Title: NOVEL POLYMORPHS OF ETORICOXIB

Abstract: The present invention provides new crystalline forms of Etoricoxib of formula I or mixture thereof. Another objective of the present invention is to provide a process for the preparation of novel forms of Etoricoxib or mixture thereof. Yet another objective is to provide novel crystalline forms or mixture of Etoricoxib which are stable. Yet another objective is to provide a process for the preparation of pharmaceutical composition comprising the said novel forms of Etoricoxib. An embodiment of the present invention pharmaceutical compositions containing one or more of the new forms described in the present invention is provided. A further objective of the present invention is to provide uses of the novel forms of Etoricoxib for the treatment of COX-2 mediated disorders in a mammal including human.
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
NOVEL POLYMORPHS OF ETORICOXIB

Field of invention:
The present invention describes novel forms of Etoricoxib, process for their preparation and pharmaceutical compositions containing them. More particularly, the present invention reveals new polymorphs of Etoricoxib, process for preparing them and various pharmaceutical compositions containing them. The present invention also describes the method of treatment of COX-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of the said novel polymorph and pharmaceutical composition containing them. The present invention relates to the use of novel polymorphs of Etoricoxib disclosed herein and pharmaceutical compositions containing them for the treatment of COX-2 mediated disorders.

Background of the invention:
Etoricoxib is a selective COX-2 inhibitor which has been shown to be as effective as non-selective non-steroidal anti-inflammatory drugs in the management of chronic pain in rheumatoid arthritis, osteoarthritis and other COX-2 mediated disorders. Etoricoxib is 5-chloro-6'-methyl-3-[4-methylsulfonyl]phenyl]-2,3'-bipyridine having structural formula I.

![Etoricoxib](image)

Etoricoxib is a potent and selective cyclooxygenase-2 (COX-2) inhibitor. Etoricoxib belongs to a class of drugs known as COX-2 inhibitors that are used in the treatment of COX-2 mediated disorders. The therapeutic application of Etoricoxib as a COX-2 inhibitor is disclosed in WO 96/10012 and WO 96/16934. This compound is disclosed in US 5861419 which is hereby incorporated by reference in its entirety.

A process for preparation of this compound is disclosed in US6040319 which is hereby incorporated by reference in its entirety.
WO 01/992230 discloses Form V of this compound. It further discloses five polymorphic forms, one amorphous form and two hydrated forms, which also hereby incorporated by reference in its entirety. Thus it describes eight new forms of Etoricoxib.

Our endeavor of developing new forms of Etoricoxib has led to the development of eight new forms of Etoricoxib.

The present invention discloses eight different crystalline forms of Etoricoxib i.e. Form IX, Form X, Form XI, Form XII, Form XIII, Form XIV, Form XV and Form XVI.

**Summary of the Invention:**

Accordingly, the present invention provides new crystalline forms of Etoricoxib of formula I or mixture thereof.

![Etoricoxib](image)

Another objective of the present invention is to provide a process for the preparation of the novel forms of Etoricoxib or mixture thereof.

Yet another objective is to provide novel crystalline forms or there mixture of Etoricoxib which are stable.

Yet another objective is to provide a process for the preparation of pharmaceutical composition comprising the said novel forms of Etoricoxib.

As an embodiment of the present invention pharmaceutical compositions containing one or more of the new forms described in the present invention is provided.

A further objective of the present invention is to provide uses of the novel forms of Etoricoxib for the treatment of COX-2 mediated disorders in a mammal including human.

**Brief Description of Drawings**

Fig 1: X-ray powder diffraction (XRD) pattern of novel form IX of Etoricoxib
Fig 2 : X-ray powder diffraction (XRD) pattern of novel form X of Etoricoxib
Fig 3 : X-ray powder diffraction (XRD) pattern of novel form XI of Etoricoxib
Fig 4 : X-ray powder diffraction (XRD) pattern of novel form XII of Etoricoxib
Fig 5 : X-ray powder diffraction (XRD) pattern of novel form XIII of Etoricoxib
Fig 6 : X-ray powder diffraction (XRD) pattern of novel form XIV of Etoricoxib
Fig 7 : X-ray powder diffraction (XRD) pattern of novel form XV of Etoricoxib
Fig 8 : X-ray powder diffraction (XRD) pattern of novel form XVI of Etoricoxib

Description of Invention:

The present invention provides novel crystalline forms of Etoricoxib which have different XRD patterns than so far known forms.

The novel forms of Etoricoxib are characterized by unique XRD pattern as shown in fig. 1 to 8 which are different from various forms reported in application nos. WO 01/92230, WO 96/10012 and WO 96/16934.

The present invention also discloses processes for the preparation of the said novel forms of Etoricoxib and pharmaceutical compositions containing them and their use in medicine particularly in the treatment of COX-2 mediated disorders.

Preparation of Form IX

The novel form IX of Etoricoxib may be prepared by a process comprising of the following steps:

a. Preparing a solution of Etoricoxib in toluene at a suitable temperature selected in the range of 60 °C to 75 °C.

b. Cooling the solution.

c. Adding of an antisolvent selected from the group consisting of heptane, diisopropyl ether and the like or mixtures thereof. (in two equal lots.)

d. Filtering and drying the separated solids to obtain Form IX of Etoricoxib.

Form IX is characterized by its unique XRD pattern as given in Fig 1.

Preparation of Form X

The novel form X of Etoricoxib may be prepared by a process comprising of the following steps:
a. Preparing a solution of Etoricoxib in toluene at a suitable temperature selected in the range of 60 °C to 75 °C.
b. Cooling the solution.
c. Isolating the product by adding suitable antisolvent heptane (in one lot).
d. Filtering and drying the separated solids to obtain Form X of Etoricoxib.

Form X is characterized by its unique XRD pattern as given in Fig 2.

Preparation of Form XI

The novel form XI of Etoricoxib may be prepared by a process comprising of the following steps:

a. Preparing a solution of Etoricoxib in ethyl acetate or isopropyl acetate at room temperature.
b. Filtering the reaction mixture.
c. Concentrating the filtrate under reduced pressure to give solid residue,
d. Isolating the product by adding suitable antisolvent selected from the group consisting of hexane, diisopropyl ether and the like or mixtures thereof.
e. Filtering and drying the separated solids to obtain Form XI of Etoricoxib.

Form XI is characterized by its unique XRD pattern as given in Fig 3.

Preparation of Form XII

The novel form XII of Etoricoxib may be prepared by a process comprising of the following steps:

a. Preparing a solution of Etoricoxib in ethyl acetate at room temperature,
b. Filtering the reaction mixture.
c. Concentrating the filtrate under reduced pressure to give solid residue.
d. Isolating the product by adding suitable antisolvent hexane.
e. Filtering and drying the separated solids to obtain the Form XII of Etoricoxib.

Form XII is characterized by its unique XRD pattern as given in Fig 4.
Preparation of Form XIII

The novel form XIII of Etoricoxib may be prepared by a process comprising of the following steps:

a. Preparing a solution of Etoricoxib in isopropyl alcohol at room temperature.
b. Filtering the reaction mixture.
c. Isolating the product by cooling to 0 °C.
d. Filtering and drying the isolated product to obtain Form XIII of Etoricoxib.

Form XIII is characterized by its unique XRD pattern as given in Fig 5.

Preparation of Form XIV

The novel form XIV of Etoricoxib may be prepared by a process comprising of the following steps:

a. Preparing a solution of Etoricoxib in ethyl acetate at room temperature, and washed with water.
b. Separating the organic layer and treating with silica-gel and charcoal.
c. Drying and concentrating under reduced pressure to get solid residue.
d. Isolating the product by adding suitable antisolvent such as diisopropyl ether.
e. Filtering and drying the isolated product to obtain Form XIV of Etoricoxib.

Form XIV is characterized by its unique XRD pattern as given in Fig 6.

Preparation of Form XV

The novel form XV of Etoricoxib may be prepared by a process comprising of the following steps:

a. Preparing a solution of Etoricoxib in aqueous HCl at atmospheric temperature.
b. Treating the solution with toluene.
c. Separating the aqueous layer, treating it with charcoal and filtering it.
d. Isolating the material by basifying the filtrate using ammonia solution.
e. Filtering and drying the residue to obtain the Form XV of Etoricoxib.
Form XV is characterized by its unique XRD pattern as given in Fig 7.

**Preparation of Form XVI**

The novel form XVI of Etoricoxib may be prepared by a process comprising of the following steps:

a. Preparing a solution of Etoricoxib in isopropyl acetate at a temperature selected from the range 70–75 °C.
b. Cooling the solution to 0 °C.
c. Separating, filtering and drying the solids to obtain the Form XVI of Etoricoxib.

Form XVI is characterised by its unique XRD pattern as given in Fig 8.

The various pharmaceutical compositions and formulations of the novel forms of Etoricoxib of the present invention can be prepared by known processes.

The dosage of novel forms of Etoricoxib of the present invention is selected according to the usage and may vary as per the requirement of the patient.

The novel forms of Etoricoxib of the present invention can be used for the treatment of COX-2 mediated disorders such as osteoarthritis, rheumatoid arthritis, pain and inflammatory disorders in a mammal including human.

The novel forms of Etoricoxib are characterized by unique XRD pattern which are different from the various forms previously reported.

The process described in the present invention is illustrated in the following examples which should not be construed to limit the scope of the invention in any way.

**EXAMPLE 1**

**PREPARATION OF FORM --IX OF ETORICOXIB**

Pure Etoricoxib (1 gm) was dissolved in toluene at a suitable temperature between the range from 60°C to 75°C (in different batches) and the solution was cooled. Then product was isolated by drop wise addition of heptan (in two equal lots having interval
of 5 minutes). The product was filtered and dried in an oven to constant weight to obtain form IX of Etoricoxib (88% yield, 99.08 % purity).

**EXAMPLE 2**

**PREPARATION OF FORM -X OF ETORICOXIB**

Pure Etoricoxib (1 gm) was dissolved in toluene at a suitable temperature between the range from 60°C to 75°C (in different batches) and the solution was cooled. Then material was isolated with antisolvent such as heptane (one lot) to get the reaction mixture. The crystals were filtered and dried in an oven to constant weight to obtain form X of Etoricoxib (41% yield, 99.92 % purity).

**EXAMPLE 3**

**PREPARATION OF FORM -XI OF ETORICOXIB**

Pure Etoricoxib (1 gm) was dissolved in ethyl acetate or isopropyl acetate at atmospheric temperature. After that the reaction mixture was filtered through hyflow bed and the filtrate was concentrated under reduced pressure to obtain solid residue which was isolated by a solution of hexane:diisopropyl ether (1:1). The isolated residues were filtered and dried in an oven to constant weight to obtain form XI of Etoricoxib (82% yield, ≥ 98% purity).

**EXAMPLE 4**

**PREPARATION OF FORM -XI OF ETORICOXIB**

Pure Etoricoxib (1 gm) was dissolved in ethyl acetate or isopropyl acetate at atmospheric temperature. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to obtain solid residue which was isolated by a solution of hexane. The isolated residues were filtered and dried in an oven to constant weight to obtain form XI of Etoricoxib (82% yield, ≥ 98% purity).

**EXAMPLE 5**

**PREPARATION OF FORM -XII OF ETORICOXIB**
Pure Etoricoxib (1 gm) was dissolved in ethyl acetate at atmospheric temperature. After that the reaction mixture was filtered & concentrated under reduced pressure to give solid residue which was isolated by adding antisolvent hexane. The isolated residues were filtered and dried in an oven to constant weight to obtain form XII of Etoricoxib (85% yield, ≥ 98% purity).

EXAMPLE 6
PREPARATION OF FORM -XIII OF ETORICOXIB

Pure Etoricoxib (1 gm) was dissolved in isopropyl alcohol at atmospheric temperature. After that the reaction mixture was filtered and the solution was cooled at 0°C to isolate the solids which were filtered and dried in an oven to constant weight to get form XIII of Etoricoxib (61% yield, ≥ 98% purity).

EXAMPLE 7
PREPARATION OF FORM -XIV OF ETORICOXIB

Pure Etoricoxib (1 gm) was dissolved in ethyl acetate at atmospheric temperature. The solution was washed with water and the organic layer was separated and treated with silica gel and charcoal, then dried and concentrated under reduced pressure to get solid residue. Antisolvent diisopropyl ether was used to isolate the product. The product was filtered and dried in an oven to constant weight to get form XIV of Etoricoxib (83% yield, ≥ 98% purity).

EXAMPLE 8
PREPARATION OF FORM -XV OF ETORICOXIB

Pure Etoricoxib (1 gm) was dissolved in aqueous HCl solution (pH=2) at atmospheric temperature. The solution was washed with toluene and aqueous layer was separated and treated with charcoal and then filtered. Basifying the filtrate by using 25% ammonia solution isolated the product. The product was filtered and dried in an oven to constant weight to get form XV of Etoricoxib (69% yield, ≥ 98% purity).
EXAMPLE 9
PREPARATION OF FORM -XVI OF ETORICOXIB

Pure Etoricoxib (1 gm) was dissolved in isopropyl acetate at suitable temperature between 70°C-75°C. Then the reaction mixture was cooled at 0°C to isolate the product. The product was filtered and dried in an oven to constant weight to get form XVI of Etoricoxib (60% yield, ≥ 98% purity).
We claim:

1. A novel polymorph of Etoricoxib characterized by X-ray diffraction pattern substantially as depicted in fig 1.


3. A novel polymorph of Etoricoxib characterized by X-ray diffraction pattern substantially as depicted in fig 2.


5. A novel polymorph of Etoricoxib characterized by X-ray diffraction pattern substantially as depicted in fig 3.


7. A novel polymorph of Etoricoxib characterized by X-ray diffraction pattern substantially as depicted in fig 4.


9. A novel polymorph of Etoricoxib characterized by X-ray diffraction pattern substantially as depicted in fig 5.

11. A novel polymorph of Etoricoxib characterized by X-ray diffraction pattern substantially as depicted in fig 6.


13. A novel polymorph of Etoricoxib characterized by X-ray diffraction pattern substantially as depicted in fig 7.


15. A novel polymorph of Etoricoxib characterized by X-ray diffraction pattern substantially as depicted in fig 8.


17. A process for the preparation of the novel polymorph of Etoricoxib as claimed in claims 1 or 2 comprising,

   a) Contacting/Dissolving Etoricoxib with toluene at 60-75 °C temperature followed by cooling.

   b) Adding suitable antisolvent selected from the group consisting of heptane, diisopropyl ether or mixtures thereof, in two equal lots.

   c) Removing the solvent.

18. A process for the preparation of the novel polymorph of Etoricoxib as claimed in claims 3 or 4 comprising,

   a) Contacting/Dissolving Etoricoxib with toluene at 60-75 °C temperature followed by cooling.

   b) Adding suitable antisolvent selected from the group consisting of heptane, diisopropyl ether or mixtures thereof, in one lot.

   c) Removing the solvent.
19. A process for the preparation of the novel polymorph of Etoricoxib as claimed in claims 5 or 6 comprising,
   a) Contacting/Dissolving Etoricoxib with a suitable solvent ethyl acetate and isopropyl acetate at room temperature.
   b) Filtering the solution.
   c) Concentrating the filtrate.
   d) Adding an antisolvent selected from the group consisting of heptane, diisopropyl ether or mixtures thereof.
   e) Removing the solvent.
20. A process for the preparation of the novel polymorph of Etoricoxib as claimed in claims 7 or 8 comprising,
   a) Contacting/Dissolving Etoricoxib with ethyl acetate at room temperature.
   b) Filtering the mixture.
   c) Concentrating the filtrate.
   d) Adding hexane to the filtrate.
   e) Removing the solvent.
21. A process for the preparation of the novel polymorph of Etoricoxib as claimed in claims 9 or 10 comprising,
   a) Contacting/Dissolving Etoricoxib with isopropyl alcohol at room temperature.
   b) Filtering the solution.
   c) Isolating the product by cooling to 0-5 °C.
22. A process for the preparation of the novel polymorph of Etoricoxib as claimed in claims 11 or 12 comprising,
   a) Contacting/Dissolving Etoricoxib with ethyl acetate at room temperature and washing with water.
   b) Separating the organic layer and purifying.
   c) Concentrating the organic layer.
   d) Adding diisopropyl ether to the organic layer.
   e) Removing the solvent to obtain the product.
23. A process for the preparation of the novel polymorph of Etoricoxib as claimed in claims 13 or 14 comprising,
   a) Contacting/Dissolving Etoricoxib with aqueous HCl.
   b) Treating the solution with toluene.
   c) Separating the aqueous layer and purifying.
d) Basifying the filtrate.
e) Filtering and drying to obtain the product.

24. A process for the preparation of the novel polymorph of Etoricoxib as claimed in claims 11 or 12 comprising,

a) Contacting/Dissolving Etoricoxib with isopropyl acetate at 70-75°C temperature.
b) Cooling the solution to 0-5 °C.
c) Filtering and drying to obtain the product.

25. A pharmaceutical composition comprising the novel polymorphs of Etoricoxib of the present invention as claimed in any of the preceding claims, comprising either a single polymorph or their mixtures in combination with the pharmaceutically acceptable excipients.

26. A pharmaceutical dosage form comprising the pharmaceutical compositions containing the novel polymorphs of Etoricoxib of the present invention as claimed in claim 25.

27. Use of the novel forms of Etoricoxib of the present invention or their pharmaceutical compositions as claimed in any preceding claims, for preparing medicaments suitable for the treatment of COX-2 mediated disorders such as osteoarthritis, rheumatoid arthritis, pain and inflammatory disorders in a mammal including human.

28. Method of treatment comprising administering to a person in need thereof, pharmaceutical compositions or pharmaceutically acceptable dosage forms containing the new forms of Etoricoxib of the present invention, as claimed in any preceding claims, for the treatment of COX-2 mediated disorders.
Fig 1: X-ray powder diffraction (XPRD) pattern of novel form IX of Etoricoxb
Figure 4: X-ray powder diffraction (XRPD) pattern of novel form XI of Ploceus
### INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

IPA 7 C07D213/22 A61K31/444 A61P29/00

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)

IPA 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>X</td>
<td>WO 01/37833 A (MERCK FROSST CANADA &amp; CO; CLAS, SOPHIE, DOROTHEE; O'SHEA, PAUL; DALTON) 31 May 2001 (2001-05-31) the whole document</td>
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* 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 document but published on or after the international filing date
- **"L"** document which may throw doubts on priority claims(s) or which is cited to establish the publication date or 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

- **"I"** 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.
- **"T"** document member of the same patent family

**Date of the actual completion of the international search**

19 July 2005

**Date of mailing of the international search report**

01/08/2005

**Name and mailing address of the ISA**

European Patent Office, P.B. 5018 Patentlaan 2 NL - 2280 HT Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl Fax: (+31-70) 340-3016

**Authorized officer**

Österle, C
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INTERNATIONAL SEARCH REPORT

Box II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.; because they relate to subject matter not required to be searched by this Authority, namely:
   Although claim 28 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.; because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.; because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- [ ] The additional search fees were accompanied by the applicant's protest.
- [ ] No protest accompanied the payment of additional search fees.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1,2,17,25-28 (part)

Polymorph of Etoricoxib having the X-ray pattern shown in Fig. 1, its synthesis, pharmaceutical composition comprising this compound, use of this compound and method of treatment using this compound.

2. claims: 3,4,18,25-28 (part)

Polymorph of Etoricoxib having the X-ray pattern shown in Fig. 2, its synthesis, pharmaceutical composition comprising this compound, use of this compound and method of treatment using this compound.

3. claims: 5,6,19,25-28 (part)

Polymorph of Etoricoxib having the X-ray pattern shown in Fig. 3, its synthesis, pharmaceutical composition comprising this compound, use of this compound and method of treatment using this compound.

4. claims: 7,8,20,25-28 (part)

Polymorph of Etoricoxib having the X-ray pattern shown in Fig. 4, its synthesis, pharmaceutical composition comprising this compound, use of this compound and method of treatment using this compound.

5. claims: 9,10,21,25-28 (part)

Polymorph of Etoricoxib having the X-ray pattern shown in Fig. 5, its synthesis, pharmaceutical composition comprising this compound, use of this compound and method of treatment using this compound.

6. claims: 11,12,22,25-28 (part)

Polymorph of Etoricoxib having the X-ray pattern shown in Fig. 6, its synthesis, pharmaceutical composition comprising this compound, use of this compound and method of treatment using this compound.

7. claims: 13,14,23,25-28 (part)
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Polymorph of Etoricoxib having the X-ray pattern shown in Fig. 7, its synthesis, pharmaceutical composition comprising this compound, use of this compound and method of treatment using this compound.

8. claims: 15, 16, 24, 25-28 (part)

Polymorph of Etoricoxib having the X-ray pattern shown in Fig. 8, its synthesis, pharmaceutical composition comprising this compound, use of this compound and method of treatment using this compound.
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