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(54) **Title:** A PARENTERAL DOSAGE FORM OF SELECTIVE COX-2 INHIBITORS

(57) **Abstract:** The present invention relates to parenteral dosage forms of selective cyclooxygenase-2 (COX-2) inhibitory drugs and salts thereof. More particularly, the invention relates to a pharmaceutical dosage form of selective COX-2 inhibitors wherein the dosage form can be administered intramuscularly.

A PARENTERAL DOSAGE FORM OF SELECTIVE COX-2 INHIBITORS

Technical Field of the Invention

The present invention relates to parenteral dosage forms of selective cyclooxygenase-2 (COX-2) inhibitory drugs and salts thereof. More particularly, the invention relates to a pharmaceutical dosage form of selective COX-2 inhibitors wherein the composition can be administered intramuscularly.

Background of the Invention

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed as effective analgesics, antipyretic and anti-inflammatory agents. Their mechanism for action is based on their ability to inhibit prostaglandin synthesis, which is controlled by the enzyme cyclooxygenase. Cyclooxygenase exists in two isomers- COX1 and COX-2. COX-1 is present in most tissue-synthesized prostaglandins and is important in regulating cell function. It is responsible for most of the gastro-protective prostaglandin synthesis which is important in regulating cell function. COX-2 is generally undetectable in most tissues but increases its expression by 10-20 fold during acute inflammation. Inhibition of COX-2 by NSAIDs would give an anti-inflammatory effect, whereas inhibition of COX-1 would result in adverse effects such as gastrointestinal toxicity and nephrotoxicity.

Selective COX-2 inhibitory drugs represent a major advance in the art. Among such drugs are substituted pyrazolyl benzenesulfonamides, substituted Isoxazolyl benzenesulfonamides and substituted (methyl sulfonyl)phenylfuranones. In particular, 4-[5-4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzene sulfonamide, commonly known as celecoxib, 4-[5-methyl-3-phenylisoxazol-4-yl) benzene sulfonamide, commonly known as valdecoxib, 4-[4-(methylsulfonyl)phenyl]-3-phenyl-5h-furan-2-one, also referred to as rofecoxib, 4-[4-methylsulfonyl) phenyl]-2-cyclopenten-1-one, deracoxib and etoricoxib are relevant. Almost all of these COX-2 inhibitory drugs are only available in a variety of oral dosage forms.

Celecoxib was first described in US Patent No. 5,466,823 assigned to Searle. Celecoxib is commercially available as 100mg capsules to be administered twice a day for the treatment of osteo-arthritis and rheumatoid arthritis. No other dosage forms of celecoxib have been reported. Rofecoxib was described in US Patent No. 5,474,995 assigned to Merck

& Co. Rofecoxib is commercially available as 12.5 mg, 25 mg and 50 mg tablets to be administered once daily and as 12.5mg/5 ml or 25 mg/5 ml oral suspensions for the treatment of osteo-arthritis and the management of acute pain. Valdecoxib has been described in US Patent No. 5,633,272 assigned to Searle. It is marketed as 10 and 20mg tablets for treating symptoms associated with osteo-arthritis and rheumatoid arthritis.

Although oral administration is the most convenient and widely used route, it is associated with a delayed onset of the desired pharmacological action. It is known that upon oral administration, the COX-2 inhibitors take approximately 3.0 hours for peak plasma concentrations to be achieved and have an onset of action 0.5 to 0.75 hours after administration. Additionally, the intake of food further influences drug absorption. However, acute pain, as in the case of arthritis and cancer, demands immediate relief. In such cases, a parenteral route is more efficient and prompt, as compared to the oral route.

Parenteral routes of administration offer numerous benefits over oral delivery. Apart from providing quicker onset of action, parenteral administration results in more predictable blood serum concentrations of the drug and losses in the gastrointestinal tract due to metabolism, binding to food and other causes are eliminated. For similar reasons, parenteral administration permits dose reduction. It is also the preferred method of drug delivery in emergency situations and is useful in non-cooperative patients.

Furthermore, COX-2 inhibitors have an oral bioavailability ranging from 80-85%, hence parenteral administration would bring about a reduction in the dose in comparison to oral dose.

Currently, the only available injectable dosage form comprising COX-2 inhibitors is parecoxib, a prodrug of valdecoxib. Parecoxib, when administered parenterally, is hydrolyzed to valdecoxib within the blood stream. It is commercially available as parecoxib sodium powder which may be reconstituted in a parenterally acceptable solvent liquid.

Pharmacia Corporation has filed a PCT Application, WO 02/080912, relating to parenterally deliverable formulations of water-soluble selective COX-2 inhibitory drugs and salts and prodrugs thereof. The invention describes dosage forms that are prepared as lyophilized powders for reconstitution.

U.S. Patent No. 6,589,557, assigned to Acusphere, describes porous matrices of celecoxib with an enhanced rate of dissolution. The porous matrix may be reconstituted with an aqueous medium and administered parenterally.

Another PCT application WO 03/035063, describes a clear stable pharmaceutical preparation of selective COX-2 inhibitors preferably in the parenteral form. Those applicants assert that injectable formulations of COX-2 inhibitors can be obtained only when dissolved in a selective isosorbide type solvent.

COX-2 inhibitors have extremely low solubility in water, which is the main reason for preparing a reconstitutable powder composition. Due to limited chemical stability, it is preferable to reconstitute the composition within a short period of time before administration.

The process of developing stable parenteral dosage forms for selective COX-2 inhibitors is challenging for the pharmaceutical formulator because of low chemical and physical stability. Attempts have been made to formulate parenteral dosage forms for COX-2 inhibitors as lyophilized powders for reconstitution. An injectable solution composition prepared by reconstituting a powder composition in a parenterally acceptable solvent, preferably an aqueous solvent has limited chemical stability, in which case it is preferred to reconstitute the composition within a short period of time before administration. Moreover, lyophilized powders require increased handling and processing time. Furthermore, it requires costly and complex equipment.

Amongst all the parenteral routes known, i.e. intravenous, intramuscular, intra-arterial, subcutaneous, intraperitoneal, etc., intramuscular, is the most convenient and easily administrable routes. This route is considered less hazardous than the intravenous route.

Therefore, there is a need for stable parenteral dosage forms of COX-2 inhibitors which are available as clear solutions, ready for immediate administration.

Summary of the Invention

In one general aspect there is provided a parenteral pharmaceutical dosage form comprising at least one selective COX-2 inhibitor dissolved in at least one non-aqueous protic solvent, other than isosorbide type solvent. This dosage form can be administered

intramuscularly. Further, in this general aspect the dosage form my include various selective COX-2 inhibitors including celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib and parecoxib. The non-aqueous protic solvent of the dosage form comprises one or more of polyethylene glycol, polyvinylpyrrolidone, propylene glycol and glycerol.

In this general aspect, the dosage form may also comprise co-solvents, for example ethyl alcohol and water. The dosage form may also comprise other pharmaceutically acceptable excipients, for example surfactants or solubilizers, preservatives and antioxidants. Suitable surfactants or solubilizers include polyoxyethylene sorbitan fatty acid esters and ethoxylated alcohols. Suitable preservatives include one or more of methylparaben, propylparaben and benzyl alcohol. Suitable antioxidants comprise one or more of ascorbic acid, alpha-tocopherol, ascorbyl palmitate, butylated hydroxy anisole and butylated hydroxy toluene.

In another general aspect, the dosage form comprises the selective COX-2 inhibitor celecoxib at a concentration of about 1 mg to about 400 mg/ml.

In another general aspect, the dosage form comprises the selective COX-2 inhibitor comprises valdecoxib, at a concentration of about 1 mg to about 25 mg/ml.

In another general aspect, the dosage form comprises the selective COX-2 inhibitor comprises rofecoxib at a concentration of about 1 mg to about 25 mg/ml.

In yet another general aspect, there is provided a process for preparing a parenteral pharmaceutical dosage form of selective COX-2 inhibitors comprising dissolving the COX-2 inhibitor in a non-aqueous protic solvent, sterilizing the solution, and filling the solution into ampoules or vials. The dosage form may further comprise co-solvents and pharmaceutically acceptable excipients. Suitable sterilization techniques include aseptic filtration, autoclaving, steaming or irradiation. In the preferred embodiment, aseptic filtration is utilized.

In a final general aspect, there is provided a method of treating or preventing COX-2 mediated disorders in a human subject, comprising administering a parenteral pharmaceutical dosage form comprising at least one selective COX-2 inhibitor dissolved in at least one non-

aqueous protic solvent. In this embodiment, the parenteral administration comprises intramuscular injection.

Detailed Description of the Invention

Herein is provided an injectable formulation of selective COX-2 inhibitors that is stable, clear and cost -effective to obtain.

The pharmaceutical dosage form of the present invention comprises at least one therapeutic agent selected from selective COX-2 inhibitory drugs and at least one non-aqueous protic solvents other than isosorbide type solvents.

Selective COX-2 inhibitory drugs include those drugs, prodrugs or salts of drugs which exhibit selective inhibition of COX-2, such as celecoxib, rofecoxib, etoricoxib, valdecoxib, parecoxib and deracoxib.

The term "non-aqueous protic solvent" means a non-aqueous solvent which contains hydrogen attached to oxygen or nitrogen so that it is able to form hydrogen bonds or donate a proton. The solvents used in the parenteral dosage forms should be non-irritating, non-toxic, non-sensitizing, should not have pharmacological activity of its own and should not affect the activity of the drug. Examples of non-aqueous protic solvents are polyvinylpyrrolidone (PVP), polyethylene glycols (PEGs), propylene glycol (PG) and glycerol.

The term "chemical stability" means that an acceptable percentage of degradation products produced by chemical pathways, such as oxidation or hydrolysis, is formed. In particular, a formulation is considered chemically stable if it passes a standard test for chemical purity of the therapeutic agent, as may be required for approval by a regulatory authority.

It is another general aspect to provide a process for the preparation of an intramuscular injectable dosage form such that it delivers to the systemic circulation a dose ranging from about 10 to about 400mg/ml and has low toxicity as shown by the toxicity studies reported herein.

The process for the preparation of the injection dosage forms of the present invention involves the dissolution of the active ingredient in a suitable non aqueous protic solvent. Apart from the drug and the solvent, the pharmaceutical dosage forms may optionally comprise co-solvents such as ethyl alcohol and water. The pharmaceutical dosage forms may optionally comprise pharmaceutically acceptable excipients such as surfactants or solubilizers, preservatives and antioxidants. Suitable surfactants or solubilizers may comprise one or more of polyoxyethylene sorbitan fatty acid esters and ethoxylated alcohols. Suitable preservatives may comprise one or more of methylparaben, propylparaben and benzyl alcohol. Suitable antioxidants may comprise one or more of ascorbic acid, alpha-tocopherol, ascorbyl palmitate, butylated hydroxy anisole and butylated hydroxy toluene.

In all cases, the final dosage form must be sterile and stable. Techniques such as aseptic filtration, autoclaving, steaming and irradiation may be used for sterilization.

Compositions of the invention are useful in the treatment and prevention of a wide range of disorders in humans mediated by COX-2, including but not restricted to disorders characterized by inflammation, pain and/or fever. Such compositions are especially useful as anti-inflammatory agents, such as in treatment of arthritis, with the additional benefit of having significantly less harmful side effects than compositions of conventional NSAIDs that lack selectivity for COX-2. In particular, the dosage forms of the present invention have a reduced potential for gastrointestinal toxicity and irritation, including upper gastrointestinal ulceration and bleeding, by comparison with compositions of conventional NSAIDs. Thus, the dosage forms of the invention are particularly useful as an alternative to conventional NSAIDs where NSAIDs are contraindicated.

Such dosage forms are useful in the treatment of pain, including but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer. Particularly, the dosage forms are used for the treatment of rheumatoid arthritis and osteoarthritis, for pain management, for treatment of Alzheimer's disease, and for colon cancer chemoprevention. Besides being useful for human treatment, compositions of the invention are useful for veterinary treatment of animals, particularly mammals.

The present invention is further directed to a therapeutic method of treating a condition or disorder where treatment with a COX-2 inhibitory drug is indicated, the method

comprising parenteral administration of the dosage form of the invention to a subject in need thereof. The dosage regimen to prevent, give relief from, or ameliorate the condition or disorder preferably corresponds to once-a-day or twice-a-day treatment, but can be modified in accordance with a variety of factors. These include the type, age, weight, sex, diet and medical condition of the subject and the nature and severity of the disorder. Thus, the dosage regimen actually employed can vary widely and can therefore deviate from the preferred dosage regimens set forth above.

The following examples illustrate various aspects of the present invention. These examples are for illustration only and should not be construed as limiting the scope of the invention.

EXAMPLE 1

Ingredients	**quantity / ml**
Celecoxib	100mg
Benzyl alcohol	2% v/v
Pure Anhydrous Ethyl Alcohol	10% v/v
Polyethylene glycol 400	18% w/v
Propylene glycol q.s. to	1.0ml

PEG 400 and propylene glycol (65% of the total) were added to Pure Anhydrous Ethyl Alcohol in a dry vessel and the solution was stirred to get a clear solution. Celecoxib was dissolved in this solution followed by the addition of benzyl alcohol and the volume was made up with propylene glycol. The solution was filtered through 0.2-micron filter and filled into 3 ml clear glass ampoules.

The intramuscular injectable formulation made in accordance with example 1 was subjected to sub chronic intramuscular toxicity study in Swiss albino mice. Celecoxib injections were administered to mice via intramuscular route at dose levels ranging from 0 mg/kg to 200mg /kg body weight and the results of the study showed that:

(i) Male and female animals from different dose groups survived the dosing period of 14 days.

(ii) Hematological analysis revealed no abnormalities attributable to treatment.

(iii) Biochemical analysis revealed no abnormalities attributable to the treatment.

(iv) Urine analysis revealed no abnormalities attributable to the treatment.

(v) Gross pathological examination revealed focal necrosis at the site of injection from control as well as all treatment dose groups.

(vi) Histopathological examination revealed minimal focal necrosis at the site of injection in control and all treatment dose groups.

(vii) Food intake of animals from control and different dose groups was found to be comparable throughout the dosing period of 14 days.

(viii) Three male and three female animals treated at the dose level of 200mg / kg exhibited reduced locomotor activity during the dosing period of 14 days. Animals from 50mg/kg and 100mg / kg dose groups exhibited no signs of intoxication throughout the dosing period of 14 days.

Based on these findings the "no observed effect level" (NOEL) of celecoxib injection 100 mg/ml (3.0 ml) when administered to Swiss Albino mice via intramuscular route over a period of 14 days was found to be about 100mg /kg in male and female animals.

An accelerated stability study was performed on celecoxib intramuscular solution prepared according to Example 1 (and sterilized by aseptic filtration) for 3 months at 40°±2°C and 75±5% relative humidity. The results of the study are presented in Table 1.

Table 1: Accelerated stability studies of celecoxib intramuscular solution at 40°±2°C and 75±5% relative humidity

Test	0 month	1 month	2 month	3 month
Description	Clear, colourless solution	Clear, colourless solution	Clear, colourless solution	Clear, colourless solution
Assay (mg/ml)	100.5	99.6	99.1	98.5
Benzyl alcohol (%w/v)	2.01	2.00	1.99	1.99
Pure Anhydrous Ethyl Alcohol (%v/v)	9.98%	9.95%	9.89%	9.87%
Particulate matter	complies	complies	complies	complies
Sterility	complies	-	-	complies
Bacterial Endotoxin Test	complies	-	-	complies

EXAMPLE 2

Ingredients	Quantity / ml
Rofecoxib	25.0 mg
Polyethylene glycol 400	q.s. to 3 ml
Polyoxyethylene sorbitan ester	0.1% w/v
Benzyl alcohol	2% w/v

A slurry (10%w/v) of rofecoxib was made in water for injection and it was nanonised to a particle size of less than 1.0 micron for rofecoxib. Polyethylene glycol 400 was added under stirring to a nanonised slurry of rofecoxib till it dissolved completely. To this bulk, polyoxyethylene sorbitan ester was added and was stirred continuously to get a clear solution. Benzyl alcohol was added to this solution and stirred till it mixes completely. The volume was made up with polyethylene glycol 400. The solution was filtered through 0.2-micron filter and filled into 3.0 ml clear glass sterile USP Type-I ampoules.

EXAMPLE 3

Ingredients	Quantity / ml
Valdecoxib	10.0 mg
Pure Anhydrous Ethyl Alcohol	10.0% v/v
Polyethylene glycol 400	18.0% w/v
Water for injection	30.0% w/v
Benzyl alcohol	2.0% w/v
Propylene glycol	q.s to 1 ml

Procedure:

1. Polyethylene glycol 400, Pure Anhydrous Ethyl Alcohol and a portion of propylene glycol were stirred to mix completely.
2. Valdecoxib was added to the bulk of step 1 under constant stirring till it solubilizes completely.
3. Water for injection was added to the bulk of step 2 under constant stirring.
4. Benzyl alcohol was added to the bulk of step 3 under constant stirring to mix completely.
5. The volume was made up with propylene glycol.

6. The solution of step 5 was filtered through 2.0 / 0.2 μ nylon membrane filter and filled in 2 ml clear glass vials (USP Type I) and sealed with rubber stopper and aluminum seal.

An accelerated stability study was performed on the valdecoxib intramuscular solution prepared according to Example 3 (and sterilized by aseptic filtration) for 3 months at 40°±2°C and 75±5% relative humidity. The results of the study are presented in Table 2.

Table 2: Accelerated stability studies of valdecoxib intramuscular solution at 40°±2°C and 75±5% relative humidity

Test	0 month	1 month	2 month	3 month
Description	Clear, colourless solution	Clear, colourless solution	Clear, colourless solution	Clear, colourless solution
Assay (mg/ml)	10.02	9.92	9.88	9.80
Benzyl alcohol (%w/v)	2.00	1.99	1.98	1.98
Pure Anhydrous Ethyl Alcohol (%v/v)	9.95%	9.89%	9.87%	9.85%
Particulate matter	complies	complies	complies	complies
Sterility	complies	-	-	complies
Bacterial Endotoxin Test	complies	-	-	complies

EXAMPLE 4

Ingredients	Quantity / ml
Valdecoxib	11.33 mg
Pure Anhydrous Ethyl Alcohol	10.0% v/v
Polyethylene glycol 400	18.0% w/v
Water for injection	25.0% w/v
Benzyl alcohol	2.0% w/v
Propylene glycol	q.s to 1 ml

Procedure: Similar to Example 3

EXAMPLE 5

Ingredients	Quantity / ml
Valdecoxib	17.0 mg
Pure Anhydrous Ethyl Alcohol	10.0% v/v
Polyethylene glycol 400	18.0% w/v
Water for injection	15.0% w/v
Benzyl alcohol	2.0% w/v
Propylene glycol	q.s to 1 ml

Procedure: Similar to Example 3

While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the invention. Further, it is contemplated that any single feature or any combination of optional features of the inventive variations described herein may be specifically excluded from the claimed invention and be so described as a negative limitation. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

WE CLAIM:

1. A parenteral pharmaceutical dosage form comprising at least one selective COX-2 inhibitor dissolved in at least one non-aqueous protic solvent, wherein the non-aqueous solvent is not an isosorbide type solvent.
2. The dosage form according to claim 1 wherein the dosage form is administered intramuscularly.
3. The dosage form according to claim 1 wherein the selective COX-2 inhibitor comprises one or more of celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib and parecoxib.
4. The dosage form according to claim 1 wherein the non-aqueous protic solvent comprises one or more of polyethylene glycol, polyvinylpyrrolidone, propylene glycol and glycerol.
5. The dosage form according to claim 1 further comprising one or more co-solvents.
6. The dosage form according to claim 5 wherein co-solvent comprises one or more of ethyl alcohol and water.
7. The dosage form according to claim 1 further comprising one or more pharmaceutically acceptable excipients.
8. The dosage form according to claim 7 wherein the one or more pharmaceutically acceptable excipients comprise surfactants or solubilizers, preservatives and antioxidants.
9. The dosage form according to claim 8 wherein the surfactants or solubilizers comprise one or more of polyoxyethylene sorbitan fatty acid esters and ethoxylated alcohols.
10. The dosage form according to claim 8 wherein the preservatives comprise one or more of methylparaben, propylparaben and benzyl alcohol.
11. The dosage form according to claim 8 wherein the antioxidants comprise one or more of ascorbic acid, alpha-tocopherol, ascorbyl palmitate, butylated hydroxy anisole and butylated hydroxy toluene.
12. The dosage form according to claim 3 wherein the selective COX-2 inhibitor comprises celecoxib.
13. The dosage form according to claim 12 wherein the concentration of celecoxib comprises about 1 mg to about 400 mg/ml.
14. The dosage form according to claim 3 wherein the selective COX-2 inhibitor comprises valdecoxib.

15. The dosage form according to claim 14 wherein the concentration of valdecoxib comprises about 1 mg to about 25 mg/ml.
16. The dosage form according to claim 3 wherein the selective COX-2 inhibitor comprises rofecoxib.
17. The dosage form according to claim 16 wherein the concentration of rofecoxib comprises about 1 mg to about 25 mg/ml.
18. A process for preparing a parenteral pharmaceutical dosage form of selective COX-2 inhibitors comprising:
    i. dissolving the COX-2 inhibitor in a non-aqueous protic solvent, wherein the solvent is not isosorbide;
    ii. sterilizing the solution; and
    iii. filling the solution into ampoules or vials.
19. The process according to claim 18 wherein the dosage form further comprises co-solvents.
20. The process according to claim 18 wherein the dosage form further comprises one or more pharmaceutically acceptable excipients.
21. The process according to claim 18 wherein sterilization comprises one or more of aseptic filtration, autoclaving, steaming or irradiation.
22. The process according to claim 21 wherein sterilization comprises aseptic filtration.
23. A method of treating or preventing COX-2 mediated disorders in a human subject, comprising administering a parenteral pharmaceutical dosage form comprising at least one selective COX-2 inhibitor dissolved in at least one non-aqueous protic solvent, wherein the protic solvent is not isosorbide.
24. The method of claim 22, wherein the parenteral administration comprises intramuscular injection.

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/IB 03/03219

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/10 A61K31/415

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)
IPC 7 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 practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 21585 A (UNION PHARMA SCIENT APPL) 6 May 1999 (1999-05-06) examples 1D,1E,2D,2E,3D,3E,4D,4E	1,2,4-9, 18-21, 23,24
X	WO 00 32189 A (GAO DANCHEN ;SEARLE & CO (US); MAZHARY AHMAD M (US); HLINAK ANTHON) 8 June 2000 (2000-06-08) examples 11-1,11-2	1-8,12, 18-21, 23,24
E	EP 1 362 585 A (OSMOTICA CORP. TORTOLA) 19 November 2003 (2003-11-19) example 9	1-8, 16-24
X	-& WO 02 058620 A 1 August 2002 (2002-08-01) example 9	1-8, 16-24

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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 document 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)

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"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
21 November 2003	04/12/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Epskamp, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 03/03219

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 05799 A (HASSAN FRED ;FORBES JAMES C (US); PHARMACIA CORP (US)) 24 January 2002 (2002-01-24) examples 1,5-7,10	1-9, 11-15, 18-21, 23,24

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-24 relate to compounds defined by reference to their pharmacological activity, namely "selective COX-2 inhibitors".
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.
Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of claim 2. Also the concept of "selective COX-2 inhibitor" was included in the search.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/IB 03/03219

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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 claims 23 and 24 are 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 composition.

2. [X] 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:

see FURTHER INFORMATION sheet PCT/ISA/210

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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

2. [ ] 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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