrogen heteroatom.

(C₆-C₁₀)aryl when used herein refers to phenyl or naphthyl.

The compounds used in this invention include all conformational isomers (e.g., cis and trans isomers. The compounds used in present invention have asymmetric centers and are therefore chiral and exist in different enantiomeric and diastereomeric forms. This invention relates to the resolution of optical isomers and stereoisomers of the precursors of constituents and thereby compounds of the present invention, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment that may employ or contain them. In this regard, the invention includes both the E and Z configurations. The compounds of formula I may also exist as tautomers. This invention relates to such tautomers and mixtures thereof. In particular, resolution of racemic mixtures of enantiomers of compounds, used in providing the R¹ substituent of formula I, is effected by treating the racemic mixture with a specific optical isomer of a disubstituted tartaric acid or tartrate in an appropriate solvent such as ethanol with or without water as a co-solvent. Resolution in obtaining the desired enantiomer in excess of 90% is possible in accordance with the method of the present invention with the use of resolving agents such as the optical isomers of tartaric acid and tartaric acid derivatives such as di-p-toluoyl-L-tartaric acid and (S)-(+)-Andeno acid (pencyphos, (S)-(+)-2-hydroxy-5,5-dimethyl-4-phenyl-1,3,2-dioxaphosphorinane-2-oxide) salt.

Interaction between antipodes of the resolving material and specific enantiomer provides a resolution of the racemic mixture whereby a precipitate of the resolving material and enantiomer provides one of the desired stereospecific materials and wherein the remaining enantiomer in solution can be separately isolated thereby. Thus, depending on the specific enantiomer desired and the separation method to be used (i.e., from precipitate or solution), the stereospecific nature of the resolving nature can be concomitantly selected; e.g. an "L" form of the resolving agent such as a tartrate derivative provides a precipitate of an "R" form of the R¹ substituent and a solution containing the "L" form and vice versa.

The aforementioned resolving agents are effective in providing a 3R,4R enantiomer of the compound of the formula (either in precipitate or solution, as described):



In accordance with the present invention the method of resolution of the compound of formula III is effected by the steps of:

a) mixing a racemic mixture of the compound of formula III in an appropriate solution with a resolving compound, having a defined stereospecificity, for a time sufficient to allow substantial precipitation of a stereospecific isomer of the racemic mixture from the solution;

b) depending on the stereospecific form of the compound which is desired, collecting either the precipitate and purifying it or collecting the mother liquor and recrystallizing the enantiomer contained therein.

With some materials a slurry rather than a solution is formed with the resolution of the present invention involving a slurry to slurry conversion. The term "solution" encompasses both a solution and a slurry.

The temperature at which the resolution and precipitation is effected is preferably ambient temperature and while precipitation time is not restricted for

efficiency the time is preferably no more than about four hours. In order to facilitate the resolution it is desirable to use enantiomers in the racemic mixture which are in a stable form and the compound of formula II is most stable in acid addition salt

- 5 that the racemic compound mixture be accordingly converted prior to resolution. Thus, for example, formation of the hydrochloride salt of the compound of formula II is effected preferably in ethanol with a small amount of toluene as cosolvent. Alternatively, methanol, isopropanol, acetonitrile, or tetrahydrofuran (or mixtures thereof with or without water as a cosolvent) with cosolvents of toluene, ethylacetate, dichloromethane, dichloroethane, or tetrahydrofuran may be used in the salt formation. The HCl salt is particularly preferred since this form provides a superior purification and enriched of other stereomers from the prior step.

A preferred displacement solvent to be used in the resolution is ethyl acetate. Toluene, acetonitrile, or heptanes are also useful as solvents.

- 15 A preferred isolation solvent is acetone. Other solvents useful in this regard include isopropanol, ethanol, methyl ethyl ketone, methyl isopropyl ketone, acetonitrile, and tetrahydrofuran. The solvents may also be used as co-solvents with each other or with water.

- 20 Preferred resolution compounds include tartaric acid and its derivatives such as toluoyl and benzoyl tartaric acids in stereospecific conformation, as described. Other resolution compounds include spereospecific adeno acid and derivatives thereof.

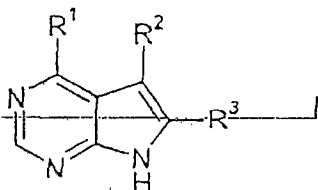
To facilitate precipitation and recrystallization addition of seeds is optional, but preferred in order to obtain higher ee material with fewer recrystallizations.

- 25 In order to illustrate the procedure and efficacy of the present invention the following examples are presented. It is understood that such examples are details contained therein are not to be construed as limitations on the present invention.

The present invention also relates to a method for preparing the compound of the formula

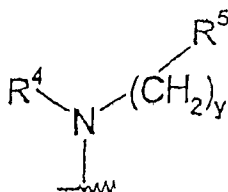
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or the pharmaceutically acceptable salt thereof; wherein

R¹ is a group of the formula

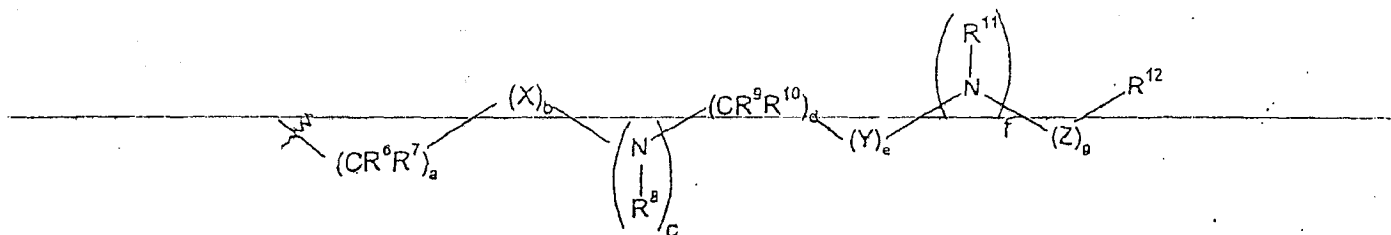


5 wherein y is 0, 1 or 2;

R⁴ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₄)alkoxy, (C₁-C₆)acyloxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, nitro, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl or (C₁-C₆)acylamino; or R⁴ is (C₃-C₁₀)cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₆)acyloxy, (C₁-C₆)acylamino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, cyano(C₁-C₆)alkyl, trifluoromethyl(C₁-C₆)alkyl, nitro, nitro(C₁-C₆)alkyl or (C₁-C₆)acylamino;

15 R⁵ is (C₁-C₆)heterocycloalkyl wherein the heterocycloalkyl groups must be substituted by one to five carboxy, cyano, amino, deuterium, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, halo, (C₁-C₆)acyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH, (C₁-C₆)alkylamino-CO-, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, nitro, cyano(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, nitro(C₁-C₆)alkyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)acylamino, (C₁-C₆)acylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)acylamino, amino(C₁-C₆)acyl, amino(C₁-C₆)acyl(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)acyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)acyl, R¹⁵R¹⁶N-CO-O-, R¹⁵R¹⁶N-CO-(C₁-C₆)alkyl, (C₁-C₆)alkyl-S(O)_m, R¹⁵R¹⁶NS(O)_m, R¹⁵R¹⁶NS(O)_m(C₁-C₆)alkyl, R¹⁵S(O)_mR¹⁶N, R¹⁵S(O)_mR¹⁶N(C₁-C₆)alkyl wherein m is 0, 1 or 2 and R¹⁵ and R¹⁶ are each independently selected from hydrogen or (C₁-C₆)alkyl; or a group of the formula II

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II

wherein a is 0, 1, 2, 3 or 4;

b, c, e, f and g are each independently 0 or 1;

d is 0, 1, 2, or 3;

5 X is $S(O)_n$ wherein n is 0, 1 or 2; oxygen, carbonyl or $-C(=N\text{-cyano})-$;

Y is $S(O)_n$ wherein n is 0, 1 or 2; or carbonyl; and

Z is carbonyl, $C(O)O-$, $C(O)NR-$ or $S(O)_n$ wherein n is 0, 1 or 2;

R^6 , R^7 , R^8 , R^9 , R^{10} and R^{11} are each independently selected from the group consisting of hydrogen or (C_1-C_6) alkyl optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C_1-C_6) acyloxy, (C_1-C_6) acylamino, (C_1-C_6) alkylamino, $((C_1-C_6)alkyl)_2$ amino, cyano, cyano $(C_1-C_6)alkyl$, trifluoromethyl $(C_1-C_6)alkyl$, nitro, nitro $(C_1-C_6)alkyl$ or (C_1-C_6) acylamino;

R^{12} is carboxy, cyano, amino, oxo, deuterium, hydroxy, trifluoromethyl, $(C_1-C_6)alkyl$, trifluoromethyl $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, halo, $(C_1-C_6)acyl$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2$ amino, amino $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy-CO-NH$, $(C_1-C_6)alkylamino-CO-$, $(C_2-C_6)alkenyl$, $(C_2-C_6)alkynyl$, $(C_1-C_6)alkylamino$, hydroxy $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)alkyl$, $(C_1-C_6)acyloxy(C_1-C_6)alkyl$, nitro, cyano $(C_1-C_6)alkyl$, halo $(C_1-C_6)alkyl$, nitro $(C_1-C_6)alkyl$, trifluoromethyl, trifluoromethyl $(C_1-C_6)alkyl$, $(C_1-C_6)acylamino$, $(C_1-C_6)acylamino(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)acylamino$, amino $(C_1-C_6)acyl$, amino $(C_1-C_6)acyl(C_1-C_6)alkyl$, $(C_1-C_6)alkylamino(C_1-C_6)acyl$, $((C_1-C_6)alkyl)_2$ amino $(C_1-C_6)acyl$, $R^{15}R^{16}N-CO-O-$, $R^{15}R^{16}N-CO-(C_1-C_6)alkyl$, $R^{15}C(O)NH$, $R^{15}OC(O)NH$, $R^{15}NHC(O)NH$, $(C_1-C_6)alkyl-S(O)_m$, $(C_1-C_6)alkyl-S(O)_m-(C_1-C_6)alkyl$, $R^{15}R^{16}NS(O)_m$, $R^{15}R^{16}NS(O)_m(C_1-C_6)alkyl$, $R^{15}S(O)_mR^{16}N$, $R^{15}S(O)_mR^{16}N(C_1-C_6)alkyl$ wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or $(C_1-C_6)alkyl$;

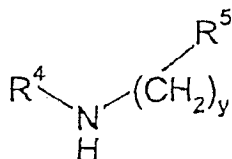
R^2 and R^3 are each independently selected from the group consisting of hydrogen, deuterium, amino, halo, hydroxy, nitro, carboxy, $(C_2-C_6)alkenyl$, $(C_2-C_6)alkynyl$, trifluoromethyl, trifluoromethoxy, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, $(C_3-$

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- C_{10})cycloalkyl wherein the alkyl, alkoxy or cycloalkyl groups are optionally substituted by one to three groups selected from halo, hydroxy, carboxy, amino (C_1-C_6) alkylthio, (C_1-C_6) alkylamino, $((C_1-C_6)alkyl)_2$ amino, (C_5-C_9) heteroaryl, (C_2-C_9) heterocycloalkyl, (C_3-C_9) cycloalkyl or (C_6-C_{10}) aryl; or R^2 and R^3 are each independently (C_3-C_{10}) cycloalkyl, (C_3-C_{10}) cycloalkoxy, (C_1-C_6) alkylamino, $((C_1-C_6)alkyl)_2$ amino, (C_6-C_{10}) arylamino, (C_1-C_6) alkylthio, (C_6-C_{10}) arylthio, (C_1-C_6) alkylsulfinyl, (C_6-C_{10}) arylsulfinyl, (C_1-C_6) alkylsulfonyl, (C_6-C_{10}) arylsulfonyl, (C_1-C_6) acyl, (C_1-C_6) alkoxy-CO-NH-, (C_1-C_6) alkylamino-CO-, (C_5-C_9) heteroaryl, (C_2-C_9) heterocycloalkyl or (C_6-C_{10}) aryl wherein the heteroaryl, heterocycloalkyl and aryl groups are optionally substituted by one to three halo, (C_1-C_6) alkyl, (C_1-C_6) alkyl-CO-NH-, (C_1-C_6) alkoxy-CO-NH-, (C_1-C_6) alkyl-CO-NH- (C_1-C_6) alkyl, (C_1-C_6) alkoxy-CO-NH- (C_1-C_6) alkyl, (C_1-C_6) alkoxy-CO-NH- (C_1-C_6) alkoxy, carboxy, carboxy (C_1-C_6) alkyl, carboxy (C_1-C_6) alkoxy, benzyloxycarbonyl (C_1-C_6) alkoxy, (C_1-C_6) alkoxycarbonyl (C_1-C_6) alkoxy, (C_6-C_{10}) aryl, amino, amino (C_1-C_6) alkyl, (C_1-C_6) alkoxycarbonylamino, (C_6-C_{10}) aryl (C_1-C_6) alkoxycarbonylamino, (C_1-C_6) alkylamino, $((C_1-C_6)alkyl)_2$ amino, (C_1-C_6) alkylamino (C_1-C_6) alkyl, $((C_1-C_6)alkyl)_2$ amino (C_1-C_6) alkyl, hydroxy, (C_1-C_6) alkoxy, carboxy, carboxy (C_1-C_6) alkyl, (C_1-C_6) alkoxycarbonyl, (C_1-C_6) alkoxycarbonyl (C_1-C_6) alkyl, (C_1-C_6) alkoxy-CO-NH-, (C_1-C_6) alkyl-CO-NH-, cyano, (C_5-C_9) heterocycloalkyl, amino-CO-NH-, (C_1-C_6) alkylamino-CO-NH-, $((C_1-C_6)alkyl)_2$ amino-CO-NH-, (C_6-C_{10}) arylamino-CO-NH-, (C_5-C_9) heteroarylamino-CO-NH-, (C_1-C_6) alkylamino-CO-NH- (C_1-C_6) alkyl, $((C_1-C_6)alkyl)_2$ amino-CO-NH- (C_1-C_6) alkyl, (C_6-C_{10}) arylamino-CO-NH- (C_1-C_6) alkyl, (C_5-C_9) heteroarylamino-CO-NH- (C_1-C_6) alkyl, (C_1-C_6) alkylsulfonyl, (C_1-C_6) alkylsulfonylamino, (C_1-C_6) alkylsulfonylamino (C_1-C_6) alkyl, (C_6-C_{10}) arylsulfonyl, (C_6-C_{10}) arylsulfonylamino, (C_6-C_{10}) arylsulfonylamino (C_1-C_6) alkyl, (C_1-C_6) alkylsulfonylamino, (C_1-C_6) alkylsulfonylamino (C_1-C_6) alkyl, (C_5-C_9) heteroaryl or (C_2-C_9) heterocycloalkyl;

said method comprising the steps of:

- a) mixing a racemic mixture of enantiomeric compounds of the formula

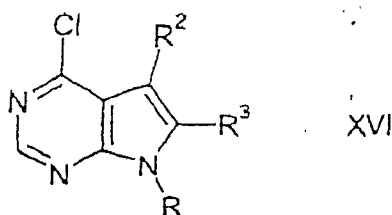


- 30 wherein y , R^4 and R^5 are as defined above, in a solvent, with a resolving compound having a defined stereospecificity, to form a solution and with said resolving agent

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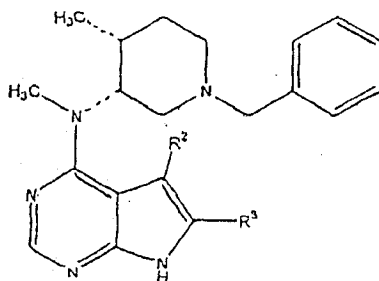
being capable of binding with at least one but not all of said enantiomers to form a precipitate, containing said at least one of said enantiomers.

- ~~b) allowing the mixture to stand for a time sufficient to allow substantial~~
precipitation of a stereospecific enantiomer of the racemic mixture from the solution
5 and wherein another of said enantiomers remains in said solution;
c) depending on the stereospecific enantiomer of the compound which is desired, collecting either the precipitate and purifying it or collecting the solution with contained other of said enantiomers and recrystallizing the enantiomer contained in said solution; and
10 d) reacting the desired stereospecific enantiomer so formed with a compound of the formula



wherein R is hydrogen or a protecting group and R^2 and R^3 are as defined above.

The present invention also relates to a compound of the formula



- 15 wherein R^2 and R^3 are each independently selected from the group consisting of hydrogen, deuterium, amino, halo, hydroxy, nitro, carboxy, (C_2 - C_6)alkenyl, (C_2 - C_6)alkynyl, trifluoromethyl, trifluoromethoxy, (C_1 - C_6)alkyl, (C_1 - C_6)alkoxy, (C_3 - C_{10})cycloalkyl wherein the alkyl, alkoxy or cycloalkyl groups are
20 optionally substituted by one to three groups selected from halo, hydroxy, carboxy, amino (C_1 - C_6)alkylthio, (C_1 - C_6)alkylamino, $((C_1$ - C_6)alkyl)₂amino, (C_5 - C_9)heteroaryl,

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- (C₂-C₉)heterocycloalkyl, (C₃-C₉)cycloalkyl or (C₆-C₁₀)aryl; or R² and R³ are each independently (C₃-C₁₀)cycloalkyl, (C₃-C₁₀)cycloalkoxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, (C₆-C₁₀)arylamino, (C₁-C₆)alkylthio, (C₆-C₁₀)arylthio, (C₁-C₆)alkylsulfinyl, (C₆-C₁₀)arylsulfinyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl, (C₁-C₆)acyl, (C₁-C₆)alkoxy-CO-NH-, (C₁-C₆)alkylamino-CO-, (C₅-C₉)heteroaryl, (C₂-C₉)heterocycloalkyl or (C₆-C₁₀)aryl wherein the heteroaryl, heterocycloalkyl and aryl groups are optionally substituted by one to three halo, (C₁-C₆)alkyl, (C₁-C₆)alkyl-CO-NH-, (C₁-C₆)alkoxy-CO-NH-, (C₁-C₆)alkyl-CO-NH-(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH-(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH-(C₁-C₆)alkoxy, carboxy, carboxy(C₁-C₆)alkyl, carboxy(C₁-C₆)alkoxy, benzyloxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₆-C₁₀)aryl, amino, amino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonylamino, (C₆-C₁₀)aryl(C₁-C₆)alkoxycarbonylamino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, (C₁-C₆)alkylamino(C₁-C₆)alkyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, carboxy, carboxy(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH-, (C₁-C₆)alkyl-CO-NH-, cyano, (C₅-C₉)heterocycloalkyl, amino-CO-NH-, (C₁-C₆)alkylamino-CO-NH-, ((C₁-C₆)alkyl)₂amino-CO-NH-, (C₆-C₁₀)arylamino-CO-NH-, (C₅-C₉)heteroarylamino-CO-NH-, (C₁-C₆)alkylamino-CO-NH-(C₁-C₆)alkyl, ((C₁-C₆)alkyl)₂amino-CO-NH-(C₁-C₆)alkyl, (C₆-C₁₀)arylamino-CO-NH-(C₁-C₆)alkyl, (C₅-C₉)heteroarylamino-CO-NH-(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl, (C₆-C₁₀)arylsulfonylamino, (C₆-C₁₀)arylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₅-C₉)heteroaryl or (C₂-C₉)heterocycloalkyl.

The present invention also relates to specifically preferred compounds selected from the group consisting of:

Methyl-[(3R,4R)-4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;

(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid methyl ester;

3,3,3-Trifluoro-1-[(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-propan-1-one;

(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid dimethylamide;

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{(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carbonyl)-amino)-acetic acid ethyl ester;

~~3-[(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-3-oxo-propionitrile;~~

5 3,3,3-Trifluoro-1-[(3R,4R)-4-methyl-3-[methyl-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-propan-1-one;

1-[(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-but-3-yn-1-one;

1-[(3R,4R)-3-[(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl]-propan-1-one;

1-[(3R,4R)-3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl]-propan-1-one;

(3R,4R)-N-cyano-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-N'-propyl-piperidine-1-carboxamide; and

15 (3R,4R)-N-cyano-4,N',N'-Trimethyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxamide.

The present invention also relates to a pharmaceutical composition for (a) treating or preventing a disorder or condition selected from organ transplant rejection, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I
20 diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia, and other autoimmune diseases or (b) the inhibition of protein kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising an amount of an above described specifically preferred compound or a pharmaceutically
25 acceptable salt thereof, effective in such disorders or conditions and a pharmaceutically acceptable carrier.

The present invention also relates to a method for the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising administering to said mammal an effective amount of an above described
30 specifically preferred compound or a pharmaceutically acceptable salt thereof.

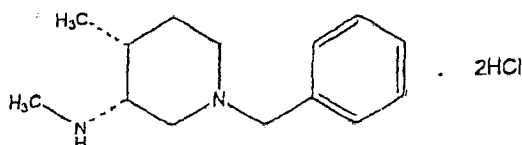
The present invention also relates to a method for treating or preventing a disorder or condition selected from organ transplant rejection, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid

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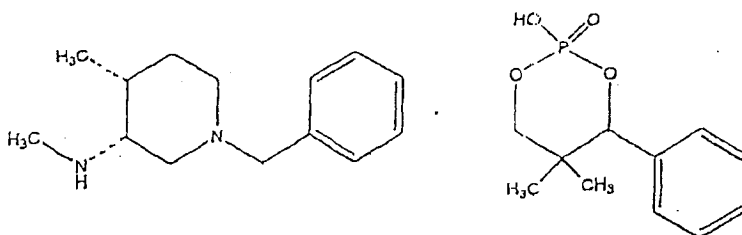
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disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia, and other autoimmune diseases in a mammal, including a human, comprising administering to said mammal an amount of an above-described specifically preferred compound or a pharmaceutically acceptable salt thereof, effective in treating such a condition.

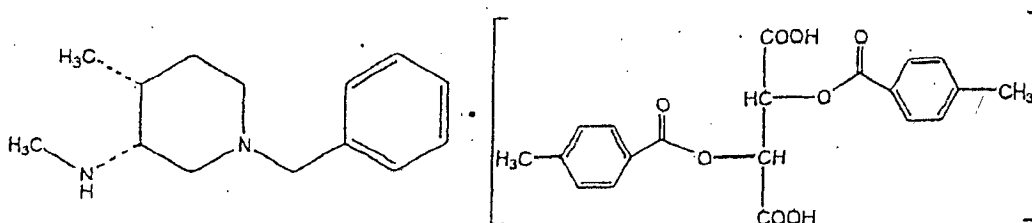
The present invention also relates to a compound of the formula



The present invention also relates to a compound of the formula



The present invention also relates to a compound of the formula



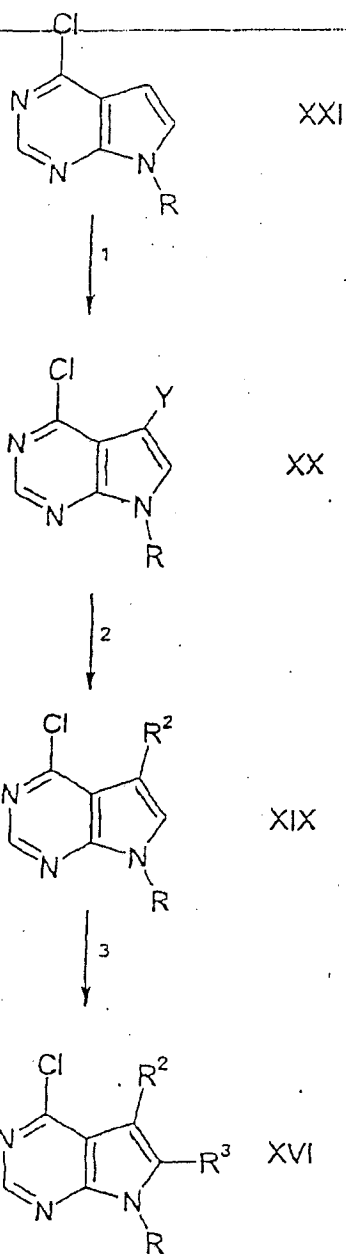
Detailed Description of the Invention

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated R^2 , R^3 , R^4 and R^5 in the reaction

Schemes and the discussion that follow are defined as above.

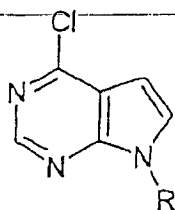
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PREPARATION A

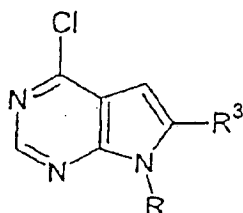
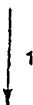


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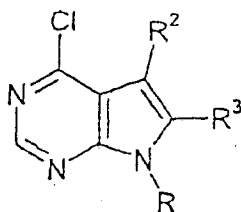
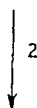
PREPARATION B



XXI



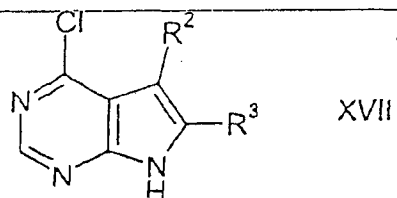
XXII



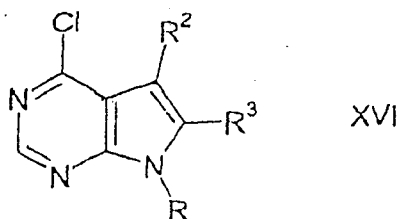
XVI

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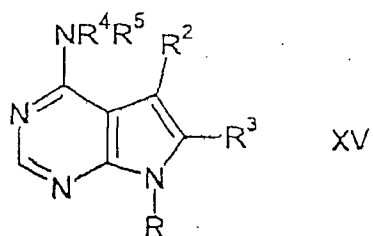
SCHEME 1



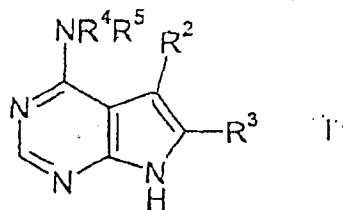
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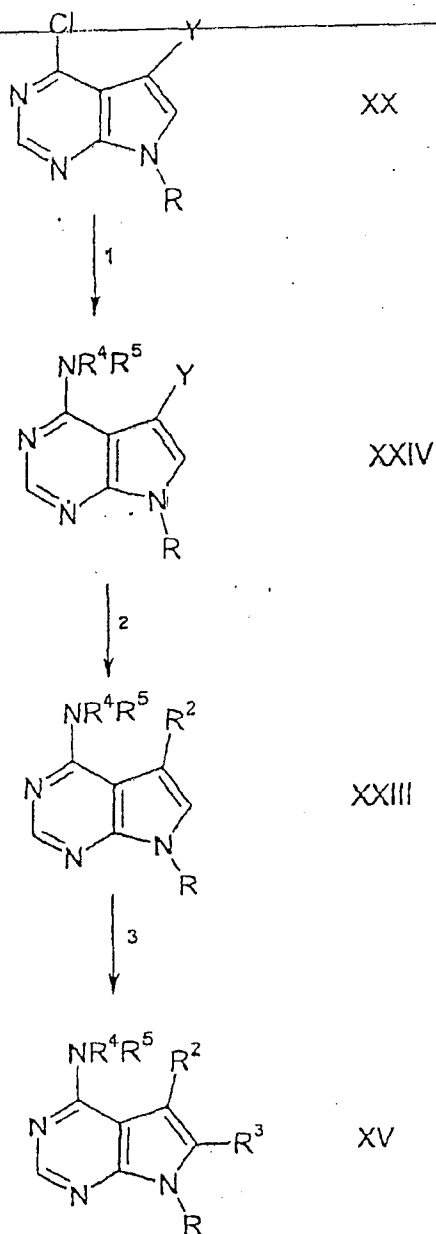


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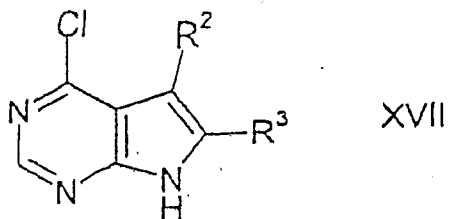
SCHEME 2



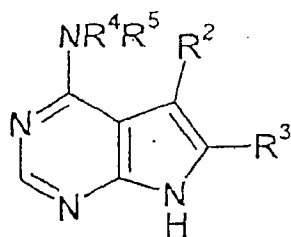
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SCHEME 3

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- In reaction 1 of Preparation A, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula XXI, wherein R is hydrogen or a protecting group such as benzenesulfonyl or benzyl, is converted to the 4-chloro-5-halopyrrolo[2,3-d]pyrimidine compound of formula XX, wherein Y is chloro, bromo or iodo, by reacting XXI with N-chlorosuccinimide, N-bromosuccinimide or N-iodosuccinimide. The reaction mixture is heated to reflux, in chloroform, for a time period between about 1 hour to about 3 hours, preferably about 1 hour. Alternatively, in reaction 1 of Preparation A, the 4-chloropyrrolo[2,3-d]pyrimidine of formula XXI, wherein R is hydrogen, is converted to the corresponding 4-chloro-5-nitropyrrolo[2,3-d]pyrimidine of formula XX, wherein Y is nitro, by reacting XXI with nitric acid in sulfuric acid at a temperature between about -10°C to about 10°C, preferably about 0°C, for a time period between about 5 minutes to about 15 minutes, preferably about 10 minutes. The compound of formula XXI, wherein Y is nitro, is converted to the corresponding 4-chloro-5-aminopyrrolo[2,3-d]pyrimidine of the formula XX, wherein Y is amino, by reacting XXI under a variety of conditions known to one skilled in the art such as palladium hydrogenolysis or tin(IV)chloride and hydrochloric acid.

- In reaction 2 of Preparation A, the 4-chloro-5-halopyrrolo[2,3-d]pyrimidine compound of formula XX, wherein R is hydrogen, is converted to the corresponding compound of formula XIX, wherein R² is (C₁-C₆)alkyl or benzyl, by treating XX with N-butyllithium, at a temperature of about -78°C, and reacting the dianion intermediate so formed with an alkylhalide or benzylhalide at a temperature between about -78°C to room temperature, preferably room temperature. Alternatively, the dianion so formed is reacted with molecular oxygen to form the corresponding 4-chloro-5-hydroxypyrrrolo[2,3-d]pyrimidine compound of formula XIX, wherein R² is hydroxy.
- The compound of formula XX, wherein Y is bromine or iodine and R is benzenesulfonate, is converted to the compound of formula XIX, wherein R² is (C₆-C₁₂)aryl or vinyl, by treating XX with N-butyllithium, at a temperature of about -78°C, followed by the addition of zinc chloride, at a temperature of about -78°C. The corresponding organo zinc intermediate so formed is then reacted with aryl iodide or vinyl iodide in the presence of a catalytic quantity of palladium. The reaction mixture is stirred at a temperature between about 50°C to about 80°C, preferably about 70°C, for a time period between about 1 hour to about 3 hours, preferably about 1 hour.

In reaction 3 of Preparation A, the compound of formula XIX is converted to the corresponding compound of formula XVI by treating XIX with N-butyllithium,

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lithium diisopropylamine or sodium hydride, at a temperature of about -78°C , in the presence of a polar aprotic solvent, such as tetrahydrofuran. The anionic intermediate so formed is further reacted with (a) alkylhalide or benzylhalide, at a temperature between about -78°C to room temperature, preferably -78°C , when R^3 is alkyl or benzyl; (b) an aldehyde or ketone, at a temperature between about -78°C to room temperature, preferably -78°C , when R^3 is alkoxy; and (c) zinc chloride, at a temperature between about -78°C to room temperature, preferably -78°C , and the corresponding organozinc intermediate so formed is then reacted with aryl iodide or vinyl iodide in the presence of a catalytic quantity of palladium. The resulting reaction mixture is stirred at a temperature between about 50°C to about 80°C , preferably about 70°C , for a time period between about 1 hour to about 3 hours, preferably about 1 hour. Alternatively, the anion so formed is reacted with molecular oxygen to form the corresponding 4-chloro-6-hydroxypyrrolo[2,3-d]pyrimidine compound of formula XVI, wherein R^3 is hydroxy.

In reaction 1 of Preparation B, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula XXI is converted to the corresponding compound of formula XXII, according to the procedure described above in reaction 3 of Preparation A.

In reaction 2 of Preparation B, the compound of formula XXII is converted to the corresponding compound of formula XVI, according to the procedures described above in reactions 1 and 2 of Preparation A.

In reaction 1 of Scheme 1, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula XVII is converted to the corresponding compound of formula XVI, wherein R is benzenesulfonyl or benzyl, by treating XVII with benzenesulfonyl chloride, benzylchloride or benzylbromide in the presence of a base, such as sodium hydride or potassium carbonate, and a polar aprotic solvent, such as dimethylformamide or tetrahydrofuran. The reaction mixture is stirred at a temperature between about 0°C to about 70°C , preferably about 30°C , for a time period between about 1 hour to about 3 hours, preferably about 2 hours.

In reaction 2 of Scheme 1, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula XVI is converted to the corresponding 4-aminopyrrolo[2,3-d]pyrimidine compound of formula XV by coupling XVI with an amine of the formula HNR^4R^5 . The reaction is carried out in water or an alcohol solvent, such as tert-butanol, methanol or ethanol, or other high boiling organic solvents, such as dimethylformamide, triethylamine, 1,4-dioxane or 1,2-dichloroethane, at a temperature between about

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60°C to about 120°C, preferably about 80°C. Typical reaction times are between about 2 hours to about 100 hours, preferably about 48 hours. When R⁵ is a nitrogen containing heterocycloalkyl group, each nitrogen must be protected by a protecting group, such a benzyl. Removal of the R⁵ protecting group is carried out under conditions appropriate for that particular protecting group in use which will not affect the R protecting group on the pyrrolo[2,3-d]pyrimidine ring. Removal of the R⁵ protecting group, when benzyl, is carried out in an alcohol solvent, such as ethanol, in the present of hydrogen and a catalyst, such as palladium hydroxide on carbon, at temperatures ranging from room temperature to about 70°C. The R⁵ nitrogen containing hetrocycloalkyl group so formed may be further reacted with a variety of different electrophiles of formula II. For urea formation, electrophiles of formula II such as isocyanates, carbamates and carbamoyl chlorides are reacted with the R⁵ nitrogen of the heteroalkyl group in a solvent, such as acetonitrile or dimethylformamide, in the presence of a base, such as sodium or potassium carbonate, at a temperature between about 20°C to about 100 °C for a time period between about 24 hours to about 72 hours. For amide and sulfonamide formation, electrophiles of formula II, such as acylchlorides and sulfonyl chlorides, are reacted with the R⁵ nitrogen of the heteroalkyl group in a solvent such as methylene chloride in the presence of a base such as pyridine at ambient temperatures for a time period between about 12 hours to about 24 hours. Amide formation may also be carried out by reacting a carboxylic acid with the heteroalkyl group in the presence of a carbodiimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide in a solvent such as methylene chloride at ambient temperatures for about 12 to about 24 hours, or with an activated ester, such as N-hydroxysuccinimide ester, or 4-nitrophenyl ester in a solvent such as methylene chloride, tetrahydrofuran or ethanol. For alkyl formation, electrophiles of formula II, such as α,β -unsaturated amides, acids, nitriles, esters, and α -halo amides, are reacted with the R⁵ nitrogen of the heteroalkyl group in a solvent such as methanol at ambient temperatures for a time period between about 12 hours to about 18 hours. Alkyl formation may also be carried out by reacting aldehydes with the heteroalkyl group in the presence of a reducing agent, such as sodium cyanoborohydride, in a solvent, such as methanol, at ambient temperature for a time period between about 12 hours to about 18 hours.

In reaction 3 of Scheme 1, removal of the protecting group from the compound of formula XV, wherein R is benzenesulfonyl, to give the corresponding

compound of formula I, is carried out by treating XV with an alkali base, such as sodium hydroxide or potassium hydroxide, in an alcohol solvent, such as methanol or ethanol, or mixed solvents, such as alcohol/tetrahydrofuran or alcohol/water. The reaction is carried out at room temperature for a time period between about 15 minutes to about 1 hour, preferably 30 minutes. Removal of the protecting group from the compound of formula XV, wherein R is benzyl, is conducted by treating XV with sodium in ammonia at a temperature of about -78°C for a time period between about 15 minutes to about 1 hour.

In reaction 1 of Scheme 2, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula XX is converted to the corresponding 4-aminopyrrolo[2,3-d]pyrimidine compound of formula XXIV, according to the procedure described above in reaction 2 of Scheme 1.

In reaction 2 of Scheme 2, the 4-amino-5-halopyrrolo[2,3-d]pyrimidine compound of formula XXIV, wherein R is benzenesulfonate and Z is bromine or iodine, is converted to the corresponding compound of formula XXIII by reacting XXIV with (a) arylboronic acid, when R² is aryl, in an aprotic solvent, such as tetrahydrofuran or dioxane, in the presence of a catalytic quantity of palladium (0) at a temperature between about 50°C to about 100°C, preferably about 70°C, for a time period between about 2 hours to about 48 hours, preferably about 12 hours; (b) alkynes, when R² is alkynyl, in the presence of a catalytic quantity of copper (I) iodide and palladium (0), and a polar solvent, such as dimethylformamide, at room temperature, for a time period between about 1 hour to about 5 hours, preferably about 3 hours; and (c) alkenes or styrenes, when R² is vinyl or styrenyl, in the presence of a catalytic quantity of palladium in dimethylformamide, dioxane or tetrahydrofuran, at a temperature between about 80°C to about 100°C, preferably about 100°C, for a time period between about 2 hours to about 48 hours, preferably about 48 hours.

In reaction 3 of Scheme 2, the compound of formula XXIII is converted to the corresponding compound of formula XV, according to the procedure described above in reaction 3 of Preparation A.

In reaction 1 of Scheme 3, the compound of formula XVII is converted to the corresponding compound of formula I, according to the procedure described above in reaction 2 of Scheme 1.

The compounds of the present invention that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids.

Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as acetone, methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid.

Those compounds of the present invention that are acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the calcium, sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of the present invention. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous) or rectal administration

or in a form suitable for administration by inhalation or insufflation. The active compounds of the invention may also be formulated for sustained delivery.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with

the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (e.g., rheumatoid arthritis) is 0.1 to 1000 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

Aerosol formulations for treatment of the conditions referred to above (e.g., asthma) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20 µg to 1000 µg of the compound of the invention. The overall daily dose with an aerosol will be within the range 0.1 mg to 1000 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

A compound of formula (I) administered in a pharmaceutically acceptable form either alone or in combination with one or more additional agents which modulate a mammalian immune system, or with antiinflammatory agents, agents which may include but are not limited to cyclosporin A (e.g. Sandimmune® or Neoral®, rapamycin, FK-506 (tacrolimus), leflunomide, deoxyspergualin, mycophenolate (e.g. Cellcept®, azathioprine (e.g. Imuran®), daclizumab (e.g. Zenapax®), OKT3 (e.g. Orthoclone®), AtGam, aspirin, acetaminophen, ibuprofen, naproxen, piroxicam, and antiinflammatory steroids (e.g. prednisolone or dexamethasone); and such agents may be administered as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice.

FK506 (Tacrolimus) is given orally at 0.10-0.15 mg/kg body weight, every 12 hours, within first 48 hours postoperative. Does is monitored by serum Tacrolimus trough levels.

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Cyclosporin A (Sandimmune oral or intravenous formulation, or Neoral[®]; oral solution or capsules) is given orally at 5 mg/kg body weight, every 12 hours within 48 hours postoperative. ~~Dose is monitored by blood Cyclosporin A trough levels.~~

The active agents can be formulated for sustained delivery according to methods well known to those of ordinary skill in the art. Examples of such formulations can be found in United States Patents 3,538,214, 4,060,598, 4,173,626, 3,119,742, and 3,492,397.

The ability of the compounds of formula I or their pharmaceutically acceptable salts to inhibit Janus Kinase 3 and, consequently, demonstrate their effectiveness for treating disorders or conditions characterized by Janus Kinase 3 is shown by the following in vitro assay tests.

Biological Assay

JAK3 (JH1:GST) Enzymatic Assay

The JAK3 kinase assay utilizes a protein expressed in baculovirus-infected SF9 cells (a fusion protein of GST and the catalytic domain of human JAK3) purified by affinity chromatography on glutathione-Sepharose. The substrate for the reaction is poly-Glutamic acid-Tyrosine (PGT (4:1), Sigma catalog # P0275), coated onto Nunc Maxi Sorp plates at 100 µg/ml overnight at 37°C. The morning after coating, the plates are washed three times and JAK3 is added to the wells containing 100 µl of kinase buffer (50 mM HEPES, pH 7.3, 125 mM NaCl, 24 mM MgCl₂) + 0.2 µM ATP + 1 mM Na orthovanadate.) The reaction proceeds for 30 minutes at room temperature and the plates is washed three more times. The level of phosphorylated tyrosine in a given well is quantitated by standard ELISA assay utilizing an anti-phosphotyrosine antibody (ICN PY20, cat. #69-151-1).

Inhibition of Human IL-2 Dependent T-Cell Blast Proliferation

This screen measures the inhibitory effect of compounds on IL-2 dependent T-Cell blast proliferation *in vitro*. Since signaling through the IL-2 receptor requires JAK-3, cell active inhibitors of JAK-3 should inhibit IL-2 dependent T-Cell blast proliferation.

The cells for this assay are isolated from fresh human blood. After separation of the mononuclear cells using Accuspin System-Histopaque-1077 (Sigma # A7054), primary human T-Cells are isolated by negative selection using Lympho-Kwik T (One Lambda, Inc., Cat # LK-50T). T-Cells are cultured at $1-2 \times 10^6$ /ml in Media (RPMI + 10% heat-inactivated fetal calf serum (Hyclone Cat # A-1111-L) + 1%

Penicillin/Streptomycin (Gibco)) and induce to proliferate by the addition of 10ug/ml PHA (Murex Diagnostics, Cat # HA 16). After 3 days at 37°C in 5% CO₂, cells are washed 3 times in Media, resuspended to a density of $1-2 \times 10^6$ cells/ml in Media plus 100 Units/ml of human recombinant IL-2 (R&D Systems, Cat # 202-IL). After 1 week the cells are IL-2 dependent and can be maintained for up to 3 weeks by feeding twice weekly with equal volumes of Media + 100 Units/ml of IL-2.

To assay for a test compounds ability to inhibit IL-2 dependent T-Cell proliferation, IL-2 dependent cells are washed 3 times, resuspended in media and then plated (50,000 cells/well/0.1ml) in a Flat-bottom 96-well microtiter plate (Falcon # 353075). From a 10 mM stock of test compound in DMSO, serial 2-fold dilutions of compound are added in triplicate wells starting at 10 uM. After one hour, 10 Units/ml of IL-2 is added to each test well. Plates are then incubated at 37°C, 5% CO₂ for 72 hours. Plates are then pulsed with ³H-thymidine (0.5 uCi/well) (NEN Cat # NET-027A), and incubated an additional 18 hours. Culture plates are then harvested with a 96-well plate harvester and the amount of ³H-thymidine incorporated into proliferating cells is determined by counting on a Packard Top Count scintillation counter. Data is analyzed by plotting the % inhibition of proliferation verses the concentration of test compound. An IC₅₀ value (uM) is determined from this plot.

The following Examples illustrate the preparation of the compounds of the present invention but it is not limited to the details thereof. Melting points are uncorrected. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform unless otherwise specified). Commercial reagents were utilized without further purification. THF refers to tetrahydrofuran. DMF refers to N,N-dimethylformamide. Low Resolution Mass Spectra (LRMS) were recorded on either a Hewlett Packard 5989®, utilizing chemical ionization (ammonium), or a Fisons (or Micro Mass) Atmospheric Pressure Chemical Ionization (APCI) platform which uses a 50/50 mixture of acetonitrile/water with 0.1% formic acid as the ionizing agent. Room or ambient temperature refers to 20-25°C.

EXAMPLE 1 (stable salt formation)

(1-benzyl-4-methylpiperidin-3-yl)-methylamine bishydrochloride

To a solution of 23.4kg of (1-benzyl-4-methylpiperidin-3-yl)-methylamine in 10 liters of toluene and 120 liters of ethanol at 3°C was added 25 liters of 32% HCl in water, keeping the reaction temperature below 10°C. 100 liters of solvent was

distilled off under partial vacuum, and 215 liters of ethyl acetate was added at 30°C. 210 liters of solvent was distilled off under partial vacuum, and a second 215 liters of ethyl acetate was added and another 210 liters of solvent was distilled off under partial vacuum. 111 liters of acetone was added at 35°C, the suspension was cooled to 0°C, and then the product, (1-benzyl-4-methylpiperidin-3-yl)-methylamine bishydrochloride, was filtered off and washed with 55 liters of acetone. The wet-cake was reslurried 3 times in ethanol (10 volume equivalents at reflux) to upgrade the diastomeric ratio of cis:trans from 91:9 to greater than 97:3. Total recovery was 19.4kg, 62% yield. ¹H NMR (CD₃OD, 400 MHz): 7.55 (m, 5H), 4.88 (s, 3H), 4.52 (d, J = 12.8 Hz, 1H), 4.45 (d, J = 12.8 Hz, 1H), 3.76 (m, 1H), 3.67 (m, 1H), 3.40-3.00 (m, 3H), 2.78 (3, 3H), 2.55 (m, 1H), 2.14 (m, 1H), 1.90 (m, 1H), 1.16 (d, J = 7.2 Hz, 3H)

EXAMPLE 2 (resolution)

bis[(1-benzyl-4-methylpiperidin-3-yl)-methylamine] di-p-toluy-L-tartrate

To a solution of 9.5kg of (1-benzyl-4-methylpiperidin-3-yl)-methylamine bishydrochloride in 16 liters of water was added 33 liters of 2N sodium hydroxide. Solids precipitated from the mixture. The slurry was diluted with 43 liters of isopropanol and 11 liters of methanol to redissolve the solids. Di-p-toluy-L-tartaric acid (6.3kg) was added, with precipitation of solids. The slurry was heated to reflux to redissolve the solids, then slowly cooled to 72°C. Seeds of bis[(1-benzyl-4-methylpiperidin-3-yl)-methylamine] di-p-toluy-L-tartrate were added (180grams), and the hazy solution was slowly cooled to 15°C. The solids were filtered and washed with isopropanol to yield 5.9kg of bis[(1-benzyl-4-methylpiperidin-3-yl)-methylamine] di-p-toluy-L-tartrate in 44% yield. ¹H NMR (CD₃OD, 400 MHz): 8.04 (d, J = 8.4 Hz, 2H), 7.30 (m, 7H), 5.86 (s, 1H), 4.91 (s, 3H), 3.64 (d, J = 12.8 Hz, 1H), 3.41 (d, J = 12.8 Hz, 1H), 3.09 (s, 1H), 2.90 (m, 2H), 2.40 (s, 3H), 2.22 (m, 2H), 1.92 (m, 1H), 1.57 (m, 2H), 1.03 (d, J = 7.2 Hz, 3H)

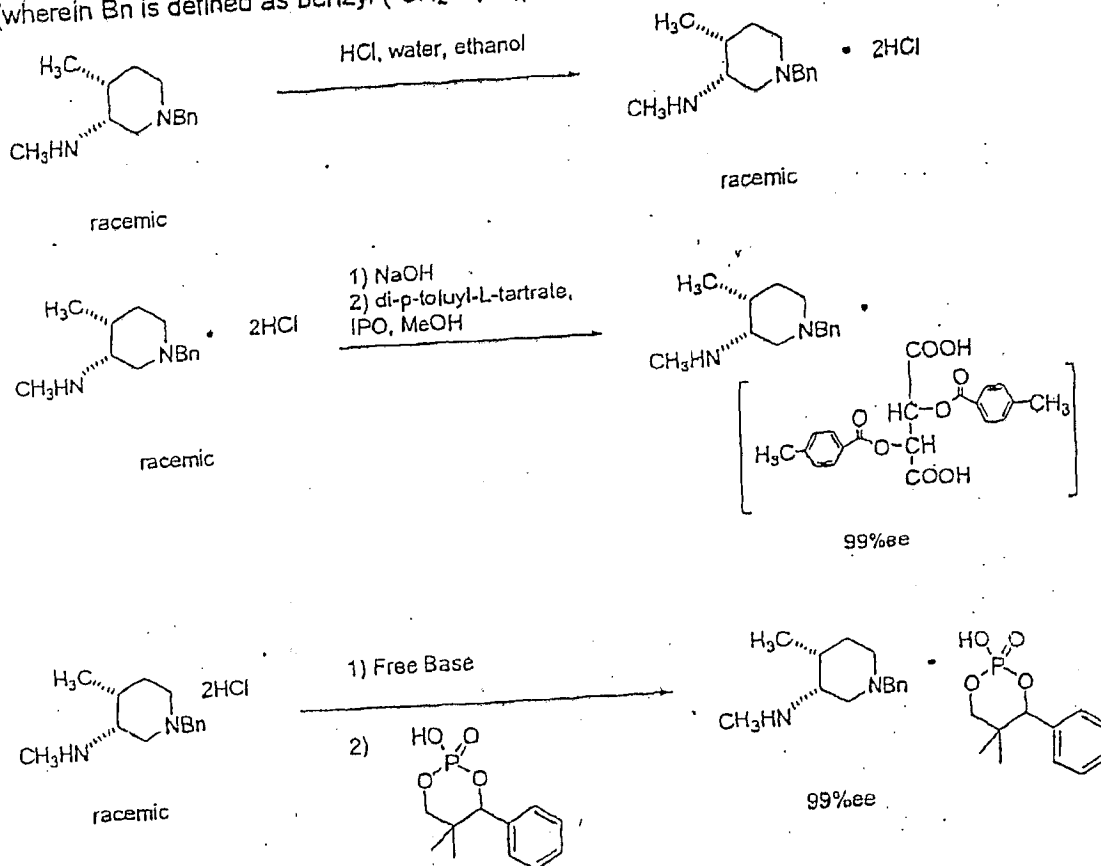
EXAMPLE 3 (phencyphos resolution)

To a solution of 6.83 grams (31.3 mmol) in 250 ml IPA and 10 ml water was added 7.57 g (+) phencyphos (31.3 mmol), and the mixture was heated to reflux in order to obtain a clear solution. At a temperature of approximately 65° C seeding crystals with an ee of 90% were added. Crystallization started within one hour and the mixture was allowed to reach room temperature overnight. Isolation afforded 6.85 g (47%) with an ee of 99%. The filtrate was concentrated, TBME, water and K₂CO₃

were added, and the layers separated. The organic layer was dried (Na_2SO_4) and the solvent evaporated. The resulting oil (3.99 grams) was dissolved in 200 ml IPA and 10 ml water and 4.4 grams (-) pheneyphos was added. The mixture was heated

- 5 (41%) salt with an ee of 99.9+% Analyses were performed on the free amine. The free amine was obtained by treatment of the salt with TBME, water and K_2CO_3 .

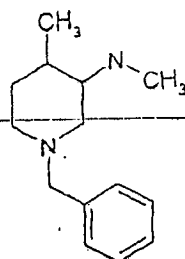
The following schematically illustrate the methods of Examples 1 to 3 (wherein Bn is defined as benzyl ($-\text{CH}_2-\text{C}_6\text{H}_5$)):



EXAMPLE 4

A racemic mixture of the compound of formula III was resolved:

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IIISample processing:

A compound of formula III was filtered through a 0.2 um nylon 66 filter disc.

Procedure: (96% ethanol 4% water as solvent)

0.8711 grams of the compound of formula III, of the filtrate, was dissolved in 5.0 ml of a 96:4 ratio of ethanol/water. 1.544 grams of di-p-toluoyl-L-tartaric acid was added and the mixture was stirred to obtain a clear solution. The solution was allowed to stand at room temperature for approximately 4 hours. The resulting slurry was filtered onto Whatman #2 filter paper and washed with 4.0 ml of a 96:4 ratio of ethanol/water. The solids were air dried to give 0.488 grams of the diastereomer salt.

0.488 grams of the diastereomer salt was suspended in 50 ml of water then 50 ml of methylene chloride was added. The pH of the mixture was adjusted to approximately 9 using saturated sodium bicarbonate followed by 1.0N sodium hydroxide. Upon completion of the pH adjustment, the layers were separated and the methylene chloride layer was filtered through Whatman #2 filter paper. Solvents were then removed by reduced pressure evaporation to give a light orange colored oil. Weight not determined. This oil was evaluated by gas chromatography.

Analytical assay: 97.3% desired enantiomer by normalized area percent.

EXAMPLE 5Procedure: (100% ethanol as solvent)

0.8714 grams of (1-benzyl-4-methyl-piperidin-3-yl)-methyl-amine was dissolved in 5.0 ml of 200 proof ethanol. 1.544 grams of di-p-toluoyl-L-tartaric acid was added and the mixture was stirred to obtain a clear solution. The solution was allowed to stand at room temperature for approximately 4 hours. The resulting slurry was filtered onto Whatman #2 filter paper and washed with 4.0 ml of a 96:4 ratio of ethanol/water. The solids were air dried to give 0.628 grams of the diastereomer salt.

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0.628 grams of the diastereomer salt was suspended in 50 ml of water then 50 ml of methylene chloride was added. The pH of the mixture was adjusted to approximately 9 using saturated sodium bicarbonate followed by 0.1N sodium hydroxide. Upon completion of the pH adjustment, the layers were separated and the methylene chloride layer was filtered through Whatman #2 filter paper. Solvents were then removed by reduced pressure evaporation to give a light yellow colored oil. Weight not determined. Evaluation of the oil provided the analytical assay: 90.5% desired enantiomer by normalized area percent.

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EXAMPLE 6

3-((3R, 4R)-4-Methyl-3-(methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino)-
piperidin-1-yl)-3-oxo-propionitrile

Method A-

5 (3R, 4R)-(1-Benzyl-4-methyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-
4-yl)-amine

4-Chloropyrrolo[2,3-d]pyrimidine (5.37 grams, 34.9 mmol), prepared by the method of Davoll, J. Am. Chem. Soc., 82, 131 (1960), which is incorporated by reference in its entirety, the product from Example 2 (6 grams, 27.5 mmol) and
10 potassium carbonate (11.4 grams, 82.5 mmol) were combined in water (60 ml). The slurry was heated at reflux for 90 hrs. The mixture was cooled to 90°C and toluene (60 ml) was added. The biphasic mixture was filtered through filter aid and the layers were separated. The aqueous layer was extracted with toluene. The combined
15 toluene layers were washed with 1N NaOH, treated with activated charcoal, and filtered through filter aid. The toluene was evaporated in vacuo and the residue crystallized from a 1:1 mixture of isopropyl acetate and hexanes to afford 5 grams of an off-white solid; 54% yield. LRMS: 336.1 (M+1).

Method B

Methyl-((3R, 4R)-4-methyl-piperidin-3-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

20 To the product from Method A (0.7 grams, 2.19 mmol) dissolved in 15 mL of ethanol was added 1.5 mL of 2 N hydrochloric acid and the reaction mixture degassed by nitrogen purge. To the reaction mixture was then added 0.5 grams of 20% palladium hydroxide on carbon (50% water) (Aldrich) and the resulting mixture shaken (Parr-Shaker) under a 50 psi atmosphere of hydrogen at room temperature
25 for 2 days. The Celite filtered reaction mixture was concentrated to dryness in vacuo and the residue purified by flash chromatography (silica; 5% methanol in dichloromethane) affording 0.48 grams (90%) of the title compound. LRMS: 246.1 (M+1).

Method C3-((3R, 4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile

To a stirred solution of the product from Method B (1.0 g) dissolved in 30 mL of ethanol was added 0.82 g of cyano-acetic acid 2,5-dioxo-pyrrolidin-1-yl ester and the resulting mixture stirred at room temperature for 2 h. The reaction mixture was filtered through Celite® and concentrated in vacuo. The residue was redissolved in dichloromethane, washed with saturated, aqueous sodium bicarbonate, dried over sodium sulfate, filtered and concentrated to dryness in vacuo affording 1.1 g (86%) of the title compound as a yellow foam. LRMS: 313 (M + 1).

Example 71-((3R, 4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-ethanone

To a stirred solution of the product from Method B (0.03 grams, 0.114 mmol) dissolved in 5 mL of 10:1 dichloromethane/pyridine was added (0.018 grams, 0.228 mmol) of acetylchloride and the resulting mixture stirred at room temperature for 18 hours. The reaction mixture was then partitioned between dichloromethane and saturated sodium bicarbonate (NaHCO₃). The organic layer was washed again with saturated NaHCO₃, dried over sodium sulfate and concentrated to dryness in vacuo. The residue was purified by preparative thin layer chromatography (PTLC) (silica; 4% methanol in dichloromethane) affording 0.005 g (15%) of the title compound as a colorless oil.

The title compounds for examples 8-31 were prepared by a method analogous to that described in Example 7.

Example 8(3R,4R)-[1-(2-Amino-ethanesulfonyl)-4-methyl-piperidin-3-yl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amineExample 9(3R,4R)-[1-Ethanesulfonyl-4-methyl-piperidin-3-yl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amineExample 10(3R,4R)-[1-(Butane-1-sulfonyl)-4-methyl-piperidin-3-yl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amineExample 11

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(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-
piperidine-1-carboxylic acid isobutyl ester

Example 12

N-(2-((3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-
piperidine-1-sulfonyl)-ethyl)-propionamide

5

Example 13

(2-((3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-
piperidine-1-sulfonyl)-ethyl)-carbamic acid methyl ester

Example 14

N-(2-((3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-
piperidine-1-sulfonyl)-ethyl)-isobutyramide

10

Example 15

(3R,4R)-(1-Methanesulfonyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-
4-yl)-amine

15

Example 16

((3R,4R)-1-Ethanesulfonyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-
4-yl)-amine

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Example 17

(3R,4R)-Methyl-[1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Example 18

5 (3R,4R)-[1-(Butane-1-sulfonyl)-piperidin-3-yl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Example 19

2,2-Dimethyl-N-((3R,4R)-2-[4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-sulfonyl]-ethyl)-propionamide

Example 20

10 (3-[(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-3-oxo-propyl)-carbamic acid tert-butyl ester

Example 21

15 Methyl-[(3R,4R)-4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Example 22

3-Amino-1-[(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-propan-1-one

Example 23

20 2-Methoxy-1-[(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-ethanone

Example 24

2-Dimethylamino-1-[(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-ethanone

Example 25

25 (3-[(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-3-oxo-propyl)-carbamic acid tert-butyl ester

Example 26

30 3,3,3-Trifluoro-1-[(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-propan-1-one

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Example 27

N-(2-((3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-
piperidin-1-yl)-2-oxo-ethyl)-acetamide

Example 28

5 3-Ethoxy-1-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-
yl)-amino]-piperidin-1-yl)-propan-1-one

Example 29

(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-
piperidine-1-carboxylic acid methylamide

Example 30

10 (3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-
piperidine-1-carboxylic acid diethylamide

Example 31

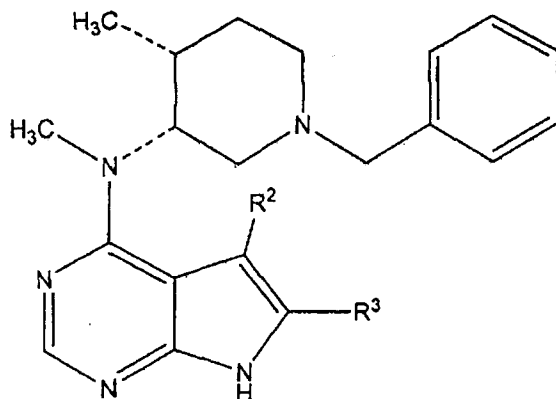
15 (3R,4R)-Methyl-[4-methyl-1-(2-methylamino-ethanesulfonyl)-piperidin-
3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

ABSTRACT

"CHIRAL SALT RESOLUTION"

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A compound of the formula



wherein R² and R³ are each independently selected from the group consisting of hydrogen, deuterium, amino, halo, hydroxy, nitro, carboxy, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, trifluoromethyl, trifluoromethoxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₃-C₁₀)cycloalkyl wherein the alkyl, alkoxy or cycloalkyl groups are optionally substituted by one to three groups selected from halo, hydroxy, carboxy, amino (C₁-C₆)alkylthio, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, (C₅-C₉)heteroaryl, (C₂-C₉)heterocycloalkyl, (C₃-C₉)cycloalkyl or (C₆-C₁₀)aryl.

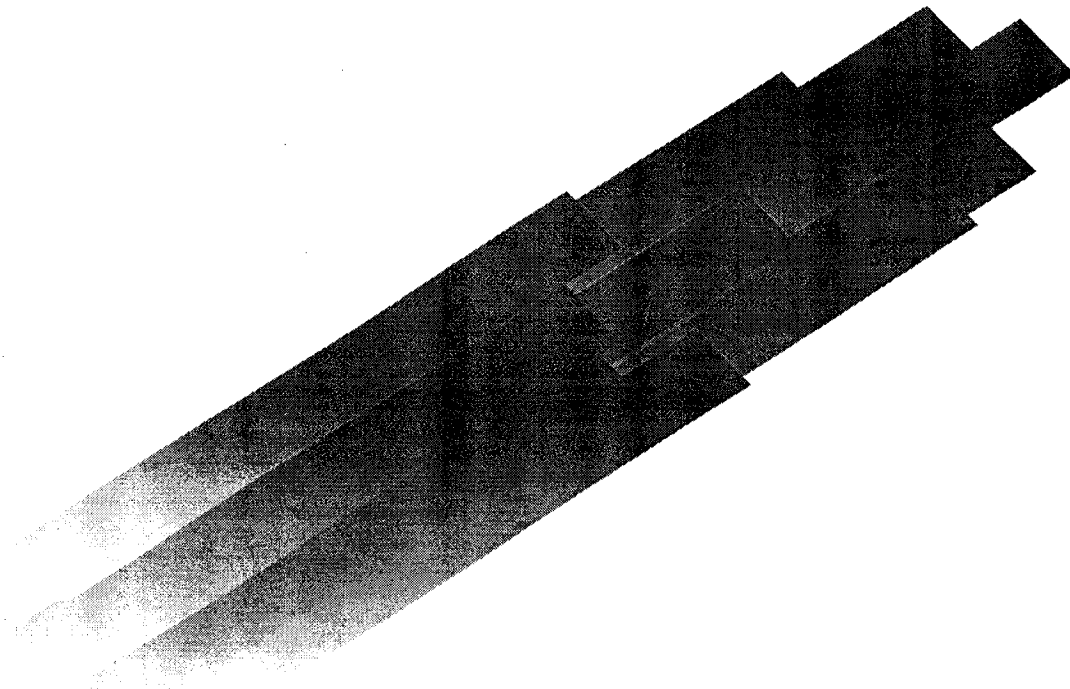
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27 JAN 2009

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Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1998
Clinical 6

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Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products

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U.S. Department of Health and Human Services
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GUIDANCE FOR INDUSTRY¹

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Providing Clinical Evidence of Effectiveness² for Human Drug and Biological Products

I. INTRODUCTION

This document is intended to provide guidance to applicants planning to file new drug applications (NDAs), biologics license applications (BLAs), or applications for supplemental indications on the evidence to be provided to demonstrate effectiveness.

This document is also intended to meet the requirements of subsections 403(b)(1) and (2) of the Food and Drug Administration Modernization Act (the Modernization Act) of 1997 for human drug and biological products (P.L. 105-115).³ Subsection 403(b)(1) directs FDA to provide guidance on the circumstances in which published matter may be the basis for approval of a supplemental application for a new indication. Section III of this guidance satisfies this requirement by describing circumstances in which published matter may partially or entirely support approval of a supplemental application. Subsection 403(b)(2) directs FDA to provide guidance on data requirements that will avoid duplication of previously submitted data by recognizing the availability of data previously submitted in support of an original application to support approval of a supplemental application. Section II of this guidance satisfies this requirement by describing a range of circumstances in which related existing data, whether from an original application or other sources, may be used to support approval of a supplemental application.

In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act to add a requirement that, to obtain marketing approval, manufacturers demonstrate the effectiveness of their products through the conduct of adequate and well-controlled studies. Since then, the issue of what constitutes sufficient evidence of effectiveness has been debated by the Agency, the scientific community, industry, and others. Sound evidence of effectiveness is a crucial component of the Agency's benefit-risk assessment of a new product or use. At the same time, the demonstration of effectiveness represents a major component of drug development time and cost; the amount

¹ This guidance document represents the agency's current thinking on providing clinical evidence of effectiveness for human drug and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

² As used in this guidance, the term efficacy refers to the findings in an adequate and well-controlled clinical trial or the intent of conducting such a trial and the term effectiveness refers to the regulatory determination that is made on the basis of clinical efficacy and other data.

³ The Modernization Act requirements in Section 403 also apply to animal drugs and medical devices. These products will be addressed in separate guidances.

and nature of the evidence needed can therefore be an important determinant of when and whether new therapies become available to the public. The public health is best served by the development of sound evidence of effectiveness in an efficient manner.

The science and practice of drug development and clinical evaluation have evolved significantly since the effectiveness requirement for drugs was established, and this evolution has implications for the amount and type of data needed to support effectiveness in certain cases. As a result of medical advances in the understanding of pathogenesis and disease staging, it is increasingly likely that clinical studies of drugs will be more narrowly defined to focus, for example, on a more specific disease stage or clinically distinct subpopulation. As a consequence, product indications are often narrower, the universe of possible indications is larger, and data may be available from a number of studies of a drug in closely related indications that bear on a determination of its effectiveness for a new use. Similarly, there may be studies of a drug in different populations, studies of a drug alone or in combination, and studies of different doses and dosage forms, all of which may support a particular new use of a drug. At the same time, progress in clinical evaluation and clinical pharmacology have resulted in more rigorously designed and conducted clinical efficacy trials, which are ordinarily conducted at more than one clinical site. This added rigor and scope has implications for a study's reliability, generalizability, and capacity to substantiate effectiveness.

Given this evolution, the Agency has determined that it would be appropriate to articulate its current thinking concerning the quantitative and qualitative standards for demonstrating effectiveness of drugs and biologics. FDA hopes that this guidance will enable sponsors to plan drug development programs that are sufficient to establish effectiveness without being excessive in scope. The guidance should also bring greater consistency and predictability to FDA's assessment of the clinical trial data needed to support drug effectiveness.

Another major goal of this guidance is to encourage the submission of supplemental applications to add new uses to the labeling of approved drugs. By articulating how it currently views the quantity and quality of evidence necessary to support approval of a new use of a drug, FDA hopes to illustrate that the submission of supplements for new uses need not be unduly burdensome.

II. QUANTITY OF EVIDENCE NECESSARY TO SUPPORT EFFECTIVENESS

A. Legal Standards for Drug and Biological Products

Drugs: The effectiveness requirement for drug approval was added to the Federal Food, Drug, and Cosmetic Act (the Act or the FDC Act) in 1962. Between passage of the Act in 1938 and the 1962 amendments, drug manufacturers were required to show only that their drugs were safe. The original impetus for the effectiveness requirement was Congress's growing concern about the misleading and unsupported claims being made by pharmaceutical companies about their drug products coupled with high drug prices. After two years of hearings on these issues, Congress adopted the 1962 Drug Amendments,

which included a provision requiring manufacturers of drug products to establish a drug's effectiveness by "substantial evidence." *Substantial evidence* was defined in section 505(d) of the Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

Since the 1962 Amendments added this provision to the statute, discussions have ensued regarding the quantity and quality of the evidence needed to establish effectiveness. With regard to quantity, it has been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness. (See e.g., Final Decision on Benylin, 44 FR 51512, 518 (August 31, 1979); *Warner-Lambert Co. V. Heckler*, 787 F. 2d 147 (3d Cir. 1986)). FDA's position is based on the language in the statute⁴ and the legislative history of the 1962 amendments. Language in a Senate report suggested that the phrase "adequate and well-controlled investigations" was designed not only to describe the quality of the required data but the "quantum" of required evidence. (S. Rep. No. 1744, Part 2, 87th Cong. 2d Sess. 6 (1962))

Nevertheless, FDA has been flexible within the limits imposed by the congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing. In some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use. In these cases, although there is only one study of the exact new use, there are, in fact, multiple studies supporting the new use, and expert judgment could conclude that the studies together represent substantial evidence of effectiveness. In other cases, FDA has relied on only a single adequate and well-controlled efficacy study to support approval — generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds.

In section 115(a) of the Modernization Act, Congress amended section 505(d) of the Act to make it clear that the Agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial

⁴ Section 505(d) of the Act uses the plural form in defining "substantial evidence" as "adequate and well-controlled investigations, including clinical investigations." See also use of "investigations" in section 505(b) of the Act, which lists the contents of a new drug application.

evidence if FDA determines that such data and evidence are sufficient to establish effectiveness. In making this clarification, Congress confirmed FDA's interpretation of the statutory requirements for approval and acknowledged the Agency's position that there has been substantial progress in the science of drug development resulting in higher quality clinical trial data.

Biologics. Biological products are approved under authority of section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. § 262). Under section 351, as in effect since 1944, licenses for biologics have been issued only upon a showing that the products meet standards designed to ensure the "continued safety, purity, and potency" of the products. *Potency* has long been interpreted to include effectiveness (21 CFR 600.3(s)). In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biologics. The Agency stated then that proof of effectiveness would consist of controlled clinical investigations as defined in the provision for "adequate and well-controlled studies" for new drugs (21 CFR 314.126), unless waived as not applicable to the biological product or essential to the validity of the study when an alternative method is adequate to substantiate effectiveness (21 CFR 601.25 (d) (2)). One such adequate alternative was identified to be serological response data where a previously accepted correlation with clinical effectiveness exists. As with nonbiological drug products, FDA has approved biological products based on single, multicenter studies with strong results.

Although section 123(a) of the Modernization Act amended section 351 of the PHS Act to make it clear that separate licenses are not required for biological products and the establishments at which the products are made, the evidentiary standard for a biological product was not changed: the product must be shown to be "safe, pure, and potent" (section 351 (a)(2) of the PHS Act as amended). In the Modernization Act (section 123(f)) Congress also directed the agency to take measures to "minimize differences in the review and approval" of products required to have approved BLAs under section 351 of the PHS Act and products required to have approved NDAs under section 505(b)(1) of the FDC Act.

B. Scientific Basis for the Legal Standard

The usual requirement for more than one adequate and well-controlled investigation reflects the need for *independent substantiation* of experimental results. A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support for a conclusion of effectiveness. The reasons for this include the following.

- Any clinical trial may be subject to unanticipated, undetected, systematic biases. These biases may operate despite the best intentions of sponsors and investigators, and may lead to flawed conclusions. In addition, some investigators may bring conscious biases to evaluations.

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- The inherent variability in biological systems may produce a positive trial result by chance alone. This possibility is acknowledged, and quantified to some extent, in the statistical evaluation of the result of a single efficacy trial. It should be noted, however, that hundreds of randomized clinical efficacy trials are conducted each year with the intent of submitting favorable results to FDA. Even if all drugs tested in such trials were ineffective, one would expect one in forty of those trials to “demonstrate” efficacy by chance alone at conventional levels of statistical significance.⁵ It is probable, therefore, that false positive findings (i.e., the chance appearance of efficacy with an ineffective drug) will occur and be submitted to FDA as evidence of effectiveness. Independent substantiation of a favorable result protects against the possibility that a chance occurrence in a single study will lead to an erroneous conclusion that a treatment is effective.
- Results obtained in a single center may be dependent on site or investigator specific factors (e.g., disease definition, concomitant treatment, diet). In such cases, the results, although correct, may not be generalizable to the intended population. This possibility is the primary basis for emphasizing the need for independence in substantiating studies.
- Rarely, favorable efficacy results are the product of scientific fraud.

Although there are statistical, methodologic, and other safeguards to address the identified problems, they are often inadequate to address these problems in a single trial. Independent substantiation of experimental results addresses such problems by providing consistency across more than one study, thus greatly reducing the possibility that a biased, chance, site-specific, or fraudulent result will lead to an erroneous conclusion that a drug is effective.

The need for independent substantiation has often been referred to as the need for replication of the finding. Replication may not be the best term, however, as it may imply that precise repetition of the same experiment in other patients by other investigators is the only means to substantiate a conclusion. Precise replication of a trial is only one of a number of possible means of obtaining independent substantiation of a clinical finding and, at times, can be less than optimal as it could leave the conclusions vulnerable to any systematic biases inherent to the particular study design. Results that are obtained from studies that are of different design and independent in execution, perhaps evaluating different populations, endpoints, or dosage forms, may provide support for a conclusion of effectiveness that is as convincing as, or more convincing than, a repetition of the same study.

⁵ p-value = 0.05, two-tailed, which implies an error rate in the efficacy (false positive) tail of 0.025 or one in forty.

C. The Quantity of Evidence to Support Effectiveness

The following three sections provide guidance on the quantity of evidence needed in particular circumstances to establish substantial evidence of effectiveness. Section 1 addresses situations in which effectiveness of a new use may be extrapolated entirely from existing efficacy studies. Section 2 addresses situations in which a single adequate and well-controlled study of a specific new use can be supported by information from other related adequate and well-controlled studies, such as studies in other phases of a disease, in closely related diseases, of other conditions of use (different dose, duration of use, regimen), of different dosage forms, or of different endpoints. Section 3 addresses situations in which a single multicenter study, without supporting information from other adequate and well-controlled studies, may provide evidence that a use is effective.

In each of these situations, it is assumed that any studies relied on to support effectiveness meet the requirements for adequate and well-controlled studies in 21 CFR 314.126. It should also be appreciated that reliance on a single study of a given use, whether alone or with substantiation from related trial data, leaves little room for study imperfections or contradictory (nonsupportive) information. In all cases, it is presumed that the single study has been appropriately designed, that the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in analysis, or other factors is judged to be minimal, and that the results reflect a clear prior hypothesis documented in the protocol. Moreover, a single favorable study among several similar attempts that failed to support a finding of effectiveness would not constitute persuasive support for a product use unless there were a strong argument for discounting the outcomes in the studies that failed to show effectiveness (e.g., study obviously inadequately powered or lack of assay sensitivity as demonstrated in a three-arm study by failure of the study to show efficacy of a known active agent).

Whether to rely on a single study to support an effectiveness determination is not often an issue in contemporary drug development. In most drug development situations, the need to find an appropriate dose, to study patients of greater and lesser complexity or severity of disease, to compare the drug to other therapy, to study an adequate number of patients for safety purposes, and to otherwise know what needs to be known about a drug before it is marketed will result in more than one adequate and well-controlled study upon which to base an effectiveness determination.

This guidance is not intended to provide a complete listing of the circumstances in which existing efficacy data may provide independent substantiation of related claims; rather, it provides examples of the reasoning that may be employed. The examples are applicable whether the claim arises in the original filing of an NDA or BLA, or in a supplemental application.

1. Extrapolation from Existing Studies

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In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form. The following are examples of situations in which effectiveness might be extrapolated from efficacy data for another claim or product.

a. Pediatric uses

The rule revising the Pediatric Use section of product labeling (21 CFR 201.57(f)(9)(iv)) makes allowance for inclusion of pediatric use information in labeling without controlled clinical trials of the use in children. In such cases, a sponsor must provide other information to support pediatric use, and the Agency must conclude that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation from adult efficacy data to pediatric patients. Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions. Examples in which pediatric use labeling information has been extrapolated from adult efficacy data include ibuprofen for pain and loratidine for seasonal allergic rhinitis.

b. Bioequivalence

The effectiveness of alternative formulations and new dosage strengths may be assessed on the basis of evidence of bioequivalence.

c. Modified-release dosage forms

In some cases, modified release dosage forms may be approved on the basis of pharmacokinetic data linking the new dosage form to a previously studied immediate-release dosage form. Because the pharmacokinetic patterns of modified-release and immediate-release dosage forms are not identical, it is generally important to have some understanding of the relationship of blood concentration to response, including an understanding of the time course of that relationship, to extrapolate the immediate-release

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data to the modified-release dosage form.

d. Different doses, regimens, or dosage forms

Dose-response relationships are generally continuous such that information about the effectiveness of one dose, dosage regimen, or dosage form is relevant to the effectiveness of other doses, regimens, or dosage forms. Where blood levels and exposure are not very different, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data alone. Even if blood levels are quite different, if there is a well-understood relationship between blood concentration and response, including an understanding of the time course of that relationship, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial. In this situation, pharmacokinetic data, together with the well-defined pharmacokinetic/pharmacodynamic (PK/PD) relationship, are used to translate the controlled trial results from one dose, regimen, or dosage form to a new dose, regimen, or dosage form (See also section II.C.2.a).

2. Demonstration of Effectiveness by a Single Study of a New Use, with Independent Substantiation From Related Study Data

The discussion that follows describes specific examples in which a single study of a new use, with independent substantiation from study data in related uses, could provide evidence of effectiveness. In these cases, the study in the new use and the related studies support the conclusion that the drug has the effect it is purported to have. Whether related studies are capable of substantiating a single study of a new use is a matter of judgment and depends on the quality and outcomes of the studies and the degree of relatedness to the new use.

a. Different doses, regimens, or dosage forms

As discussed in Sections II.C.1.d, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial where blood levels and exposure are not very different or, even if quite different, there is a well-understood relationship between blood concentration and response. Where the relationship between blood concentration and response is not so well understood and the pharmacokinetics of the new dose, regimen, or dosage form differ from the previous one, clinical efficacy data will likely be necessary to support effectiveness of a new regimen. In this case, a single additional efficacy study should ordinarily be sufficient. For example, a single controlled trial was needed to support the recent approval of a once

daily dose of risperidone because the once daily and twice daily regimens had different pharmacokinetics and risperidone's PK/PD relationship was not well understood.

b. Studies in other phases of the disease

In many cases, therapies that are effective in one phase of a disease are effective in other disease phases, although the magnitude of the benefit and benefit-to-risk relationship may differ in these other phases. For example, if a drug is known to be effective in patients with a refractory stage of a particular cancer, a single adequate and well-controlled study of the drug in an earlier stage of the same tumor will generally be sufficient evidence of effectiveness to support the new use.

c. Studies in other populations

Often, responses in subsets of a particular patient population are qualitatively similar to those in the whole population. In most cases, separate studies of effectiveness in demographic subsets are not needed (see also discussion of the pediatric population in section II.C.1.a) However, where further studies are needed, a single study would ordinarily suffice to support effectiveness in age, race, gender, concomitant disease, or other subsets for a drug already shown to be generally effective in a condition or to be effective in one population. For example, a single study was sufficient to support tamoxifen use in breast cancer in males.

d. Studies in combination or as monotherapy

For a drug known to be effective as monotherapy, a single adequate and well-controlled study is usually sufficient to support effectiveness of the drug when combined with other therapy (as part of a multidrug regimen or in a fixed-dose combination). Similarly, known effectiveness of a drug as part of a combination (i.e., its contribution to the effect of the combination is known) would usually permit reliance on a single study of appropriate design to support its use as monotherapy, or as part of a different combination, for the same use. For example, a single study of a new combination vaccine designed to demonstrate adequate immune response will ordinarily provide sufficient evidence of effectiveness if the new combination contains products or antigens already proven to be effective alone or in other combinations. These situations are common for oncologic and antihypertensive drugs, but occur elsewhere as well.

e. Studies in a closely related disease

Studies in etiologically or pathophysiologically related conditions, or studies of a symptom common to several diseases (e.g., pain) can support each other, allowing initial approval of several uses or allowing additional claims based on a single adequate and well-controlled study. For example, certain anti-coagulant or anti-platelet therapies could be approved for use in two different settings based on individual studies in unstable angina/acute coronary syndrome and in the postangioplasty state. Because the endpoints studied and the theoretical basis for use of an anti-coagulant or anti-platelet drug are similar, each study supports the other for each claim. Similarly, single analgesic studies in several painful conditions would ordinarily be sufficient to support either a general analgesic indication or multiple specific indications. The recent approval of lamotrigine for treatment of Lennox-Gastaut Syndrome (a rare, largely pediatric, generalized seizure disorder) was based on a single adequate and well-controlled trial, due in part to related data showing efficacy of the drug in partial-onset seizures in adults.

f. Studies in less closely related diseases, but where the general purpose of therapy is similar

Certain classes of drug therapy, such as antimicrobials and antineoplastics, are appropriate interventions across a range of different diseases. For therapies of this type, evidence of effectiveness in one disease could provide independent substantiation of effectiveness in a quite different disease. For example, it is possible to argue that evidence of effectiveness of an antimicrobial in one infectious disease setting may support reliance on a single study showing effectiveness in other settings where the causative pathogens, characteristics of the site of infection that affect the disease process (e.g., structure and immunology) and patient population are similar.⁶ Similarly, for an oncologic drug, evidence of effectiveness in one or more tumor types may support reliance on a single study showing effectiveness against a different kind of tumor, especially if the tumor types have a common biological origin.

g. Studies of different clinical endpoints

Demonstration of a beneficial effect in different studies on two different clinically meaningful endpoints could cross-substantiate a claim for

⁶ See Division of Anti-Infective Drug Products: Points to Consider in the Clinical Development and Labeling of Anti-Infective Drug Products, October 1992.

effectiveness for each outcome. For example, the initial claim for effectiveness of enalapril for heart failure was supported by one study showing symptom improvement over several months and a second study showing improved survival in a more severely ill population. The two different findings, each from an adequate and well-controlled study, led to the conclusion that enalapril was effective in both treating symptoms and improving survival.

h. Pharmacologic/pathophysiologic endpoints

When the pathophysiology of a disease and the mechanism of action of a therapy are very well understood, it may be possible to link specific pharmacologic effects to a strong likelihood of clinical effectiveness. A pharmacologic effect that is accepted as a validated surrogate endpoint can support ordinary approval (e.g., blood pressure effects, cholesterol-lowering effects) and a pharmacologic effect that is considered reasonably likely to predict clinical benefit can support accelerated approval under the conditions described in 21 CFR 314 Subpart H and 21 CFR 601 Subpart E (e.g., CD4 count and viral load effects to support effectiveness of anti-viral drugs for HIV infection). When the pharmacologic effect is not considered an acceptable effectiveness endpoint, but the linkage between it and the clinical outcome is strong, not merely on theoretical grounds but based on prior therapeutic experience or well-understood pathophysiology, a single adequate and well-controlled study showing clinical efficacy can sometimes be substantiated by persuasive data from a well-controlled study or studies showing the related pharmacologic effect.

For example, a single clearly positive trial can be sufficient to support approval of a replacement therapy such as a coagulation factor, when it is combined with clear evidence that the condition being treated is caused by a deficiency of that factor. Demonstration of physical replacement of the deficient factor or restoration of the missing physiologic activity provides strong substantiation of the clinical effect. The corrective treatment of an inborn error of metabolism could be viewed similarly. In the case of preventive vaccines, one adequate and well-controlled clinical trial may be supported by compelling animal challenge/protection models, human serological data, passive antibody data, or pathogenesis information. The more evidence there is linking effects on the pharmacologic endpoint to improvement or prevention of the disease, the more persuasive the argument for reliance on a single clinical efficacy study.

Note, however, that plausible beneficial pharmacologic effects have often not correlated with clinical benefit, and, therefore, caution must be observed in relying on a pharmacologic effect as contributing to evidence

of effectiveness. For example, pharmacologic effects such as arrhythmia suppression by Type 1 antiarrhythmics and increased cardiac output by phosphodiesterase inhibitors or beta adrenergic inotropes resulted in increased mortality, rather than, as was expected, decreased sudden death and improved outcome in heart failure. The reasons for the absence of an expected correlation between pharmacologic and clinical effects are diverse and can include an incompletely understood relationship between the pharmacologic effect and the clinical benefit and the presence of other pharmacologic effects attributable to a drug in addition to the effect being measured and thought to be beneficial. Generally, the utility of pharmacologic outcomes in providing independent substantiation will be greatest where there is prior experience with the pharmacologic class. Even in this case, however, it is difficult to be certain that a pharmacologic effect that correlates with a clinical benefit accounts for all the clinical benefit or that other effects are not present and relevant.

3. Evidence of Effectiveness from a Single Study

When the effectiveness requirement was originally implemented in 1962, the prevailing efficacy study model was a single institution, single investigator, relatively small trial with relatively loose blinding procedures, and little attention to prospective study design and identification of outcomes and analyses. At present, major clinical efficacy studies are typically multicentered, with clear, prospectively determined clinical and statistical analytic criteria. These studies are less vulnerable to certain biases, are often more generalizable, may achieve very convincing statistical results, and can often be evaluated for internal consistency across subgroups, centers, and multiple endpoints.

The added rigor and size of contemporary clinical trials have made it possible to rely, in certain circumstances, on a single adequate and well-controlled study, without independent substantiation from another controlled trial, as a sufficient scientific and legal basis for approval. For example, the approval of timolol for reduction of post-infarction mortality was based on a single, particularly persuasive (low p-value), internally consistent, multicenter study that demonstrated a major effect on mortality and reinfarction rate. For ethical reasons, the study was considered unrepeatable. The Center for Biologics Evaluation and Research has also approved a number of products based upon a single persuasive study. The Agency provided a general statement in 1995 describing when a single, multicenter study may suffice (60 FR 39181; August 1, 1995), but the Agency has not comprehensively described the situations in which a single adequate and well-controlled study might be considered adequate support for an effectiveness claim, or the characteristics of a single study that could make it adequate support for an effectiveness claim.

Whether to rely on a single adequate and well-controlled study is inevitably a matter of judgment. A conclusion based on two persuasive studies will always be more secure than a conclusion based on a single, comparably persuasive study. For this reason, reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. For example, sequential repetition of strongly positive trials that demonstrated a decrease in post-infarction mortality, prevention of osteoporotic fractures, or prevention of pertussis would present significant ethical concerns. Repetition of positive trials showing only symptomatic benefit would generally not present the same ethical concerns.

The discussion that follows identifies the characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim. Although no one of these characteristics is necessarily determinative, the presence of one or more in a study can contribute to a conclusion that the study would be adequate to support an effectiveness claim.

a. Large multicenter study

In a large multicenter study in which (1) no single study site provided an unusually large fraction of the patients and (2) no single investigator or site was disproportionately responsible for the favorable effect seen, the study's internal consistency lessens concerns about lack of generalizability of the finding or an inexplicable result attributable only to the practice of a single investigator. If analysis shows that a single site is largely responsible for the effect, the credibility of a multicenter study is diminished.

b. Consistency across study subsets

Frequently, large trials have relatively broad entry criteria and the study populations may be diverse with regard to important covariates such as concomitant or prior therapy, disease stage, age, gender or race. Analysis of the results of such trials for consistency across key patient subsets addresses concerns about generalizability of findings to various populations in a manner that may not be possible with smaller trials or trials with more narrow entry criteria. For example, the timolol postinfarction study randomized patients separately within three severity strata. The study showed positive effects on survival in each stratum supporting a conclusion that the drug's utility was not limited to a particular disease stage (e.g., relatively low or high severity).

c. Multiple *studies* in a single study

Properly designed factorial studies may be analyzed as a series of pairwise comparisons, representing, within a single study, separate demonstrations of activity of a drug as monotherapy and in combination with another drug. This model was successfully used in ISIS II, which showed that for patients with a myocardial infarction both aspirin and streptokinase had favorable effects on survival when used alone and when combined (aspirin alone and streptokinase alone were each superior to placebo; aspirin and streptokinase in combination were superior to aspirin alone and to streptokinase alone). This represented two separate (but not completely independent) demonstrations of the effectiveness of aspirin and streptokinase.

d. Multiple endpoints involving different events

In some cases, a single study will include several important, prospectively identified primary or secondary endpoints, each of which represents a beneficial, but different, effect. Where a study shows statistically persuasive evidence of an effect on more than one of such endpoints, the internal weight of evidence of the study is enhanced. For example, the approval of beta-interferon (Betaseron) for prevention of exacerbations in multiple sclerosis was based on a single multicenter study, at least partly because there were both a decreased rate of exacerbations and a decrease in MRI-demonstrated disease activity — two entirely different, but logically related, endpoints.

Similarly, favorable effects on both death and nonfatal myocardial infarctions in a lipid-lowering, postangioplasty, or postinfarction study would, in effect, represent different, but consistent, demonstrations of effectiveness, greatly reducing the possibility that a finding of reduced mortality was a chance occurrence. For example, approval of abciximab as adjunctive treatment for patients undergoing complicated angioplasty or atherectomy was supported by a single study with a strong overall result on the combined endpoint (decreased the combined total of deaths, new infarctions, and need for urgent interventions) and statistically significant effects in separate evaluations of two components of the combined endpoint (decreased new infarctions and decreased need for urgent interventions). In contrast, a beneficial effect on multiple endpoints that evaluate essentially the same phenomenon and correlate strongly, such as mood change on two different depression scales or SGOT and CPK levels postinfarction, does not significantly enhance the internal weight of the evidence from a single trial.

Although two consistent findings within a single study usually provide reassurance that a positive treatment effect is not due to chance, they do not protect against bias in study conduct or biased analyses. For example, a treatment assignment not well balanced for important prognostic variables could lead to an apparent effect on both endpoints. Thus, close scrutiny of study design and conduct are critical to evaluating this type of study.

e. Statistically very persuasive finding

In a multicenter study, a very low p-value indicates that the result is highly inconsistent with the null hypothesis of no treatment effect. In some studies it is possible to detect nominally statistically significant results in data from several centers, but, even where that is not possible, an overall extreme result and significance level means that most study centers had similar findings. For example, the thrombolysis trials of streptokinase (ISIS II, GISSI) had very sizable treatment effects and very low p-values, greatly adding to their persuasiveness. Preventive vaccines for infectious disease indications with a high efficacy rate (e.g., point estimate of efficacy of 80% or higher and a reasonably narrow 95% confidence interval) have been approved based on a single adequate and well-controlled trial.

4. Reliance on a Single, Multicenter Study — Caveats

While acknowledging the persuasiveness of a single, internally consistent, strong multicenter study, it must be appreciated that even a strong result can represent an isolated or biased result, especially if that study is the only study suggesting efficacy among similar studies. Recently, the apparent highly favorable effect of vesnarinone, an inotropic agent, in heart failure (60% reduction of mortality in what appeared to be a well-designed, placebo-controlled, multicenter trial with an extreme p-value) has proven to be unrepeatable. In an attempt to substantiate the finding, the same dose of the drug that seemed lifesaving in the earlier study significantly increased mortality (by 26%), and a lower dose also appeared to have a detrimental effect on survival. Although the population in the second study was, on the whole, a sicker population than in the first, the outcomes in similarly sick patients in each study were inconsistent so this factor does not explain the contradictory results.

When considering whether to rely on a single multicenter trial, it is critical that the possibility of an incorrect outcome be considered and that all the available data be examined for their potential to either support or undercut reliance on a single multicenter trial. In the case of vesnarinone, there were other data that were not consistent with the dramatically favorable outcome in the multicenter study. These data seemed to show an inverse dose-response relationship, showed no suggestion

of symptomatic benefit, and showed no effect on hemodynamic endpoints. These inconsistencies led the Agency, with the advice of its Cardio-Renal Advisory Committee, to refuse approval — a decision borne out by the results of the subsequent study.

This example illustrates how inadequacies and inconsistencies in the data, such as lack of pharmacologic rationale and lack of expected other effects accompanying a critical outcome, can weaken the persuasiveness of a single trial. Although an unexplained failure to substantiate the results of a favorable study in a second controlled trial is not proof that the favorable study was in error — studies of effective agents can fail to show efficacy for a variety of reasons — it is often reason not to rely on the single favorable study.

III. DOCUMENTATION OF THE QUALITY OF EVIDENCE SUPPORTING AN EFFECTIVENESS CLAIM

When submitting the requisite quantity of data to support approval of a new product or new use of an approved product, sponsors must also document that the studies were adequately designed and conducted. Essential characteristics of adequate and well-controlled trials are described in 21 CFR 314.126. To demonstrate that a trial supporting an effectiveness claim is adequate and well-controlled, extensive documentation of trial planning, protocols, conduct, and data handling is usually submitted to the Agency, and detailed patient records are made available at the clinical sites.

From a scientific standpoint, however, it is recognized that the extent of documentation necessary depends on the particular study, the types of data involved, and the other evidence available to support the claim. Therefore, the Agency is able to accept different levels of documentation of data quality, as long as the adequacy of the scientific evidence can be assured. This section discusses the factors that influence the extent of documentation needed, with particular emphasis on studies evaluating new uses of approved drugs.

For the purposes of this section, the phrase *documentation of the quality of evidence* refers to (1) the completeness of the documentation and (2) the ability to access the primary study data and the original study-related records (e.g., subjects' medical records, drug accountability records) for the purposes of verifying the data submitted as evidence. These interrelated elements bear on a determination of whether a study is adequate and well-controlled.

In practice, to achieve a high level of documentation, studies supporting claims are ordinarily conducted in accordance with good clinical practices (GCPs). Sponsors routinely monitor all clinical sites, and FDA routinely has access to the original clinical protocols, primary data, clinical site source documents for on-site audits, and complete study reports.

However, situations often arise in which studies that evaluate the efficacy of a drug product lack the full documentation described above (for example, full patient records may not be available) or in which the study was conducted with less monitoring than is ordinarily seen in commercially sponsored trials. Such situations are more common for supplemental indications because postapproval studies are more likely to be conducted by parties other than the drug sponsor and those parties may employ less extensive monitoring and data-gathering procedures than a sponsor. Under certain circumstances, it is possible for sponsors to rely on such studies to support effectiveness claims, despite less than usual documentation or monitoring. Some of those circumstances are described below.

A. Reliance on Less Than Usual Access to Clinical Data or Detailed Study Reports

FDA's access to primary data has proven to be important in many regulatory decisions. There are also reasons to be skeptical of the conclusions of published reports of studies. Experience has shown that such study reports do not always contain a complete, or entirely accurate, representation of study plans, conduct and outcomes. Outright fraud (i.e., deliberate deception) is unusual. However, incompleteness, lack of clarity, unmentioned deviation from prospectively planned analyses, or an inadequate description of how critical endpoint judgments or assessments were made are common flaws. Typically, journal article peer reviewers only have access to a limited data set and analyses, do not see the original protocol and amendments, may not know what happened to study subjects that investigators determined to be non-evaluable, and thus may lack sufficient information to detect critical omissions and problems. The utility of peer review can also be affected by variability in the relevant experience and expertise of peer reviewers. FDA's experiences with the Anturane Reinfarction Trial, as well as literature reports of the efficacy of tacrine and the anti-sepsis HA-1A antibody, illustrate its concerns with reliance on the published medical literature.

Notwithstanding these concerns, the presence of some of the factors discussed below can make it possible for FDA to rely on studies for which it has less than usual access to data or detailed study reports to partially or entirely (the so-called *paper* filing) support an effectiveness claim. FDA's reliance on a literature report to support an effectiveness claim is more likely if FDA can obtain additional critical study details. Section 1 below describes additional information that, if available, would increase the likelihood that a study could be relied on to support an effectiveness claim. Section 2 describes factors that may make efficacy findings sufficiently persuasive to permit reliance on the published literature alone. Note that the factors outlined in Section 2 are relevant to an assessment of the reliability of literature reports generally, whether alone, or accompanied by other important information as discussed in Section 1.

1. Submission of Published Literature or Other Reports in Conjunction with Other Important Information that Enhances the Reliability of the Data

If a sponsor wishes to rely on a study conducted by another party and cannot obtain the primary data from the study, for most well-conducted studies it is possible to obtain other important information, such as a protocol documenting the prospective plans for the trial, records of trial conduct and procedures, patient data listings for important variables, and documentation of the statistical analysis. FDA has considerable experience evaluating large multicenter outcome studies sponsored by U.S. and European government agencies (NIH, British Medical Research Council) and private organizations (the ISIS studies, the SAVE study) for which there was limited access to primary study data, but for which other critical information was available. Providing as many as possible of the following important pieces of information about a study, in conjunction with the published report, can increase the likelihood that the study can be relied on to support an effectiveness claim:

- a. The protocol used for the study, as well as any important protocol amendments that were implemented during the study and their relation to study accrual or randomization.
- b. The prospective statistical analysis plan and any changes from the original plan that occurred during or after the study, with particular note of which analyses were performed pre- and post-unblinding.
- c. Randomization codes and documented study entry dates for the subjects.
- d. Full accounting of all study subjects, including identification of any subjects with on-treatment data who have been omitted from analysis and the reasons for omissions, and an analysis of results using all subjects with on-study data.
- e. Electronic or paper record of each subject's data for critical variables and pertinent baseline characteristics. Where individual subject responses are a critical variable (e.g., objective responses in cancer patients, clinical cures and microbial eradications in infectious disease patients, death from a particular cause), detailed bases for the assessment, such as the case report, hospital records, and narratives, should be provided when possible.
- f. Where safety is a major issue, complete information for all deaths and drop-outs due to toxicity. For postapproval supplemental uses, however, there is generally less need for the results of lab tests or for details of adverse event reports and, consequently, much more limited documentation may be sufficient (e.g., only for unexpected deaths and previously undescribed serious adverse effects). Exceptions to this

approach would include situations in which the population for the supplemental use is so different that existing safety information has limited application (e.g., thrombolysis in stroke patients versus myocardial infarction patients) or where the new population presents serious safety concerns (e.g., extension of a preventive vaccine indication from young children to infants).

2. Submission of Published Literature Reports Alone

The following factors increase the possibility of reliance on published reports alone to support approval of a new product or new use:

- a. Multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where the findings across studies are consistent.
- b. A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients.
- c. Clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment (e.g., overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily interpreted than more subjective endpoints such as cause-specific mortality or relief of symptoms.
- d. Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or "evaluable" subset).
- e. Conduct of studies by groups with properly documented operating procedures and a history of implementing such procedures effectively.

There have been approvals based primarily or exclusively on published reports. Examples include the initial approval of secretin for evaluation of pancreatic function and recent approvals of bleomycin and talc for malignant pleural effusion and doxycycline for malaria.

B. Reliance on Studies with Alternative, Less Intensive Quality Control/On-Site Monitoring

Industry-sponsored studies typically use extensive on-site and central monitoring and auditing procedures to assure data quality. Studies supported by other sponsors may employ less stringent procedures and may use no on-site monitoring at all. An International Conference on Harmonisation guideline on good clinical practices,⁷ recently accepted internationally, emphasizes that the extent of monitoring in a trial should be based on trial-specific factors (e.g., design, complexity, size, and type of study outcome measures) and that different degrees of on-site monitoring can be appropriate. In recent years, many credible and valuable studies conducted by government or independent study groups, often with important mortality outcomes, had very little on-site monitoring. These studies have addressed quality control in other ways, such as by close control and review of documentation and extensive guidance and planning efforts with investigators. There is a long history of reliance on such studies for initial approval of drugs as well as for additional indications. Factors that influence whether studies with limited or no monitoring may be relied on include the following:

1. The existence of a prospective plan to assure data quality.
2. Studies that have features that make them inherently less susceptible to bias, such as those with relatively simple procedures, noncritical entry criteria, and readily assessed outcomes.
3. The ability to sample critical data and make comparisons to supporting records (e.g., hospital records).
4. Conduct of the study by a group with established operating procedures and a history of implementing such procedures effectively.

⁷ International Conference on Harmonisation Guidance for Industry E6, *Good Clinical Practice: Consolidated Guideline*, April 1996.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XELJANZ safely and effectively. See full prescribing information for XELJANZ.

XELJANZ® (tofacitinib) tablets for oral administration
Initial U.S. Approval: 2012

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

See full prescribing information for complete Boxed Warning.

- Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving XELJANZ. (5.1)
- If a serious infection develops, interrupt XELJANZ until the infection is controlled. (5.1)
- Prior to starting XELJANZ, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting XELJANZ. (5.1)
- Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)
- Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus- associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications. (5.2)

INDICATIONS AND USAGE

- XELJANZ, an inhibitor of Janus kinases (JAKs), is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).
- XELJANZ should not be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine. (1.1)

DOSAGE AND ADMINISTRATION**Rheumatoid Arthritis**

The recommended dose of XELJANZ is 5 mg twice daily.

DOSAGE FORMS AND STRENGTHS

- Tablets: 5 mg (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Serious Infections – Do not administer XELJANZ during an active infection, including localized infections. If a serious infection develops, interrupt XELJANZ until the infection is controlled. (5.1)
- Lymphomas and other malignancies have been reported in patients treated with XELJANZ. (5.2)
- Gastrointestinal Perforations – Use with caution in patients that may be at increased risk. (5.3)
- Laboratory monitoring – Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. (5.4)
- Immunizations – Live vaccines should not be given concurrently with XELJANZ. (5.5)
- Severe hepatic impairment – Not recommended (5.6)

ADVERSE REACTIONS

The most commonly reported adverse reactions during the first 3 months in controlled clinical trials (occurring in greater than or equal to 2% of patients treated with XELJANZ monotherapy or in combination with DMARDs) were upper respiratory tract infections, headache, diarrhea and nasopharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Potent inhibitors of Cytochrome P450 3A4 (CYP3A4) (e.g., ketoconazole): Reduce dose to 5 mg once daily. (2.1)
- One or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole): Reduce dose to 5 mg once daily. (2.1)
- Potent CYP inducers (e.g., rifampin): May result in loss of or reduced clinical response. (2.2)

USE IN SPECIFIC POPULATIONS

Moderate and severe renal impairment and moderate hepatic impairment: Reduce dose to 5 mg once daily. (8.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 11/2012

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with XELJANZ are at increased risk for developing serious infections that may lead to hospitalization or death [see *Warnings and Precautions (5.1) and Adverse Reactions (6.1)*]. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt XELJANZ until the infection is controlled.

Reported infections include:

- Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before XELJANZ use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ use.
- Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
- Bacterial, viral, and other infections due to opportunistic pathogens.

The risks and benefits of treatment with XELJANZ should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy [see *Warnings and Precautions (5.1)*].

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus- associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications [see *Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

- XELJANZ (tofacitinib) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).
- XELJANZ should not be used in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine.

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2 DOSAGE AND ADMINISTRATION

XELJANZ is given orally with or without food.

2.1 Rheumatoid Arthritis

XELJANZ may be used as monotherapy or in combination with methotrexate or other nonbiologic disease modifying antirheumatic drugs (DMARDs). The recommended dose of XELJANZ is 5 mg twice daily.

- Dose interruption is recommended for management of lymphopenia, neutropenia and anemia [see *Dosage and Administration* (2.3), *Warnings and Precautions* (5.4), and *Adverse Reactions* (6.1)].
- XELJANZ dosage should be reduced to 5 mg once daily in patients:
 - with moderate or severe renal insufficiency
 - with moderate hepatic impairment
 - receiving potent inhibitors of Cytochrome P450 3A4 (CYP3A4) (e.g., ketoconazole)
 - receiving one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole).

2.2 General Considerations for Administration

- XELJANZ should not be used in patients with severe hepatic impairment.
- It is recommended that XELJANZ not be initiated in patients with a lymphocyte count less than 500 cells/mm³, an absolute neutrophil count (ANC) less than 1000 cells/mm³, or who have hemoglobin levels less than 9 g/dL.
- Coadministration of XELJANZ with potent inducers of CYP3A4 (e.g., rifampin) may result in loss of or reduced clinical response to XELJANZ.

2.3 Dosage Modifications

XELJANZ treatment should be interrupted if a patient develops a serious infection until the infection is controlled.

Table 1: Dose Adjustments for Lymphopenia

Low Lymphocyte Count [see <i>Warnings and Precautions</i> (5.4)]	
Lab Value (cells/mm ³)	Recommendation
Lymphocyte count greater than or equal to 500	Maintain dose
Lymphocyte count less than 500 (Confirmed by repeat testing)	Discontinue XELJANZ

Table 2: Dose Adjustments for Neutropenia

Low ANC [see Warnings and Precautions (5.4)]	
Lab Value (cells/mm ³)	Recommendation
ANC greater than 1000	Maintain dose
ANC 500-1000	For persistent decreases in this range, interrupt dosing until ANC is greater than 1000 When ANC is greater than 1000, resume XELJANZ 5 mg twice daily
ANC less than 500 (Confirmed by repeat testing)	Discontinue XELJANZ

Table 3: Dose Adjustments for Anemia

Low Hemoglobin Value [see Warnings and Precautions (5.4)]	
Lab Value (g/dL)	Recommendation
Less than or equal to 2 g/dL decrease and greater than or equal to 9.0 g/dL	Maintain dose
Greater than 2 g/dL decrease or less than 8.0 g/dL (Confirmed by repeat testing)	Interrupt the administration of XELJANZ until hemoglobin values have normalized

3 DOSAGE FORMS AND STRENGTHS

XELJANZ is provided as 5 mg tofacitinib (equivalent to 8 mg tofacitinib citrate) tablets: White, round, immediate-release film-coated tablets, debossed with “Pfizer” on one side, and “JKI 5” on the other side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in rheumatoid arthritis patients receiving XELJANZ. The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster and urinary tract infection [see Adverse Reactions (6.1)]. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcus, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus, and BK virus were reported with XELJANZ. Some patients have presented with disseminated rather than localized disease, and were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids.

Other serious infections that were not reported in clinical studies may also occur (e.g., histoplasmosis, coccidioidomycosis, and listeriosis).

XELJANZ should not be initiated in patients with an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating XELJANZ in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ. XELJANZ should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with XELJANZ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Tuberculosis

Patients should be evaluated and tested for latent or active infection prior to administration of XELJANZ.

Anti-tuberculosis therapy should also be considered prior to administration of XELJANZ in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but who have risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision about whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Patients should be closely monitored for the development of signs and symptoms of tuberculosis, including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before administering XELJANZ.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were observed in clinical studies with XELJANZ. The impact of XELJANZ on chronic viral hepatitis reactivation is unknown. Patients who screened positive for hepatitis B or C were excluded from clinical trials.

5.2 Malignancy and Lymphoproliferative Disorder

Consider the risks and benefits of XELJANZ treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ in patients who develop a malignancy. Malignancies were observed in clinical studies of XELJANZ [see *Adverse Reactions* (6.1)].

In the seven controlled rheumatoid arthritis clinical studies, 11 solid cancers and one lymphoma were diagnosed in 3328 patients receiving XELJANZ with or without DMARD, compared to 0 solid cancers and 0 lymphomas in 809 patients in the placebo with or without DMARD group during the first 12 months of exposure. Lymphomas and solid cancers have also been observed in the long-term extension studies in rheumatoid arthritis patients treated with XELJANZ.

In Phase 2B, controlled dose-ranging trials in *de-novo* renal transplant patients, all of whom received induction therapy with basiliximab, high dose corticosteroids, and mycophenolic acid products, Epstein Barr Virus-associated post-transplant lymphoproliferative disorder was observed in 5 out of 218 patients treated with XELJANZ (2.3%) compared to 0 out of 111 patients treated with cyclosporine.

5.3 Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical studies with XELJANZ in rheumatoid arthritis patients, although the role of JAK inhibition in these events is not known.

XELJANZ should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation [see *Adverse Reactions* (6.1)].

5.4 Laboratory Parameters

Lymphocytes

Treatment with XELJANZ was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean lymphocyte counts below the baseline of approximately 10% during 12 months of therapy. Lymphocyte counts less than 500 cells/mm³ were associated with an increased incidence of treated and serious infections.

Avoid initiation of XELJANZ treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm³). In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm³ treatment with XELJANZ is not recommended.

Monitor lymphocyte counts at baseline and every 3 months thereafter. For recommended modifications based on lymphocyte counts see *Dosage and Administration* (2.3).

Neutrophils

Treatment with XELJANZ was associated with an increased incidence of neutropenia (less than 2000 cells/mm³) compared to placebo.

Avoid initiation of XELJANZ treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm³). For patients who develop a persistent ANC of 500-1000 cells/mm³, interrupt XELJANZ dosing until ANC is greater than or equal to 1000 cells/mm³. In patients who develop an ANC less than 500 cells/mm³, treatment with XELJANZ is not recommended.

Monitor neutrophil counts at baseline and after 4-8 weeks of treatment and every 3 months thereafter. For recommended modifications based on ANC results *see Dosage and Administration* (2.3).

Hemoglobin

Avoid initiation of XELJANZ treatment in patients with a low hemoglobin level (i.e. less than 9 g/dL). Treatment with XELJANZ should be interrupted in patients who develop hemoglobin levels less than 8 g/dL or whose hemoglobin level drops greater than 2 g/dL on treatment.

Monitor hemoglobin at baseline and after 4-8 weeks of treatment and every 3 months thereafter. For recommended modifications based on hemoglobin results *see Dosage and Administration* (2.3).

Liver Enzymes

Treatment with XELJANZ was associated with an increased incidence of liver enzyme elevation compared to placebo. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy.

Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is suspected, the administration of XELJANZ should be interrupted until this diagnosis has been excluded.

Lipids

Treatment with XELJANZ was associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assessment of lipid parameters should be performed approximately 4-8 weeks following initiation of XELJANZ therapy.

Manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.

5.5 Vaccinations

No data are available on the response to vaccination or on the secondary transmission of infection by live vaccines to patients receiving XELJANZ. Live vaccines should not be given concurrently with XELJANZ.

Update immunizations in agreement with current immunization guidelines prior to initiating XELJANZ therapy.

5.6 Hepatic Impairment

Treatment with XELJANZ is not recommended in patients with severe hepatic impairment [see *Adverse Reactions (6.1) and Use in Specific Populations (8.6)*].

6 ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

The following data includes two Phase 2 and five Phase 3 double-blind, controlled, multicenter trials. In these trials, patients were randomized to doses of XELJANZ 5 mg twice daily (292 patients) and 10 mg twice daily (306 patients) monotherapy, XELJANZ 5 mg twice daily (1044 patients) and 10 mg twice daily (1043 patients) in combination with DMARDs (including methotrexate) and placebo (809 patients). All seven protocols included provisions for patients taking placebo to receive treatment with XELJANZ at Month 3 or Month 6 either by patient response (based on uncontrolled disease activity) or by design, so that adverse events cannot always be unambiguously attributed to a given treatment. Therefore some analyses that follow include patients who changed treatment by design or by patient response from placebo to XELJANZ in both the placebo and XELJANZ group of a given interval. Comparisons between placebo and XELJANZ were based on the first 3 months of exposure, and comparisons between XELJANZ 5 mg twice daily and XELJANZ 10 mg twice daily were based on the first 12 months of exposure.

The long-term safety population includes all patients who participated in a double-blind, controlled trial (including earlier development phase studies) and then participated in one of two long-term safety studies. The design of the long-term safety studies allowed for modification of XELJANZ doses according to clinical judgment. This limits the interpretation of the long-term safety data with respect to dose.

6.1 Clinical Trial Experience

The most common serious adverse reactions were serious infections [see *Warnings and Precautions (5.1)*].

The proportion of patients who discontinued treatment due to any adverse reaction during the 0 to 3 months exposure in the double-blind, placebo-controlled trials was 4% for patients taking XELJANZ and 3% for placebo-treated patients.

Overall Infections

In the seven controlled trials, during the 0 to 3 months exposure, the overall frequency of infections was 20% and 22% in the 5 mg twice daily and 10 mg twice daily groups, respectively, and 18% in the placebo group.

The most commonly reported infections with XELJANZ were upper respiratory tract infections, nasopharyngitis, and urinary tract infections (4%, 3%, and 2% of patients, respectively).

Serious Infections

In the seven controlled trials, during the 0 to 3 months exposure, serious infections were reported in 1 patient (0.5 events per 100 patient-years) who received placebo and 11 patients (1.7 events per 100 patient-years) who received XELJANZ 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 1.1 (-0.4, 2.5) events per 100 patient-years for the combined 5 mg twice daily and 10 mg twice daily XELJANZ group minus placebo.

In the seven controlled trials, during the 0 to 12 months exposure, serious infections were reported in 34 patients (2.7 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 33 patients (2.7 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was -0.1 (-1.3, 1.2) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

The most common serious infections included pneumonia, cellulitis, herpes zoster, and urinary tract infection [see *Warnings and Precautions* (5.1)].

Tuberculosis

In the seven controlled trials, during the 0 to 3 months exposure, tuberculosis was not reported in patients who received placebo, 5 mg twice daily of XELJANZ, or 10 mg twice daily of XELJANZ.

In the seven controlled trials, during the 0 to 12 months exposure, tuberculosis was reported in 0 patients who received 5 mg twice daily of XELJANZ and 6 patients (0.5 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0.5 (0.1, 0.9) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

Cases of disseminated tuberculosis were also reported. The median XELJANZ exposure prior to diagnosis of tuberculosis was 10 months (range from 152 to 960 days) [see *Warnings and Precautions* (5.1)].

Opportunistic Infections (excluding tuberculosis)

In the seven controlled trials, during the 0 to 3 months exposure, opportunistic infections were not reported in patients who received placebo, 5 mg twice daily of XELJANZ, or 10 mg twice daily of XELJANZ.

In the seven controlled trials, during the 0 to 12 months exposure, opportunistic infections were reported in 4 patients (0.3 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 4 patients (0.3 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0 (-0.5, 0.5) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

The median XELJANZ exposure prior to diagnosis of an opportunistic infection was 8 months (range from 41 to 698 days) [see *Warnings and Precautions* (5.1)].

Malignancy

In the seven controlled trials, during the 0 to 3 months exposure, malignancies excluding NMSC were reported in 0 patients who received placebo and 2 patients (0.3 events per 100 patient-

years) who received either XELJANZ 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 0.3 (-0.1, 0.7) events per 100 patient-years for the combined 5 mg and 10 mg twice daily XELJANZ group minus placebo.

In the seven controlled trials, during the 0 to 12 months exposure, malignancies excluding NMSC were reported in 5 patients (0.4 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 7 patients (0.6 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0.2 (-0.4, 0.7) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ. One of these malignancies was a case of lymphoma that occurred during the 0 to 12 month period in a patient treated with XELJANZ 10 mg twice daily.

The most common types of malignancy, including malignancies observed during the long-term extension, were lung and breast cancer, followed by gastric, colorectal, renal cell, prostate cancer, lymphoma, and malignant melanoma [see *Warnings and Precautions* (5.2)].

Laboratory Tests

Lymphocytes

In the controlled clinical trials, confirmed decreases in lymphocyte counts below 500 cells/mm³ occurred in 0.04% of patients for the 5 mg twice daily and 10 mg twice daily XELJANZ groups combined during the first 3 months of exposure.

Confirmed lymphocyte counts less than 500 cells/mm³ were associated with an increased incidence of treated and serious infections [see *Warnings and Precautions* (5.4)].

Neutrophils

In the controlled clinical trials, confirmed decreases in ANC below 1000 cells/mm³ occurred in 0.07% of patients for the 5 mg twice daily and 10 mg twice daily XELJANZ groups combined during the first 3 months of exposure.

There were no confirmed decreases in ANC below 500 cells/mm³ observed in any treatment group.

There was no clear relationship between neutropenia and the occurrence of serious infections.

In the long-term safety population, the pattern and incidence of confirmed decreases in ANC remained consistent with what was seen in the controlled clinical trials [see *Warnings and Precautions* (5.4)].

Liver Enzyme Tests

Confirmed increases in liver enzymes greater than 3 times the upper limit of normal (3x ULN) were observed in patients treated with XELJANZ. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of XELJANZ, or reduction in XELJANZ dose, resulted in decrease or normalization of liver enzymes.

In the controlled monotherapy trials (0-3 months), no differences in the incidence of ALT or AST elevations were observed between the placebo, and XELJANZ 5 mg, and 10 mg twice daily groups.

In the controlled background DMARD trials (0-3 months), ALT elevations greater than 3x ULN were observed in 1.0%, 1.3% and 1.2% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively. In these trials, AST elevations greater than 3x ULN were observed in 0.6%, 0.5% and 0.4% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively.

One case of drug-induced liver injury was reported in a patient treated with XELJANZ 10 mg twice daily for approximately 2.5 months. The patient developed symptomatic elevations of AST and ALT greater than 3x ULN and bilirubin elevations greater than 2x ULN, which required hospitalizations and a liver biopsy.

Lipids

In the controlled clinical trials, dose-related elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were observed at one month of exposure and remained stable thereafter. Changes in lipid parameters during the first 3 months of exposure in the controlled clinical trials are summarized below:

- Mean LDL cholesterol increased by 15% in the XELJANZ 5 mg twice daily arm and 19% in the XELJANZ 10 mg twice daily arm.
- Mean HDL cholesterol increased by 10% in the XELJANZ 5 mg twice daily arm and 12% in the XELJANZ 10 mg twice daily arm.
- Mean LDL/HDL ratios were essentially unchanged in XELJANZ-treated patients.

In a controlled clinical trial, elevations in LDL cholesterol and ApoB decreased to pretreatment levels in response to statin therapy.

In the long-term safety population, elevations in lipid parameters remained consistent with what was seen in the controlled clinical trials.

Serum Creatinine

In the controlled clinical trials, dose-related elevations in serum creatinine were observed with XELJANZ treatment. The mean increase in serum creatinine was <0.1 mg/dL in the 12-month pooled safety analysis; however with increasing duration of exposure in the long-term extensions, up to 2% of patients were discontinued from XELJANZ treatment due to the protocol-specified discontinuation criterion of an increase in creatinine by more than 50% of baseline. The clinical significance of the observed serum creatinine elevations is unknown.

Other Adverse Reactions

Adverse reactions occurring in 2% or more of patients on 5 mg twice daily or 10 mg twice daily XELJANZ and at least 1% greater than that observed in patients on placebo with or without DMARD are summarized in Table 4.

Table 4: Adverse Reactions Occurring in at Least 2% or More of Patients on 5 or 10 mg Twice Daily XELJANZ With or Without DMARD (0-3 months) and at Least 1% Greater Than That Observed in Patients on Placebo

	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg Twice Daily	Placebo
Preferred Term	N = 1336 (%)	N = 1349 (%)	N = 809 (%)
Diarrhea	4.0	2.9	2.3
Nasopharyngitis	3.8	2.8	2.8
Upper respiratory tract infection	4.5	3.8	3.3
Headache	4.3	3.4	2.1
Hypertension	1.6	2.3	1.1

N reflects randomized and treated patients from the seven clinical trials

Other adverse reactions occurring in controlled and open-label extension studies included:

Blood and lymphatic system disorders: Anemia

Metabolism and nutrition disorders: Dehydration

Psychiatric disorders: Insomnia

Nervous system disorders: Paresthesia

Respiratory, thoracic and mediastinal disorders: Dyspnea, cough, sinus congestion

Gastrointestinal disorders: Abdominal pain, dyspepsia, vomiting, gastritis, nausea

Hepatobiliary disorders: Hepatic steatosis

Skin and subcutaneous tissue disorders: Rash, erythema, pruritus

Musculoskeletal, connective tissue and bone disorders: Musculoskeletal pain, arthralgia, tendonitis, joint swelling

General disorders and administration site conditions: Pyrexia, fatigue, peripheral edema

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7 DRUG INTERACTIONS

7.1 Potent CYP3A4 Inhibitors

Tofacitinib exposure is increased when XELJANZ is coadministered with potent inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole) [see *Dosage and Administration (2.1)* and *Figure 3*].

7.2 Moderate CYP3A4 and Potent CYP2C19 Inhibitors

Tofacitinib exposure is increased when XELJANZ is coadministered with medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole) [see *Dosage and Administration (2.1)* and *Figure 3*].

7.3 Potent CYP3A4 Inducers

Tofacitinib exposure is decreased when XELJANZ is coadministered with potent CYP3A4 inducers (e.g., rifampin) [see *Dosage and Administration (2.1)* and *Figure 3*].

7.4 Immunosuppressive Drugs

There is a risk of added immunosuppression when XELJANZ is coadministered with potent immunosuppressive drugs (e.g., azathioprine, tacrolimus, cyclosporine). Combined use of multiple-dose XELJANZ with potent immunosuppressives has not been studied in rheumatoid arthritis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects:

Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. XELJANZ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Tofacitinib has been shown to be fetocidal and teratogenic in rats and rabbits when given at exposures 146 times and 13 times, respectively, the maximum recommended human dose (MRHD).

In a rat embryofetal developmental study, tofacitinib was teratogenic at exposure levels approximately 146 times the MRHD (on an AUC basis at oral doses of 100 mg/kg/day). Teratogenic effects consisted of external and soft tissue malformations of anasarca and membranous ventricular septal defects, respectively, and skeletal malformations or variations (absent cervical arch; bent femur, fibula, humerus, radius, scapula, tibia, and ulna; sternoschisis; absent rib; misshapen femur; branched rib; fused rib; fused sternebra; and hemicentric thoracic centrum). In addition, there was an increase in post-implantation loss, consisting of early and late resorptions, resulting in a reduced number of viable fetuses. Mean fetal body weight was reduced. No developmental toxicity was observed in rats at exposure levels approximately 58 times the MRHD (on an AUC basis at oral doses of 30 mg/kg/day). In the rabbit embryofetal developmental study, tofacitinib was teratogenic at exposure levels approximately 13 times the MRHD (on an AUC basis at oral doses of 30 mg/kg/day) in the absence of signs of maternal toxicity. Teratogenic effects included thoracogastroschisis, omphalocele, membranous ventricular septal defects, and cranial/skeletal malformations (microstomia, microphthalmia),

mid-line and tail defects. In addition, there was an increase in post-implantation loss associated with late resorptions. No developmental toxicity was observed in rabbits at exposure levels approximately 3 times the MRHD (on an AUC basis at oral doses of 10 mg/kg/day).

Nonteratogenic effects:

In a peri- and postnatal rat study, there were reductions in live litter size, postnatal survival, and pup body weights at exposure levels approximately 73 times the MRHD (on an AUC basis at oral doses of 50 mg/kg/day). There was no effect on behavioral and learning assessments, sexual maturation or the ability of the F1 generation rats to mate and produce viable F2 generation fetuses in rats at exposure levels approximately 17 times the MRHD (on an AUC basis at oral doses of 10 mg/kg/day).

Pregnancy Registry: To monitor the outcomes of pregnant women exposed to XELJANZ, a pregnancy registry has been established. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

8.3 Nursing Mothers

Tofacitinib was secreted in milk of lactating rats. It is not known whether tofacitinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from tofacitinib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug for the mother.

8.4 Pediatric Use

The safety and effectiveness of XELJANZ in pediatric patients have not been established.

8.5 Geriatric Use

Of the 3315 patients who enrolled in Studies I to V, a total of 505 rheumatoid arthritis patients were 65 years of age and older, including 71 patients 75 years and older. The frequency of serious infection among XELJANZ-treated subjects 65 years of age and older was higher than among those under the age of 65. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

8.6 Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment. XELJANZ dose should be reduced to 5 mg once daily in patients with moderate hepatic impairment. The safety and efficacy of XELJANZ have not been studied in patients with severe hepatic impairment or in patients with positive hepatitis B virus or hepatitis C virus serology [see *Dosage and Administration (2.1) and Warnings and Precautions (5.6)*].

8.7 Renal Impairment

No dose adjustment is required in patients with mild renal impairment. XELJANZ dose should be reduced to 5 mg once daily in patients with moderate and severe renal impairment [see *Dosage and Administration (2.1)*]. In clinical trials, XELJANZ was not evaluated in rheumatoid arthritis patients with baseline creatinine clearance values (estimated by the Cockcroft-Gault equation) less than 40 mL/min.

10 OVERDOSAGE

Signs, Symptoms, and Laboratory Findings of Acute Overdosage in Humans

There is no experience with overdose of XELJANZ.

Treatment or Management of Overdose

Pharmacokinetic data up to and including a single dose of 100 mg in healthy volunteers indicate that more than 95% of the administered dose is expected to be eliminated within 24 hours.

There is no specific antidote for overdose with XELJANZ. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

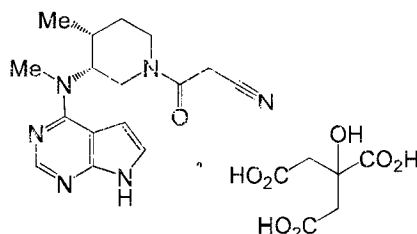
11 DESCRIPTION

XELJANZ is the citrate salt of tofacitinib, a JAK inhibitor.

Tofacitinib citrate is a white to off-white powder with the following chemical name: (3R,4R)-4-methyl-3-(methyl-7H-pyrrolo [2,3-d]pyrimidin-4-ylamino)-β-oxo-1-piperidinepropanenitrile, 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

It is freely soluble in water.

Tofacitinib citrate has a molecular weight of 504.5 Daltons (or 312.4 Daltons as the tofacitinib free base) and a molecular formula of $C_{16}H_{20}N_6O \cdot C_6H_8O_7$. The chemical structure of tofacitinib citrate is:



XELJANZ is supplied for oral administration as 5 mg tofacitinib (equivalent to 8 mg tofacitinib citrate) white round, immediate-release film-coated tablet. Each tablet of XELJANZ contains the appropriate amount of XELJANZ as a citrate salt and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, HPMC 2910/Hypromellose 6cP, titanium dioxide, macrogol/PEG3350, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tofacitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Tofacitinib modulates

the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. JAK enzymes transmit cytokine signaling through pairing of JAKs (e.g., JAK1/JAK3, JAK1/JAK2, JAK1/TyK2, JAK2/JAK2). Tofacitinib inhibited the *in vitro* activities of JAK1/JAK2, JAK1/JAK3, and JAK2/JAK2 combinations with IC_{50} of 406, 56, and 1377 nM, respectively. However, the relevance of specific JAK combinations to therapeutic effectiveness is not known.

12.2 Pharmacodynamics

Treatment with XELJANZ was associated with dose-dependent reductions of circulating CD16/56+ natural killer cells, with estimated maximum reductions occurring at approximately 8-10 weeks after initiation of therapy. These changes generally resolved within 2-6 weeks after discontinuation of treatment. Treatment with XELJANZ was associated with dose-dependent increases in B cell counts. Changes in circulating T-lymphocyte counts and T-lymphocyte subsets (CD3+, CD4+ and CD8+) were small and inconsistent. The clinical significance of these changes is unknown.

Total serum IgG, IgM, and IgA levels after 6-month dosing in patients with rheumatoid arthritis were lower than placebo; however, changes were small and not dose-dependent.

After treatment with XELJANZ in patients with rheumatoid arthritis, rapid decreases in serum C-reactive protein (CRP) were observed and maintained throughout dosing. Changes in CRP observed with XELJANZ treatment do not reverse fully within 2 weeks after discontinuation, indicating a longer duration of pharmacodynamic activity compared to the pharmacokinetic half-life.

12.3 Pharmacokinetics

Following oral administration of XELJANZ, peak plasma concentrations are reached within 0.5-1 hour, elimination half-life is ~3 hours and a dose-proportional increase in systemic exposure was observed in the therapeutic dose range. Steady state concentrations are achieved in 24-48 hours with negligible accumulation after twice daily administration.

Absorption

The absolute oral bioavailability of tofacitinib is 74%. Coadministration of XELJANZ with a high-fat meal resulted in no changes in AUC while C_{max} was reduced by 32%. In clinical trials, XELJANZ was administered without regard to meals.

Distribution

After intravenous administration, the volume of distribution is 87 L. The protein binding of tofacitinib is ~40%. Tofacitinib binds predominantly to albumin and does not appear to bind to α 1-acid glycoprotein. Tofacitinib distributes equally between red blood cells and plasma.

Metabolism and Elimination

Clearance mechanisms for tofacitinib are approximately 70% hepatic metabolism and 30% renal excretion of the parent drug. The metabolism of tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19. In a human radiolabeled study, more than 65% of the total circulating radioactivity was accounted for by unchanged tofacitinib, with the remaining

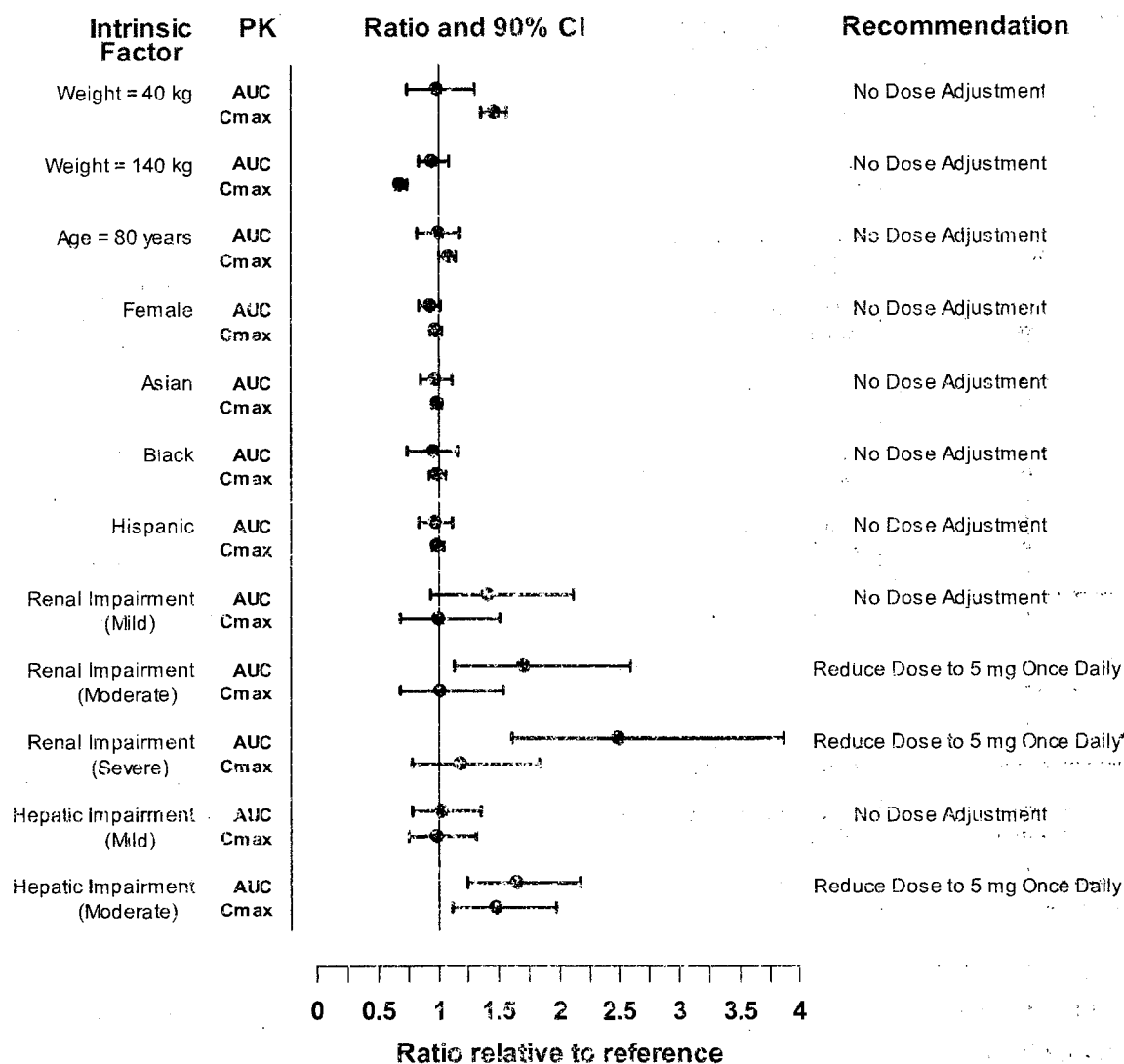
35% attributed to 8 metabolites, each accounting for less than 8% of total radioactivity. The pharmacologic activity of tofacitinib is attributed to the parent molecule.

Pharmacokinetics in Rheumatoid Arthritis Patients

Population PK analysis in rheumatoid arthritis patients indicated no clinically relevant change in tofacitinib exposure, after accounting for differences in renal function (i.e., creatinine clearance) between patients, based on age, weight, gender and race (Figure 1). An approximately linear relationship between body weight and volume of distribution was observed, resulting in higher peak (C_{\max}) and lower trough (C_{\min}) concentrations in lighter patients. However, this difference is not considered to be clinically relevant. The between-subject variability (% coefficient of variation) in AUC of tofacitinib is estimated to be approximately 27%.

Specific Populations

The effect of renal and hepatic impairment and other intrinsic factors on the pharmacokinetics of tofacitinib is shown in Figure 1.

Figure 1: Impact of Intrinsic Factors on Tofacitinib Pharmacokinetics

* Supplemental doses are not necessary in patients after dialysis

Reference values for weight, age, gender, and race comparisons are 70 kg, 55 years, male, and White, respectively; Reference groups for renal and hepatic impairment data are subjects with normal renal and hepatic function.

Drug Interactions

Potential for XELJANZ to Influence the PK of Other Drugs

In vitro studies indicate that tofacitinib does not significantly inhibit or induce the activity of the

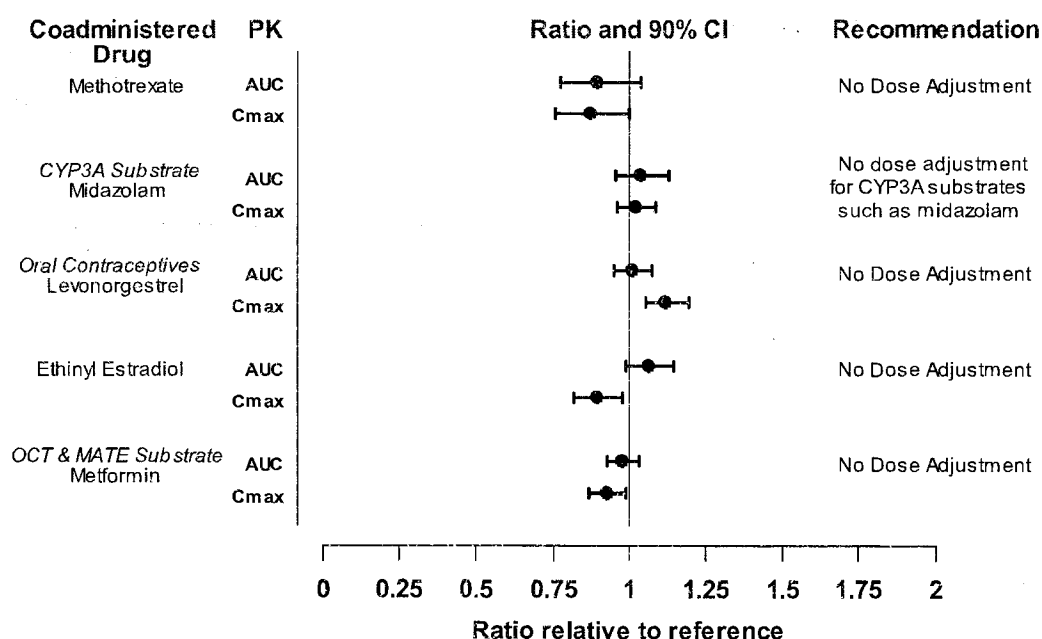
major human drug-metabolizing CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at concentrations exceeding 185 times the steady state C_{max} of a 5 mg twice daily dose. These *in vitro* results were confirmed by a human drug interaction study showing no changes in the PK of midazolam, a highly sensitive CYP3A4 substrate, when coadministered with XELJANZ.

In rheumatoid arthritis patients, the oral clearance of tofacitinib does not vary with time, indicating that tofacitinib does not normalize CYP enzyme activity in rheumatoid arthritis patients. Therefore, coadministration with XELJANZ is not expected to result in clinically relevant increases in the metabolism of CYP substrates in rheumatoid arthritis patients.

In vitro data indicate that the potential for tofacitinib to inhibit transporters such as P-glycoprotein, organic anionic or cationic transporters at therapeutic concentrations is low.

Dosing recommendations for coadministered drugs following administration with XELJANZ are shown in Figure 2.

Figure 2. Impact of XELJANZ on PK of Other Drugs



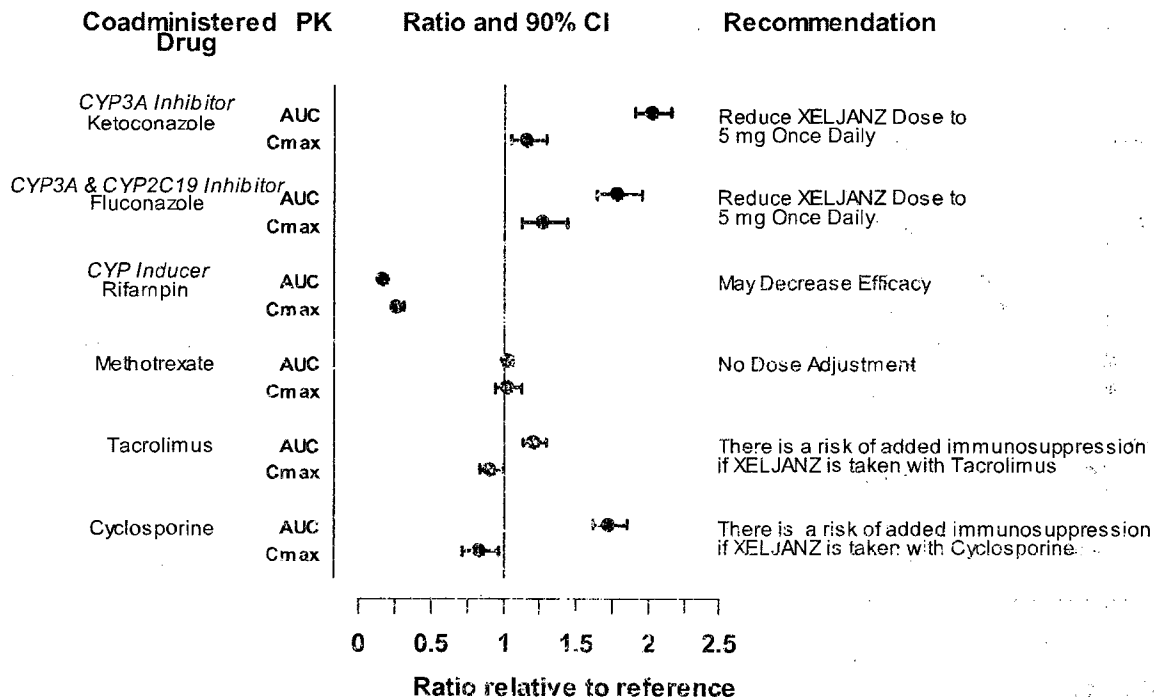
Note: Reference group is administration of concomitant medication alone; OCT = Organic Cationic Transporter; MATE = Multidrug and Toxic Compound Extrusion

Potential for Other Drugs to Influence the PK of Tofacitinib

Since tofacitinib is metabolized by CYP3A4, interaction with drugs that inhibit or induce CYP3A4 is likely. Inhibitors of CYP2C19 alone or P-glycoprotein are unlikely to substantially alter the PK of tofacitinib. Dosing recommendations for XELJANZ for administration with CYP inhibitors or inducers are shown in Figure 3.

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Figure 3. Impact of Other Drugs on PK of XELJANZ



Note: Reference group is administration of tofacitinib alone

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 39-week toxicology study in monkeys, tofacitinib at exposure levels approximately 6 times the MRHD (on an AUC basis at oral doses of 5 mg/kg twice daily) produced lymphomas. No lymphomas were observed in this study at exposure levels 1 times the MRHD (on an AUC basis at oral doses of 1 mg/kg twice daily).

The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib, at exposure levels approximately 34 times the MRHD (on an AUC basis at oral doses of 200 mg/kg/day) was not carcinogenic in mice.

In the 24-month oral carcinogenicity study in Sprague-Dawley rats, tofacitinib caused benign Leydig cell tumors, hibernomas (malignancy of brown adipose tissue), and benign thymomas at doses greater than or equal to 30 mg/kg/day (approximately 42 times the exposure levels at the MRHD on an AUC basis). The relevance of benign Leydig cell tumors to human risk is not known.

Tofacitinib was not mutagenic in the bacterial reverse mutation assay. It was positive for clastogenicity in the *in vitro* chromosome aberration assay with human lymphocytes in the presence of metabolic enzymes, but negative in the absence of metabolic enzymes. Tofacitinib was negative in the *in vivo* rat micronucleus assay and in the *in vitro* CHO-HGPRT assay and the *in vivo* rat hepatocyte unscheduled DNA synthesis assay.

In rats, tofacitinib at exposure levels approximately 17 times the MRHD (on an AUC basis at oral doses of 10 mg/kg/day) reduced female fertility due to increased post-implantation loss. There was no impairment of female rat fertility at exposure levels of tofacitinib equal to the MRHD (on an AUC basis at oral doses of 1 mg/kg/day). Tofacitinib exposure levels at approximately 133 times the MRHD (on an AUC basis at oral doses of 100 mg/kg/day) had no effect on male fertility, sperm motility, or sperm concentration.

14 CLINICAL STUDIES

The XELJANZ clinical development program included two dose-ranging trials and five confirmatory trials.

DOSE-RANGING TRIALS

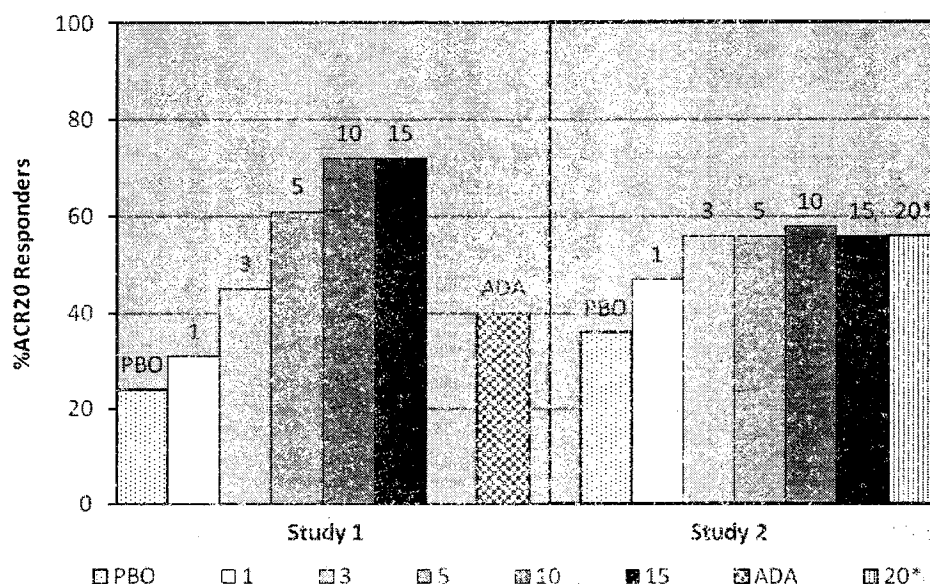
Dose selection for XELJANZ was based on two pivotal dose-ranging trials.

Dose-Ranging Study 1 was a 6-month monotherapy trial in 384 patients with active rheumatoid arthritis who had an inadequate response to a DMARD. Patients who previously received adalimumab therapy were excluded. Patients were randomized to 1 of 7 monotherapy treatments: XELJANZ 1, 3, 5, 10 or 15 mg twice daily, adalimumab 40 mg subcutaneously every other week for 10 weeks followed by XELJANZ 5 mg twice daily for 3 months, or placebo.

Dose-Ranging Study 2 was a 6-month trial in which 507 patients with active rheumatoid arthritis who had an inadequate response to MTX alone received one of 6 dose regimens of XELJANZ (20 mg once daily; 1, 3, 5, 10 or 15 mg twice daily), or placebo added to background MTX.

The results of XELJANZ-treated patients achieving ACR20 responses in Studies 1 and 2 are shown in Figure 4. Although a dose-response relationship was observed in Study 1, the proportion of patients with an ACR20 response did not clearly differ between the 10 mg and 15 mg doses. Furthermore, there was a smaller proportion of patients who responded to adalimumab monotherapy compared to those treated with XELJANZ doses 3 mg twice daily and greater. In Study 2, a smaller proportion of patients achieved an ACR20 response in the placebo and XELJANZ 1 mg groups compared to patients treated with the other XELJANZ doses. However, there was no difference in the proportion of responders among patients treated with XELJANZ 3, 5, 10, 15 mg twice daily or 20 mg once daily doses.

Figure 4: Proportion of Patients with ACR20 Response at Month 3 in Dose-Ranging Studies 1 and 2



* XELJANZ twice daily dosing in mg, except for 20 mg which is once daily dosing in mg.
PBO is placebo; ADA is adalimumab 40 mg subcutaneous injection every other week.

CONFIRMATORY TRIALS

Study I was a 6-month monotherapy trial in which 610 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a DMARD (nonbiologic or biologic) received XELJANZ 5 or 10 mg twice daily or placebo. At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of XELJANZ 5 or 10 mg twice daily. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, changes in Health Assessment Questionnaire – Disability Index (HAQ-DI), and rates of Disease Activity Score DAS28-4(ESR) less than 2.6.

Study II was a 12-month trial in which 792 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a nonbiologic DMARD received XELJANZ 5 or 10 mg twice daily or placebo added to background DMARD treatment (excluding potent immunosuppressive treatments such as azathioprine or cyclosporine). At the Month 3 visit, nonresponding patients were advanced in a blinded fashion to a second predetermined treatment of XELJANZ 5 or 10 mg twice daily. At the end of Month 6, all placebo patients were advanced to their second predetermined treatment in a blinded fashion. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, changes in HAQ-DI at Month 3, and rates of DAS28-4(ESR) less than 2.6 at Month 6.

Study III was a 12-month trial in 717 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX. Patients received XELJANZ 5 or 10 mg twice daily, adalimumab 40 mg subcutaneously every other week, or placebo added to background MTX.

Placebo patients were advanced as in Study II. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

Study IV is an ongoing 2-year trial with a planned analysis at 1 year in which 797 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX received XELJANZ 5 or 10 mg twice daily or placebo added to background MTX. Placebo patients were advanced as in Study II. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heijde-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

Study V was a 6-month trial in which 399 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to at least one approved TNF-inhibiting biologic agent received XELJANZ 5 or 10 mg twice daily or placebo added to background MTX. At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of XELJANZ 5 or 10 mg twice daily. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, HAQ-DI, and DAS28-4(ESR) less than 2.6.

Clinical Response

The percentages of XELJANZ-treated patients achieving ACR20, ACR50, and ACR70 responses in Studies I, IV, and V are shown in Table 5. Similar results were observed with Studies II and III. In all trials, patients treated with either 5 or 10 mg twice daily XELJANZ had higher ACR20, ACR50, and ACR70 response rates versus placebo, with or without background DMARD treatment, at Month 3 and Month 6. Higher ACR20 response rates were observed within 2 weeks compared to placebo. In the 12-month trials, ACR response rates in XELJANZ-treated patients were consistent at 6 and 12 months.

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Table 5: Proportion of Patients with an ACR Response

	Percent of Patients								
	Monotherapy in Nonbiologic or Biologic DMARD Inadequate Responders ^c			MTX Inadequate Responders ^d			TNF Inhibitor Inadequate Responders ^e		
	Study I			Study IV			Study V		
N ^a	PBO	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg Twice Daily	PBO + MTX	XELJANZ 5 mg Twice Daily + MTX	XELJANZ 10 mg Twice Daily + MTX	PBO + MTX	XELJANZ 5 mg Twice Daily + MTX	XELJANZ 10 mg Twice Daily + MTX
	122	243	245	160	321	316	132	133	134
ACR20									
Month 3	26%	59%	65%	27%	55%	67%	24%	41%	48%
Month 6	NA ^b	69%	70%	25%	50%	62%	NA	51%	54%
ACR50									
Month 3	12%	31%	36%	8%	29%	37%	8%	26%	28%
Month 6	NA	42%	46%	9%	32%	44%	NA	37%	30%
ACR70									
Month 3	6%	15%	20%	3%	11%	17%	2%	14%	10%
Month 6	NA	22%	29%	1%	14%	23%	NA	16%	16%

^a N is number of randomized and treated patients.^b NA Not applicable, as data for placebo treatment is not available beyond 3 months in Studies I and V due to placebo advancement.^c Inadequate response to at least one DMARD (biologic or nonbiologic) due to lack of efficacy or toxicity.^d Inadequate response to MTX defined as the presence of sufficient residual disease activity to meet the entry criteria.^e Inadequate response to at least one TNF inhibitor due to lack of efficacy and/or intolerance.

In Study IV, a greater proportion of patients treated with XELJANZ 5 mg or 10 mg twice daily plus MTX achieved a low level of disease activity as measured by a DAS28-4(ESR) less than 2.6 at 6 months compared to those treated with MTX alone (Table 6).

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Table 6: Proportion of Patients with DAS28-4(ESR) Less Than 2.6 with Number of Residual Active Joints

Study IV			
DAS28-4(ESR) Less Than 2.6	Placebo + MTX	XELJANZ 5 mg Twice Daily + MTX	XELJANZ 10 mg Twice Daily + MTX
	160	321	316
Proportion of responders at Month 6 (n)	1% (2)	6% (19)	13% (42)
Of responders, proportion with 0 active joints (n)	50% (1)	42% (8)	36% (15)
Of responders, proportion with 1 active joint (n)	0	5% (1)	17% (7)
Of responders, proportion with 2 active joints (n)	0	32% (6)	7% (3)
Of responders, proportion with 3 or more active joints (n)	50% (1)	21% (4)	40% (17)

The results of the components of the ACR response criteria for Study IV are shown in Table 7. Similar results were observed in Studies I, II, III, and V.

Table 7: Components of ACR Response at 3 Months

	Study IV					
	XELJANZ 5 mg Twice Daily + MTX		XELJANZ 10 mg Twice Daily + MTX		Placebo + MTX	
	N=321		N=316		N=160	
	Baseline	Month 3 ^a	Baseline	Month 3 ^a	Baseline	Month 3 ^a
Number of tender joints (0-68)	24 (14)	13 (14)	23 (15)	10 (12)	23 (13)	18 (14)
Number of swollen joints (0-66)	14 (8)	6 (8)	14 (8)	6 (7)	14 (9)	10 (9)
Pain ^b	58 (23)	34 (23)	58 (24)	29 (22)	55 (24)	47 (24)
Patient global assessment ^b	58 (24)	35 (23)	57 (23)	29 (20)	54 (23)	47 (24)
Disability index (HAQ-DI) ^c	1.41 (0.68)	0.99 (0.65)	1.40 (0.66)	0.84 (0.64)	1.32 (0.67)	1.19 (0.68)

Physician global assessment ^b	59 (16)	30 (19)	58 (17)	24 (17)	56 (18)	43 (22)
CRP (mg/L)	15.3 (19.0)	7.1 (19.1)	17.1 (26.9)	4.4 (8.6)	13.7 (14.9)	14.6 (18.7)

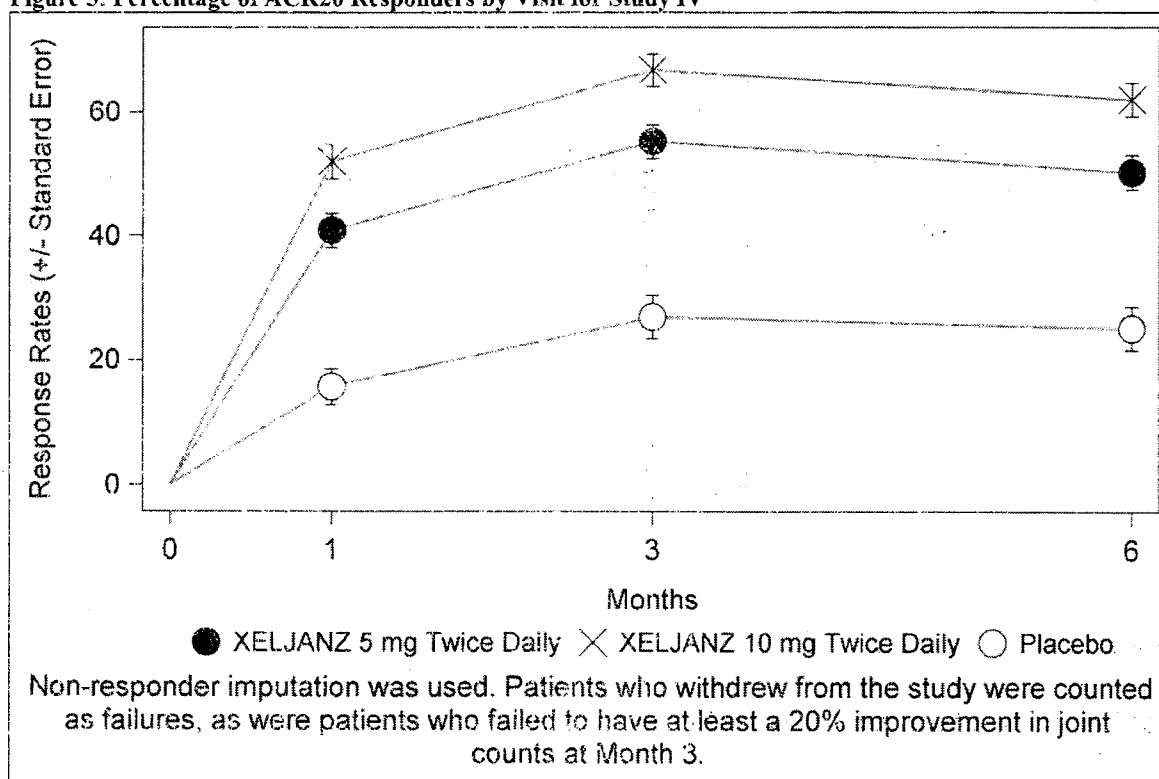
^aData shown is mean (Standard Deviation) at Month 3.

^bVisual analog scale: 0 = best, 100 = worst.

^cHealth Assessment Questionnaire Disability Index: 0 = best, 3 = worst; 20 questions; categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

The percent of ACR20 responders by visit for Study IV is shown in Figure 5. Similar responses were observed in Studies I, II, III and V.

Figure 5: Percentage of ACR20 Responders by Visit for Study IV



Physical Function Response

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving XELJANZ 5 and 10 mg twice daily demonstrated greater improvement from baseline in physical functioning compared to placebo at Month 3.

The mean (95% CI) difference from placebo in HAQ-DI improvement from baseline at Month 3 in Study III was -0.22 (-0.35, -0.10) in patients receiving 5 mg XELJANZ twice daily and -0.32 (-0.44, -0.19) in patients receiving 10 mg XELJANZ twice daily. Similar results were obtained in

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Studies I, II, IV and V. In the 12-month trials, HAQ-DI results in XELJANZ-treated patients were consistent at 6 and 12 months.

16 HOW SUPPLIED/STORAGE AND HANDLING

XELJANZ is provided as 5 mg tofacitinib (equivalent to 8 mg tofacitinib citrate) tablets: White, round, immediate-release film-coated tablets, debossed with “Pfizer” on one side, and “JKI 5” on the other side, and available in:

Bottles of 60:

NDC 0069-1001-01

Bottles of 180:

NDC 0069-1001-02

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature].

Do not repackage.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Inform patients of the availability of a Medication Guide, and instruct them to read the Medication Guide prior to taking XELJANZ. Instruct patients to take XELJANZ only as prescribed.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.



LAB-0445-1.0

MEDICATION GUIDE
XELJANZ (ZEL' JANS')
(tofacitinib)

Read this Medication Guide before you start taking XELJANZ and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about XELJANZ?

XELJANZ may cause serious side effects including:

1. Serious infections.

XELJANZ is a medicine that affects your immune system. XELJANZ can lower the ability of your immune system to fight infections. Some people have serious infections while taking XELJANZ, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections.

- Your healthcare provider should test you for TB before starting XELJANZ.
- Your healthcare provider should monitor you closely for signs and symptoms of TB infection during treatment with XELJANZ.

You should not start taking XELJANZ if you have any kind of infection unless your healthcare provider tells you it is okay.

Before starting XELJANZ, tell your healthcare provider if you:

- think you have an infection or have symptoms of an infection such as:
 - fever, sweating, or chills
 - muscle aches
 - cough
 - shortness of breath
 - blood in phlegm
 - weight loss
 - warm, red, or painful skin or sores on your body
 - diarrhea or stomach pain
 - burning when you urinate or urinating more often than normal
 - feeling very tired
- are being treated for an infection
- get a lot of infections or have infections that keep coming back
- have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB
- live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, or blastomycosis). These infections may happen or become more severe if you use XELJANZ. Ask your healthcare provider if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B or C

After starting XELJANZ, call your healthcare provider right away if you have any symptoms of an infection. XELJANZ can make you more likely to get infections or make worse any infection that you have.

2. Cancer and immune system problems.

XELJANZ may increase your risk of certain cancers by changing the way your immune system works.

- Lymphoma and other cancers can happen in patients taking XELJANZ. Tell your healthcare provider if you have ever had any type of cancer.
- Some people who have taken XELJANZ with certain other medicines to prevent kidney transplant rejection have had a problem with certain white blood cells growing out of control (Epstein Barr Virus-associated post transplant lymphoproliferative disorder).

3. Tears (perforation) in the stomach or intestines.

- Tell your healthcare provider if you have had diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people taking XELJANZ get tears in their stomach or intestine. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
- Tell your healthcare provider right away if you have fever and stomach-area pain that does not go away, and a change in your bowel habits.

4. Changes in certain laboratory test results. Your healthcare provider should do blood tests before you start receiving XELJANZ and while you take XELJANZ to check for the following side effects:

- **changes in lymphocyte counts.** Lymphocytes are white blood cells that help the body fight off infections.
- **low neutrophil counts.** Neutrophils are white blood cells that help the body fight off infections.
- **low red blood cell count.** This may mean that you have anemia, which may make you feel weak and tired.

Your healthcare provider should routinely check certain liver tests.

You should not receive XELJANZ if your lymphocyte count, neutrophil count, or red blood cell count is too low or your liver tests are too high.

Your healthcare provider may stop your XELJANZ treatment for a period of time if needed because of changes in these blood test results.

You may also have changes in other laboratory tests, such as your blood cholesterol levels. Your healthcare provider should do blood tests to check your cholesterol levels 4 to 8 weeks after you start receiving XELJANZ, and as needed after that. Normal cholesterol levels are important to good heart health.

See "What are the possible side effects of XELJANZ?" for more information about side effects.

What is XELJANZ?

XELJANZ is a prescription medicine called a Janus kinase (JAK) inhibitor. XELJANZ is used to treat adults with moderately to severely active rheumatoid arthritis in which methotrexate did not work well.

It is not known if XELJANZ is safe and effective in people with Hepatitis B or C.

XELJANZ is not for people with severe liver problems.

It is not known if XELJANZ is safe and effective in children.

What should I tell my healthcare provider before taking XELJANZ?

XELJANZ may not be right for you. Before taking XELJANZ, tell your healthcare provider if you:

- have an infection. See "What is the most important information I should know about XELJANZ?"
- have liver problems
- have kidney problems
- have any stomach area (abdominal) pain or been diagnosed with diverticulitis or ulcers in your stomach or intestines
- have had a reaction to tofacitinib or any of the ingredients in XELJANZ
- have recently received or are scheduled to receive a vaccine. People who take XELJANZ should not receive live vaccines. People taking XELJANZ can receive non-live vaccines.
- have any other medical conditions
- plan to become pregnant or are pregnant. It is not known if XELJANZ will harm an unborn baby.

Pregnancy Registry: Pfizer has a registry for pregnant women who take XELJANZ. The purpose of this registry is to check the health of the pregnant mother and her baby. If you are pregnant or become pregnant while taking XELJANZ, talk to your healthcare provider about how you can join this pregnancy registry or you may contact the registry at 1-877-311-8972 to enroll.

- plan to breastfeed or are breastfeeding. You and your healthcare provider should decide if you will take XELJANZ or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. XELJANZ and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:

- any other medicines to treat your rheumatoid arthritis. You should not take tocilizumab (Actemra®), etanercept (Enbrel®), adalimumab (Humira®), infliximab (Remicade®), rituximab (Rituxan®), abatacept (Orencia®), anakinra (Kineret®), certolizumab (Cimzia®), golimumab (Simponi®), azathioprine, cyclosporine, or other immunosuppressive drugs while you are taking XELJANZ. Taking XELJANZ with these medicines may increase your risk of infection.
- medicines that affect the way certain liver enzymes work. Ask your healthcare provider if you are not sure if your medicine is one of these.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take XELJANZ?

- Take XELJANZ as your healthcare provider tells you to take it.
- Take XELJANZ 2 times a day with or without food.
- If you take too much XELJANZ, call your healthcare provider or go the nearest hospital emergency room right away.

What are possible side effects of XELJANZ?

XELJANZ may cause serious side effects, including:

- See "What is the most important information I should know about XELJANZ?"
- **Hepatitis B or C activation infection** in people who carry the virus in their blood. If you are a carrier of the hepatitis B or C virus (viruses that affect the liver), the virus may become active while you use XELJANZ. Your healthcare provider may do blood tests before you start treatment with XELJANZ and while you are using XELJANZ. Tell your healthcare provider if you have any of the following symptoms of a possible hepatitis B or C infection:

○ feel very tired	○ fevers
○ skin or eyes look yellow	○ chills
○ little or no appetite	○ stomach discomfort
○ vomiting	○ muscle aches
○ clay-colored bowel movements	○ dark urine
	○ skin rash

Common side effects of XELJANZ include:

- upper respiratory tract infections (common cold, sinus infections)
- headache
- diarrhea
- nasal congestion, sore throat, and runny nose (nasopharyngitis)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of XELJANZ. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Pfizer at 1-800-438-1985.

How should I store XELJANZ?

Store XELJANZ at 68°F to 77°F (room temperature).

Safely throw away medicine that is out of date or no longer needed.

Keep XELJANZ and all medicines out of the reach of children.

General information about the safe and effective use of XELJANZ.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XELJANZ for a condition for which it was not prescribed. Do not give XELJANZ to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about XELJANZ. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about XELJANZ that is written for health professionals.

What are the ingredients in XELJANZ?

Active ingredient: tofacitinib citrate

Inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, HPMC 2910/Hypromellose 6cP, titanium dioxide, macrogol/PEG3350, and triacetin.

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This Medication Guide has been approved by the U.S. Food and Drug Administration.



LAB-0535-1.0
Issued: November 2012

27/06/2019

Trials

Administrative Actions

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Administrative Actions

No.	Document Title	Receipt/Delivery Date	Status	Receipt/Delivery No.
1	[Patent Application] Document according to the Article 203 of Patent Act ([특허출원]특허법 제203조에 따른 서면)	2015.10.13	Accepted (수리)	112015098879056
2	[Amendment to Description, etc.] Amendment ([명세서등 보정]보정서)	2015.10.13	Regarded as an acceptance of amendment (보정승인간주)	112015098973523
3	[Request for Examination] Request for Examination (Request for Preferential Examination) ([심사청구]심사청구(우선심사신청)서)	2015.10.13	Accepted (수리)	112015098974625
4	Notice of Acceptance (수리안내서)	2015.10.20	Completion of Transmission (발송처리완료)	152015016090718
5	Notification of change of applicant's information (출원인정보변경(경정)신고서)	2016.03.09	Accepted (수리)	412016502989108
6	Notification of reason for refusal (의견제출통지서)	2016.09.28	Completion of Transmission (발송처리완료)	952016069497132
7	[Designated Period Extension] Application of Period Extension(Reduction, Progress relief) ([지정기간연장]기간연장(단축, 경과구제)신청서)	2016.11.28	Accepted (수리)	112016116155965
8	[Amendment to Description, etc.] Amendment ([명세서등 보정]보정서)	2016.12.28	Regarded as an acceptance of amendment (보정승인간주)	112016128537153
9	[Opinion according to the Notification of Reasons for Refusal] Written Opinion(Written Reply, Written Substantiation) ([거절이유 등 통지에 따른 의견]의견(답변, 소명)서)	2016.12.28	Accepted (수리)	112016128541192
10	Decision to Refuse a Patent (거절결정서)	2017.05.23	Completion of Transmission (발송처리완료)	952017035781794

No.	Document Title	Receipt/Delivery Date	Status	Receipt/Delivery No.
11	[법정기간연장]기간연장(단축, 경과구제)신청서	2017.06.22	Accepted (수리)	112017059828633
12	법정기간연장송인서	2017.06.27	Completion of Transmission (발송처리완료)	152017008722702
13	Amendment to Description, etc(Reexamination) ([명세서등 보정]보정서(재심사))	2017.08.21	Acceptance of amendment (보정승인)	112017080273664
14	[Opinion according to the Notification of Reasons for Refusal] Written Opinion(Written Reply, Written Substantiation) ([거절이유 등 통지에 따른 의견]의견(답변, 소명 서))	2017.08.21	Accepted (수리)	112017080274610
15	Decision to Refuse a Patent (거절결정서)	2017.09.24	Completion of Transmission (발송처리완료)	952017067163940
16	[Divisional Application(International Application)] Patent Application ([분할출원(국제출원)]특허출원서)	2017.10.25	Accepted (수리)	112017105319001

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토파시티닙 경구용 지속 방출 투여 형태

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Trial Info

Kind International Application / New Application

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Request for an examination(Date) Y(2015.10.13)

Number of examination claims 22

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Abstract (Machine Translation)

The present invention relates to the sustained release formulations for the oral of the dopamine CT nib and its pharmaceutically acceptable salt. It has the pharmacodynamic characteristic which the agent written in the present application does with desirable.



Written Opinion(Written Reply, Written Substantiation)

- ◆ Documentary Classification Opinion according to the Notification of Reasons for Refusal.
- ◆ Applicant
 - Organization Name PFIZER INC.
 - Patent Customer Number 5-1998-084374-1
 - Relation with a Case Applicant.
- ◆ Agent
 - Name Yeong-Jun Yang
 - Agent number 9-1998-000361-9
 - Registration Number of General Power of Attorney 1999-037850-6
 - Name Yeong Kim
 - Agent number 9-1998-000047-8
 - Registration Number of General Power of Attorney 1999-016636-0
- ◆ Indication of Case
 - Application No. 10-2015-7029051
- ◆ Dispatch Number of Document of Submission Reason 9-5-2017-0357817-94
- ◆ Details of Opinion
 - It is the same as the attached document
- ◆ Purport
 - We respectfully submit the present document stating above with commissioner of KIPO (the President of the Intellectual Property Tribunal, and the Presiding Trial Examiner). The agent Yang YeongJun (the signature or the phosphorus) agent laver zero (the signature or the phosphorus)
- ◆ Attached Documents
 - Secure Information

Written Opinion

◆ Details of Opinion

While the applicant claims the re-examination on 2017 year May 23 decision on rejection about 2015-7029051 A (it the hereinafter says to be ' the present application ' this) the opinion is expressed like the next.

1. The gist of the reason for refusal.

[다시 심사한 결과]

심사 대상 청구항 : 제1항, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 32, 33, 34, 35항
 ○ 본원에 개제이유가 해소되지 않은 부분과 관련 법조항:

순번	기전이유가 해소되지 않은 부분	관련 법조항
1	청구항 제1항 내지 제28항, 제32항, 제33항	특허법 제20조제2항
2	발명의 상세한 설명	특허법 제42조제3항제1호



II. The correction of application.

1. In claim 1 ~ 4 and 15, specifically amount of the dopamine CT nib was limited based on the present application embodiment. According to such correction, 26 was deleted with overlapped claim 9 ~ 12, 18 ~ 21, and 25 and claim quoting relation was adjusted according to claim deletion.
2. In claim 1 and 2, the configuration which was "the rate of the geometric average plasma Cmax large Cmin is 10 ~ 100" was limited with addition.
3. The expression called "OSS bad luck" this the expression was unified into "OSS young rice plant".

The Amendment in which the detail contents of amendment is submitted on the same date of the written opinion is wanted to refer.

III. The opinion of the applicant about the decision on rejection.

1. About the reason 1 (inventive step lack) of the decision on rejection.

In the decision on rejection, it determined that the inventive step was deficient due to the difference even if it had the cited invention and difference in the point which the invention limited to the PK parameter like the average steady-state minimum serum concentration (Cmin) but such PK parameter the derivation was easy through the simulation of the software program and the detailed description of the invention was looked at by the reason of to having the better effect as compared with the agent of the cited invention.

But as shown in the circle 2011.8.12 A one's deceased father. 2010 Huh 7488 verdict (reference materials 1), factor including the kind of the emission control material of the emission control formulation like the prolonged release administration type and mixture form and rate etc.s can be restricted by the range by limiting the PK profile. Therefore it is the element of the invention in which the property like the PK profile or property limits the description of the invention and as long as the emission control formulation of the active ingredient in which the prior art is just identical is disclosed but the configuration of corresponding to the PK profile is not disclosed the novelty and inventive step of the object invention in which this has the characteristic cannot be denied in this with the prior art.

Hereinafter, specifically it will look into about such point.

a. The characteristic of the present invention.

The semi-permeable curtain coating surrounding the core in which the invention includes the dopamine CT nib of the form of its pharmaceutically acceptable salt of the dopamine CT nib of 11 mg or the equivalent and OSS young rice plant and the core including the number - insoluble polymer is included and it at this time is the once a day administration type in which the number - insoluble polymer is the cellulose acetate and it is the continuance release dosage form in which such administration type has the specific PK parameter / melting profile (in other words, the rate of the geometric average plasma Cmax large Cmin) like as described on the present case request range and the dopamine CT nib or its pharmaceutically acceptable salt is mainly delivered to the object with the osmotic pressure.

It paid attention to the necessity of the agent in which the dopamine CT nib was emitted for the improvement of the drug-fast (tolerability) profile and stability to the uniform concentration through the relative long term and the dopamine CT nib continuance - release dosage form of the prior art had the advantage which nearly made no blood level change at the patient. But the bioavailability of the dopamine CT nib was reduced as the discharge last time was surprisingly extended and in order to provide the blood level having with effect, the dopamine CT nib increased in the continuance release dosage form of the amount needed to be administered to the object and



the necessity was confirmed (the specification [0008] and [0009] short circuit reference). But in that case, the JAK3 and/or the JAK1 signal transduction increasing amount of the dopamine CT nib the excessively can be suppressed and the immune system of the body can be injured. Therefore, the normal technical engineer tried to avoid the level rising of the maximum serum concentration of the dopamine CT nib on at the time of the invention.

In order that the present application inventors surprisingly provided optimal PK profile (it rates the optimal exposure and optimal $C_{max,ss}$ / $C_{min,ss}$ while in other words, the level rising of the maximum serum concentration is avoided) toward 1 - 1 time administration of the dopamine CT nib the administration type in which the prolonged release period was shorter discovered for the first time being sweet with be desirable. (the specification [0010], and [0011] and [0014] short circuit reference).

The invention relates to therefore, patent this it was soft with provision but the formulation in which 1 1 circuit improved the convenience and compliance by providing the administration type in which the rate of the geometric average plasma C_{max} large C_{min} had about 10 ~ about 100 while having the core and the semi-transmissive cellulose acetate curtain coating including the salt of the dopamine CT nib of 11 mg or the equivalent and OSS young rice plant based on such discovery was succeeded in. And it reaches the application in order to be protected.

b. The inventive step of the invention compared for the cited invention.

(1) Because of disclosing or suggesting there is no cited invention about the PK parameter of the invention at all.

Whereas it has the technical feature which the invention mentions in the upper part the once a day osmosis administration type of the dopamine CT nib in which the cited invention has the PK property / solubility profile of the invention is unable to be disclosed and the content of technique which actually is arranged to the invention is enlightened as to.

That is, as shown in it before looks into it enlightens as to be based on the discovery that the discharge last time which is shorter than that of the invention does with desirable but the cited invention be gradually emitted like the lower part about the control discharge material of the dopamine CT nib to the uniform concentration through the relative long term and has to have the advantage which nearly makes no blood level change at the patient and recognition and the content running counter to each other of the present invention are suggested.

" The administration type of this invention discovered in spite of the high solubility of another place CT nib (it is identical with the dopamine CT nib) that another place CT nib was gradually emitted through the relative long time and the drug had the advantage maintained for the long time by the uniform concentration in the blood flow. Due to this, the administration like the once a day administration becomes possible. The administration of the oral dosage form of this invention nearly does not give the change to the blood level. It means avoiding that for the cycle when the therapeutic dose is insufficient, is connected after the cycle when the therapeutic dose as to the this, is provisionally excessive. ("Summary of the Invention" reference of the cited invention 2 ~ 3 side)

In total the invention comes, the fact that the fact had the motive for development about the agent having the discharge last time long as long as it was possible like the cited invention is confirmable in statements (2016 year January 11 statement which in the examination process of the corresponding US patent applicant US 14/211,659 of the present application of the Kouch you Joseph doctor who is the expert of the inventor interest agent development section of the present application suggests) of the reference materials 2. That is, the U.S. nutraceutical wife is *** (XELJANZ for the bis die administration the invention is developed it illustrates in the eighth the short circuit of the reference materials 2. Therefore, an object of the invention is to provide the



agent having the discharge last time long as long as it is possible if it considered the improved drug delivery system development of the dopamine CT nib.

Moreover, it illustrates that the discharge material having the advantage in which the content of the cited invention the dopamine CT nib is gradually emitted to the uniform concentration through the relative long term and which makes no blood level change at the patient and in which the Kouch you doctor avoids the cycle of the shortage therapeutic dose and which is known is suggested (the eighth the short circuit the reference of the reference materials 2).

In short, it is clear to be the literature which suggests the content that rather runs counter to each other while the cited invention ever does not suggest the PK profile which is similar to the invention.

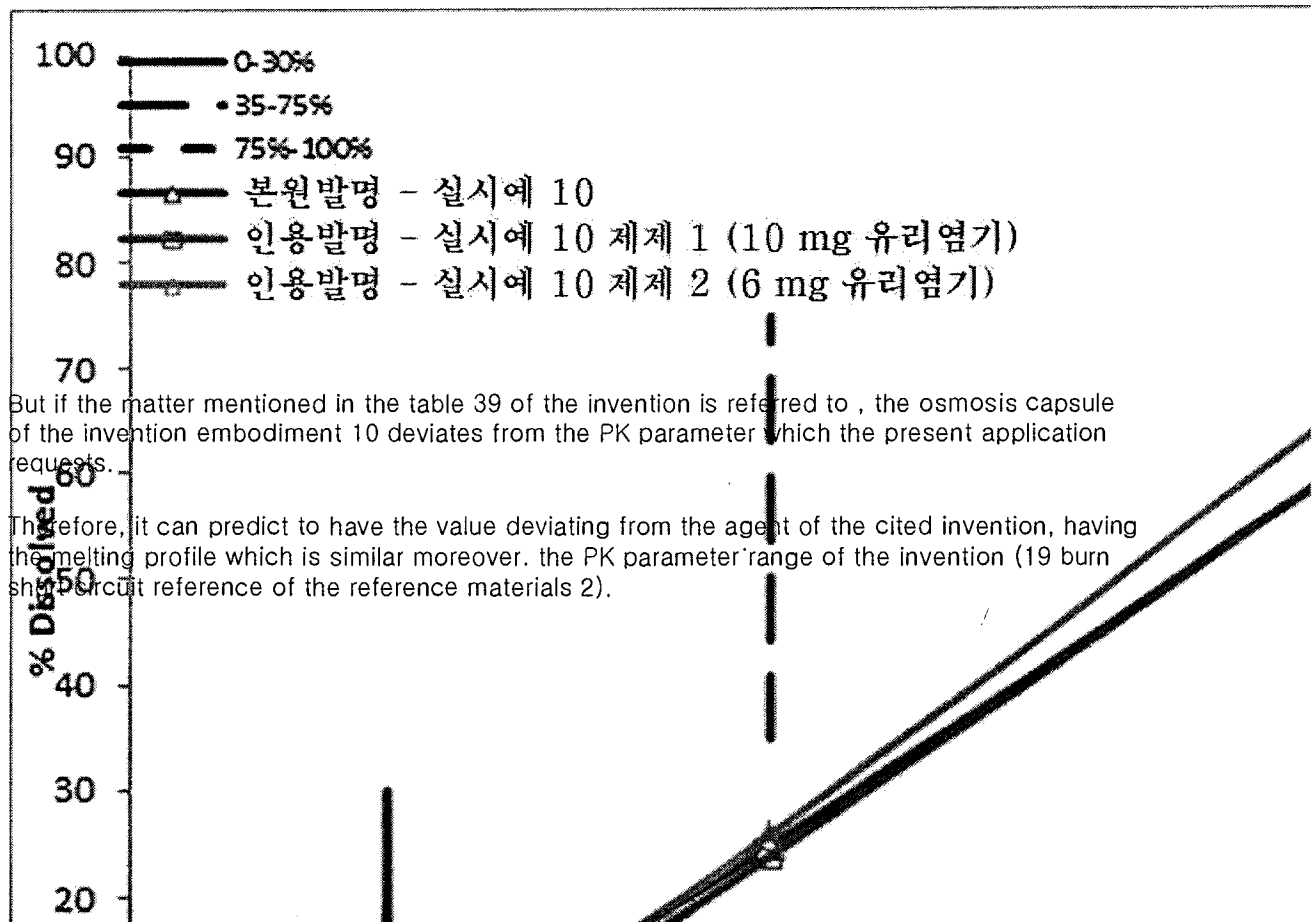
(2) The cited invention has the invention and the PK parametric value of the invention it has the different melting profile.

As shown in the reference materials 2, the Kouch you doctor manufactured two kinds of osmosis refining agent based on the embodiment 10 of the cited invention. The first agent the (the agent 1" of " cited invention embodiment 10) contains the dopamine CT nib citrate (the dopamine CT nib free base of 10 mg) of 16.2 mg and the second agent the (the agent 2" of " cited invention embodiment 10) contains the dopamine CT nib citrate (the dopamine CT nib free base of 6 mg) of 10 mg (9 ~ 15 burn short circuit reference of the reference materials 2).

In this way, the agent 1 and 2 which became with formulation were tested in the short circuit [0052] (the current claim 3) of the invention like as described to the dissolution test 1 standard and the melting ability was determined (16 burn short circuit reference of the reference materials 2).

As shown in it is proved in the table summarized with the table 1 of the reference materials 2 and fig. 1 and lower part the melting ability of embodiment 10 (the agent 1 and agent 2) of the cited invention deviate from the melting profile of the invention.

And as shown in the melting ability, of the embodiment 10 of the cited invention is the following table and the graph shown, embodiment 10 and the fact that it is similar of the present invention can be known.

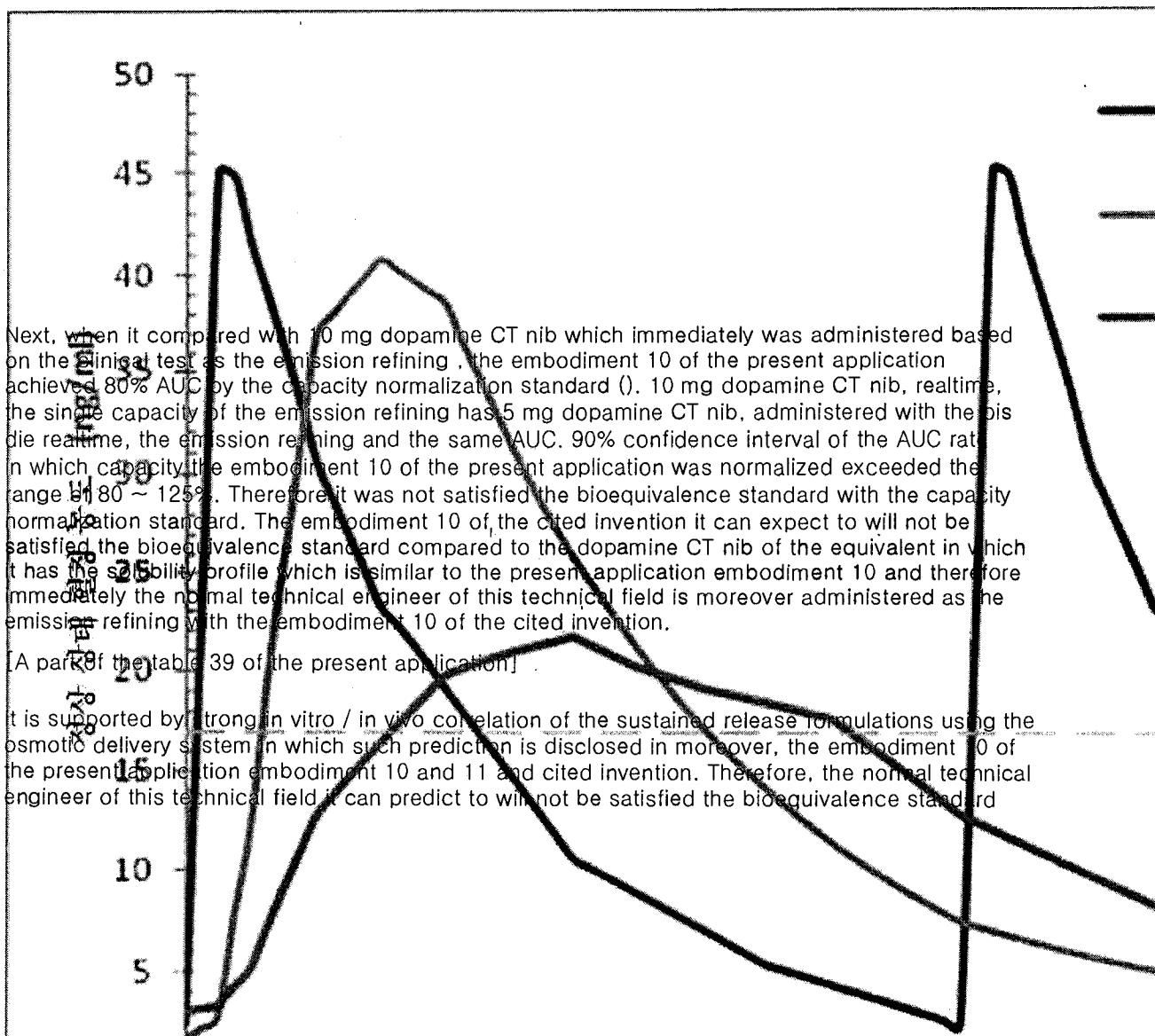




In fact, it is proved through reference materials 3s (2017 year February 2 statement which in the examination process of US 14/211,659 the Kouch you Joseph doctor suggests) that the invention and cited invention have the PK performance which is sharply dissimilar.

Specifically, fig. 1 illustrating with lower part compared the present application embodiment 14 (immediately it is evaluated in the present application embodiment 16 : the emission refining according to the research B with 5 mg) for the bis die administration, and the calculated steady-state serum concentration of the present application embodiment 10 (in the present application embodiment 15 : 20 mg tonic capsule, it is evaluated according to the research A) for the present application embodiment 1 (in the present application embodiment 17 : 11 mg osmosis refining agent, it is evaluated according to the research C) for the once a day administration and once a day administration and it calculated about 10 mg administering strength (dosage strength) (the five times short circuit reference of the reference materials 3). Before, it has the solubility profile which is similar in the comparison with the embodiment 10 of the cited invention is the present application embodiment 10 it looks into. Therefore it will predict that the normal technical engineer of this technical field has the steady-state serum concentration which is similar to the calculated steady-state serum concentration based on the embodiment 10 of the cited invention, moreover, the present application embodiment 10 (the sixth the short circuit the reference of the reference materials 3). In the meantime, the steady-state serum concentration corresponding to the present application embodiment 1 (the corresponding in the present application demand invention) and embodiment 10 (it has the solubility profile deviating from the claims and it is similar to the embodiment 10 of the cited invention) is classified like the lower part. In this way, the osmagent performance of the cited invention is fundamentally different from the PK performance of the formulation according to the present invention.

[Fig. 1]

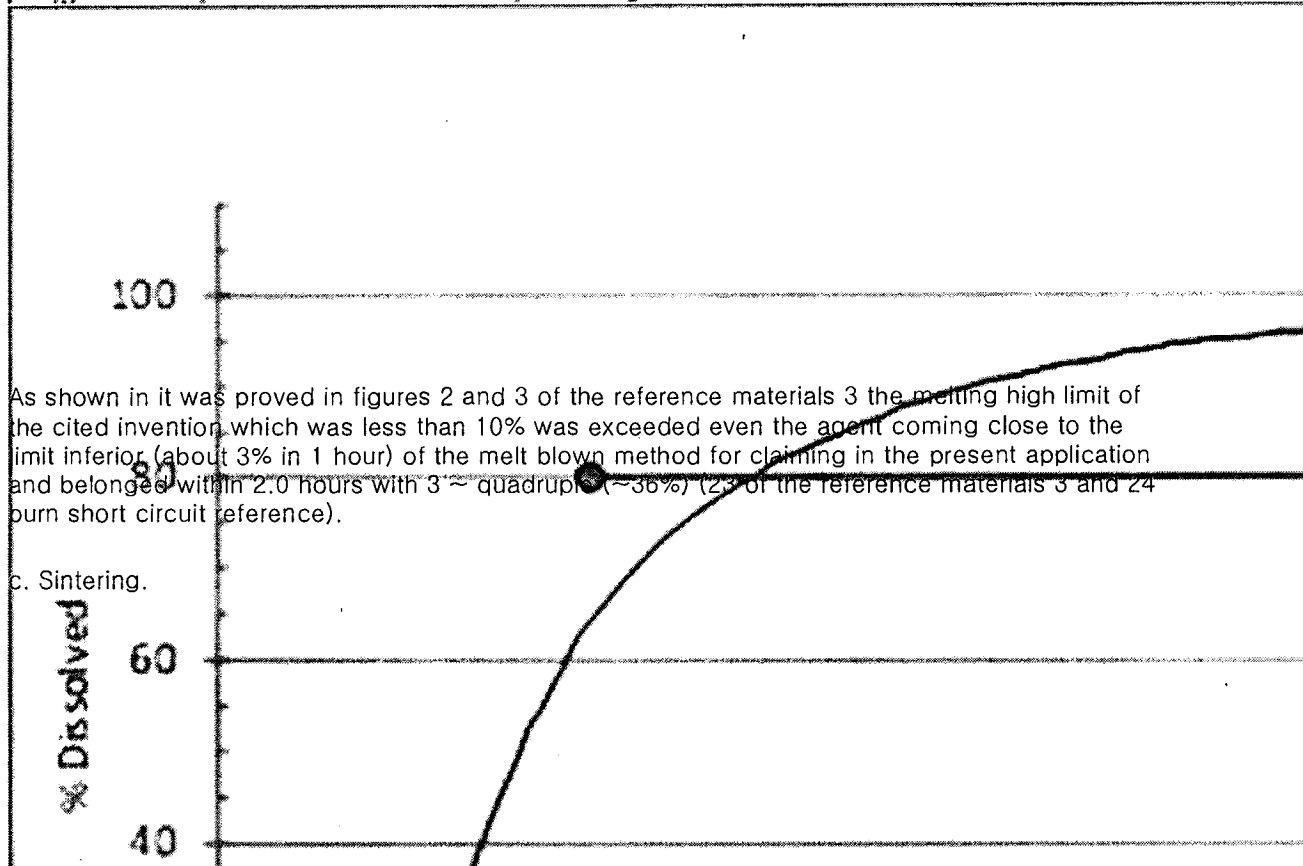
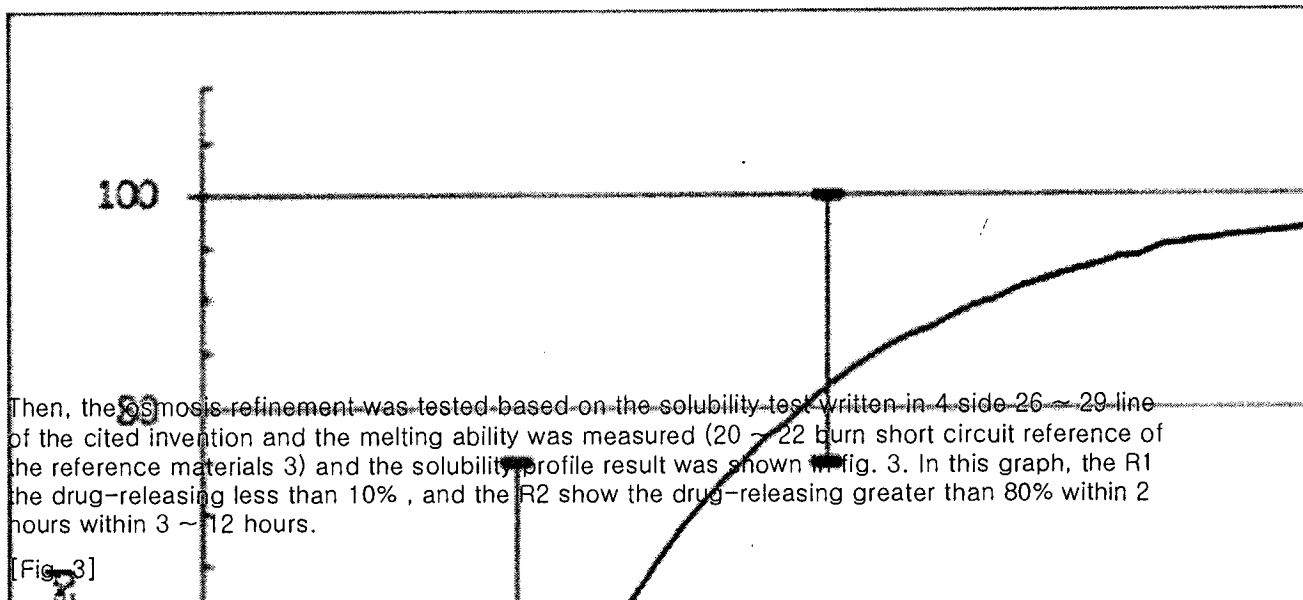




compared to the dopamine CT nib of the equivalent which immediately is moreover administered as the emission refining with the embodiment 10 of the cited invention.

Moreover, the osmosis refinement approaching the limit inferior of the solubility profile which claimed in the present application was manufactured under the supervision of the Kouch you doctor (7 ~ 16 burn short circuit reference of the reference materials 3) and the osmosis refinement was tested based on the dissolution test written in the present specification short circuit [52] (claim 3) and the melting ability was measured (17 ~ 19 burn short circuit reference of the reference materials 3). The solubility profile result clearly came close to the limit inferior of the element of the demand invention (the lower part is 2 reference). In this graph, the E1, and the E2 and E3 the dopamine CT nib less than 30% or its pharmaceutically acceptable salt is dissolved within 1 hour and the dopamine CT nib less than 75% over 35% or its pharmaceutically acceptable salt is dissolved within 2.5 hours and the dopamine CT nib more than 75% or its pharmaceutically acceptable salt is dissolved (E3) and it corresponds to the solubility profile of claim 3 within 5 hours.

[Fig. 2]





In the above, as shown in it looks into the cited invention discloses about the PK parameter / melting profile of the invention or it is unable to be suggestive. In addition the invention, different PK and the agent having the solubility profile are disclosed in fact.

According to the Patent Act circle 2010 Huh 2336 verdict, by the reason of looking as the configuration where the analogue did not show the configuration including the mixture form of the configuration elements of the formulation and rate etc. as the configuration of acting on the specify element in the comparative object invention and the concentration profile was input among the blood of the object invention in the comparative object invention the novelty and inventive step of the object invention were acknowledged.

Then, the content actually that the cited invention is arranged to the invention is enlightened as to. In addition as before looked into it cannot look as the configuration in which the PK parameter of the invention is input in the cited invention. Therefore it cannot be denied with the inventive step of the invention, moreover, the cited invention the content is clear. It hopes in their heart to collect the reason for refusal looked with the advantage amount hash.

2. About the reason 2 (detailed description of the invention deficiency in the description) of the decision on rejection.

According to "the correction of II. application" item, it limited within the range this which specifically was guaranteed by the embodiment of the present application. And the normal technical engineer as to the corrected present case request range, easily will be able to perform the invention with reference to the detailed description of the invention.

With respect to this, in the decision on rejection, that the normal technical engineer specifically understood the formulation of the claims in consideration of point if the emission pattern ran on the coating according to the polymer kind and the mixing ratio configured and it could reproduce point was indicated. But that the selection standard about the configuration elements could become the limitation of the PK profile as before inspected closely in the Patent Act circle 2010 Huh 7488 verdict it acknowledged. In addition it related like the lower part with the description requisite of the claims. That the content was considerable although to the PK profile was written in the claims and the specifically was not written about the selection and manufacture of the individual material the invention could be enough understood as the content of the embodiment and the PK profile to achieve if it was the normal technical engineer and can reproduce it determined.

It hopes in their heart that the advantage *** hash , and the reason for refusal 2 collect.

IV. The state of examination of the correspondence patent application.

For your reference, the application US14/211,659 A of the present application was granted a patent and the correspondence patent application at Japanese patent was registered to the JP6041823. Japanese hopes in their heart to refer to the advantage examination.

V. Outcome.

In the above, that the matter indicated with the opinion of the applicant and correction of the application explained in the reason for refusal was altogether solved it is taken into consideration. It reexamines as the Written Opinion and the submitted Amendment and the present application is preferred to do with Patent decision.

[Reference materials]

1. 2011.8.12 one's deceased father the Patent Act circle 2010 Huh 7488 Written judgement.
2. Copy of the manifesto under 2016 year January 11 37 C F. R. § 1.132 and excerpted translation.



3. Copy of the manifesto under 2017 year February 2 37 C F. R. § 1.132 and excerpted translation.



सत्यमेव जयते

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FORM 26
THE PATENT ACT, 1970
(39 of 1970)

241

&

THE PATENT RULES, 2003

[FORM FOR AUTHORIZATION OF A PATENT AGENT/OR ANY
PERSON IN A MATTER OF PROCEEDING UNDER THE ACT]

(Sections 127 and 132; Rule 135)

I, Sujata Sharma, D/O Lt. Birendranath Paul residing at House No. 328, Chotta Ayma, Po. Nimpura, Dist. Medinipur West, Kharagpur, West Bengal - 721304 hereby appoint and authorize Ms. Bitika Sharma, Mr. Sudeep Chatterjee, Mr. Tejveer Singh Bhatia, Ms. Saya Choudhary, Ms. Anusuya Nigam, Ms. Archana Singh, Mr. Vivek Ranjan, Mr. Ashutosh Kumar, Mr. Devanshu Khanna, Mr. Adithya Jairaj, Mr. Prateek Sehrawat, Ms. Namrita Kochhar, Ms. Nitya Sharma, Ms. Mansi Gupta, Ms. Vrinda Pathak and Mr. Luv Virmani advocates and agents of **Singh & Singh Law Firm LLP**, C-139, Defence Colony New Delhi - 110 024, India to act on our behalf in connection with all matters pertaining to obtaining permission to make patent applications outside India for our inventions made in India, grant of patent, renewals, oppositions, amendments or any other proceedings arising therefrom including signing and filing patent applications, written statements, reply statements, affidavits in evidence, interlocutory applications, renewals, assignments and any other applications or petitions, filing appeals, review, revisions and any other documents as may be required and to appear in all forums including Courts, Tribunals, Appellate Board, Registry, Commissions or any other special statutory authority and to attend to all hearings, engage agents/attorney(s) for doing the above mentioned acts and do any other things as may be required to be done in the registration/renewals/rectification proceedings pertaining to our patents in India.

We request that all notices, requisitions and communication relating thereto may be sent to such person at the above address unless otherwise specified.

We hereby revoke all previous authorization, if any made, in respect of same matter or proceeding.

We hereby assent to the action already taken by the said person in the above-matter.

Dated this 20th Day of June, 2019

Sujata Sharma

Sujata Sharma

To,
The Controller of Patents
The Patent Office
At New Delhi/Chennai/Mumbai/Kolkata