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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.

(54) Title: PHARMACEUTICAL COMBINATION OF A THROMBOXANE A₂ RECEPTOR ANTAGONIST AND A COX-2 INHIBITOR

(57) Abstract: The invention is directed to methods and compositions that can be used in the treatment of inflammation, pain and cardiovascular disorders. Methods and compositions are described involving the combination of a thromboxane A₂ receptor antagonist and an inhibitor specific for cyclooxygenase-2.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 80526/7571	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/IB 03/ 02633	International filing date (day/month/year) 03/07/2003	(Earliest) Priority Date (day/month/year) 09/07/2002
Applicant B.M.R.A. CORPORATION B.V.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

PHARMACEUTICAL COMBINATION OF A THROMBOXANE A₂ RECEPTOR ANTAGONIST AND A COX-2 INHIBITOR

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

PHARMACEUTICAL COMBINATION OF A THROMBOXANE A₂ RECEPTOR ANTAGONIST AND A COX-2 INHIBITOR

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Cross Reference to Related Applications

This application claims priority to U.S. provisional application no. 60/394,268, filed on July 9, 2002, which is incorporated in its entirety herein by reference.

10 **Field of the Invention**

The invention is directed to compositions containing both a cyclooxygenase-2 (COX-2) inhibitor and a thromboxane A₂ receptor antagonist. The compositions may be used to treat patients for pain or inflammation and have less risk of inducing adverse cardiovascular effects than when COX-2 inhibitors are administered alone. The invention
15 includes not only these compositions, but also methods in which patients are treated.

Background of the Invention*COX-2 Specific Inhibitors*

Over 15 million Americans take nonsteroidal anti-inflammatory drugs (NSAIDs)
20 each day as a treatment for pain or inflammation. Unfortunately, many of these drugs are also associated with a high incidence of gastrointestinal complications, including gastritis, dyspepsia, gastroduodenal ulcers, perforations, and bleeding. As a result, it has been estimated that as many as 15,000 people in the U.S. die each year from taking NSAIDs ([www.emedmag.com/stories/storyReader\\$118](http://www.emedmag.com/stories/storyReader$118)).

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Most NSAIDS exert their effects by nonselectively blocking two enzymes, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). It appears that inhibition of COX-2 is primarily responsible for alleviating pain and inflammation, whereas inhibition of COX-1 is primarily responsible for damage to the GI tract (Vane, *et al.*, *Am. J. Med.*
30 *104:2S-8S* (1998)). As a result, inhibitors specific for COX-2 have been developed and some are now on the market. These drugs maintain the ability to alleviate pain but are safer with respect to adverse gastrointestinal effects (Griswold, *et al.*, *Med. Res. Rev.* *16(2)*: 181-206 (1996); Lane, J. *Rheumatol* *24 (Suppl 49):20-4* (1997); Lipsky, *et al.*, *J. Rheumatol.* *24(Suppl 49):9-14* (1997)).

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More recent research has led many to reconsider the wisdom of blocking one cyclooxygenase enzyme but not the other (Mukherjee, *et al.*, *JAMA* 286:954-959 (2001); *Science* 296:539-541 (2002)). COX-1, makes thromboxane, which causes blood vessels to constrict and platelets to become sticky. These activities can contribute to a heart attack or stroke. In contrast, COX-2 promotes the production of prostacyclin which dilates blood vessels and prevents platelets from clumping together. In a normal person, the two enzymes appear to balance one another. COX-2 specific inhibitors upset this balance by only blocking the production of prostacyclin while allowing thromboxane production to remain unchecked. As a result, the COX-2 inhibitors increase the risk of adverse cardiovascular events.

Thromboxane A2 Receptor Antagonists

Thromboxane A2/prostaglandin H2 receptor antagonists have been reported to be effective in treating, *inter alia*, arterial or venous thrombosis, unstable angina, transient ischemic attacks, and hypertension, (U.S. 5,100,889). They include 7-oxabicycloheptane substituted prostaglandin analogs (U.S. 5,100,889; Rosenfeld, *et al.*, *Cardiovascular Drug Rev.* 19:97-115 (2001)), benzenealkonic acids (U.S. 5,618,941), and benzenesulfonamide derivatives (U.S. 5,597,848). In general, these compounds have not been reported to directly affect either cyclooxygenase-1 or cyclooxygenase-2.

Summary of the Invention

The present invention is based upon the concept that the cardiovascular risks associated with the administration of COX-2 specific inhibitors can be avoided by co-administering an agent that blocks the activation of the thromboxane A2 receptor by its ligand. The invention includes compositions, therapeutic packages and treatment methods.

In its first aspect, the invention is directed to a pharmaceutical composition in unit dose form which contains a COX-2 inhibitor and a thromboxane A2 receptor antagonist. Both of these drugs are present in an amount that is therapeutically effective upon the administration of one or more unit doses of the composition to a patient. The term "unit dose" or "unit dose form" refers to a single drug administration entity. By way of example, a single tablet, capsule, dragee, vial for injection or syringe combining both a COX-2 inhibitor and a thromboxane A2 receptor antagonist would be a unit dose form. As used

herein, the term "COX-2 inhibitor" refers to agents that specifically inhibit COX-2 and which have little or no effect on COX-1. For example, at a dosage that caused a 50% inhibition of COX-2, a COX-2 inhibitor would inhibit COX-1 by less than 10%. The term "therapeutically effective" means that sufficient drug is present to generate the therapeutic action for which the drug is given. For example, if a patient is being treated for pain then a
5 "therapeutically effective" amount of COX-2 would be a dosage sufficient to reduce the severity or duration of the pain. If the patient is being treated for inflammation, then enough drug would need to be present to reduce the associated pain or swelling. In the case of thromboxane A₂ receptor inhibitors, enough should be present to treat or prevent
10 cardiovascular problems associated with thromboxane A₂. This means that, in general between 0.1 mg and 500 mg., (and preferably between 1 and 100 mg) will be present.

Preferred COX-2 inhibitors for use in the compositions are celecoxib; rofecoxib; meloxicam; JTE-522; L-745,337; NS398. Thromboxane A₂ receptor antagonists include 7-oxabicycloheptane substituted prostaglandin analogs such as those described in U.S.
15 5,100,889, benzenesulfonic acids and benzenesulfonamide derivatives. The most preferred drugs are ifetroban and either celecoxib or rofecoxib. It will be understood that, unless otherwise indicated, reference to a COX-2 inhibitor or thromboxane A₂ receptor antagonist includes all pharmaceutically acceptable forms of the drug known in the art. For example,
20 any pharmaceutically acceptable salt of a drug may be used in compositions. In general, the COX-2 inhibitor will be present at between 1 and 500 mg.

The therapeutic agents described above, *i.e.*, the COX-2 inhibitor and the thromboxane A₂ receptor antagonist, may be supplied in the form of a therapeutic package. Each package has one or more finished pharmaceutical containers with the therapeutic agents in unit dose form and includes labeling directed to their use in the treatment of any condition responsive to a COX-2 inhibitor or a thromboxane A₂ receptor antagonist. These conditions include inflammation (*e.g.*, that associated with arthritis); pain (*e.g.*, pain associated with headache, muscle pain, or post-surgical pain); and cardiovascular conditions (*e.g.*, arterial or venous thrombosis, angina, or hypertension).

The invention also includes methods of treating a patient for any condition responsive to a COX-2 inhibitor or a thromboxane A₂ receptor antagonist by either

administering the pharmaceutical compositions described above or by sequentially administering the two drugs in a co-timely manner, *i.e.*, the second drug is administered while the first drug is still present in a therapeutically effective amount. Any of the specific conditions mentioned above may be treated in this manner. The preferred agents are ifetroban and either celecoxib or rofecoxib.

Detailed Description of the Invention

A. COX-2 Inhibitors and Thromboxane A2 Receptor Antagonists

The GI toxicity associated with many NSAIDs appears to be due to the inhibition of COX-1 whereas anti-inflammatory effects are due primarily to inhibition of COX-2. Drugs which selectively inhibit the COX-2 isozyme, *e.g.*, celecoxib, rofecoxib, meloxicam, piroxicam, JTE-522 and L-745,337, produce analgesia and reduce inflammation without damaging the gastrointestinal tract.

Although, as discussed above, COX-2 specific inhibitors reduce the risk of gastrointestinal complications relative to NSAIDs inhibiting both COX-1 and COX-2, they increase the risk of serious cardiovascular problems due to the continued generation of thromboxane in the absence of normal levels of prostacyclin. The present invention addresses this problem by including a thromboxane A2 receptor antagonist in therapeutic compositions and methods.

COX-2 inhibitors have been thoroughly described in the art and some (*e.g.*, celecoxib and rofecoxib) are now commercially available as therapies. Similarly, a variety of thromboxane A2 receptor antagonists have been disclosed and methods for synthesizing these compounds have been described for bicycloheptane substituted prostaglandin analogs (U.S. 5,100,889; Rosenfeld, *et al.*, *Cardiovascular Drug Rev.* 97-115 (2001)), benzenecarboxylic acids (U.S. 5,618,941), and benzenesulfonamide derivatives (U.S. 5,597,848). Any of these prior methods may be used to obtain agents suitable for use in the present invention.

B. Route of Administration

The methods and compositions discussed above are compatible with any dosage form or route of administration. Thus, agents may be administered orally, intranasally,

rectally, sublingually, buccally, parenterally, or transdermally. Dosage forms may include tablets, trochees, capsules, caplets, dragees, lozenges, parenterals, liquids, powders, and formulations designed for implantation or administration to the surface of the skin. In general, it is expected that oral dosage forms will be the most convenient. All dosage forms
5 may be prepared using methods that are standard in the art (see *e.g.*, Remington's Pharmaceutical Sciences, 16th ed. A. Oslo. ed., Easton, PA (1980)).

Active ingredients may be used in conjunction with any of the vehicles and excipients commonly employed in pharmaceutical compositions, *e.g.*, talc, gum arabic,
10 lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous solvents, oils, paraffin derivatives, glycols, etc. Coloring and flavoring agents may also be added to preparations designed for oral administration. Solutions can be prepared using water or physiologically compatible organic solvents such as ethanol, 1-2 propylene glycol, polyglycols, dimethyl sulfoxide, fatty alcohols, triglycerides, partial esters of glycerin, and
15 the like. Parenteral compositions containing active ingredients may be prepared using conventional techniques and include sterile isotonic saline, water, 1,3-butanediol, ethanol, 1,2-propylene glycol, polyglycols mixed with water, Ringer's solution, etc.

The COX-2 inhibitors are especially useful in the treatment of pain, *e.g.*, pain due to
20 migraine headache, and inflammation. Thus, the invention includes methods of treating these conditions by administering a thromboxane A2 receptor antagonist in combination with a COX-2 inhibitor. These agents should be given in a co-timely manner and should be delivered in an amount sufficient to reduce pain or inflammation. In general, it is expected that the drugs will be given within 24 hours of one another.

25 C. Dosages

With respect to therapeutic agents, it is expected that the skilled practitioner will adjust dosages on a case by case basis using methods well established in clinical medicine. Nevertheless, the following general guidelines with respect to two preferred COX-2
30 inhibitors and the most preferred thromboxane A2 receptor antagonist may be of help.

Celecoxib (Celebrex®) is particularly useful when contained in tablets of from about 100 to 200 mg. Recommended dosages are typically 100 mg twice per day or 200 mg once

per day(see, Bolten, J., *Rheumatolog. Suppl.*, 51:2-7 (May, 1998)). Celecoxib is a preferred COX-2 inhibitor in the compositions and methods of the present invention and should typically be present at 50-500 mg per unit dose. Especially preferred are methods and compositions utilizing 10 to 100 mg of ifetroban and 100 to 400 mg celecoxib.

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Rofecoxib (Vioxx®) for oral administration is available in tablets of 12.5, 25 or 50 mg and in an oral suspension containing either 12.5 mg or 25 mg rofecoxib per 5 ml. The recommended initial daily dosage for the management of acute pain is 50 mg. Peak plasma concentrations of rofecoxib typically occur about 2-3 hours after oral administration and the
10 drug has a half life of about 17 hours.

The thromboxane A2 receptor antagonist should be present at a level sufficient to treat cardiovascular disease as suggested in the various patent publications cited above. In the case of ifetroban, between 1 mg/kg/day and 100 mg/kg/day should typically be given. If
15 desired, the agents may also be given to treat any of the cardiovascular problems that have been disclosed as being amenable to treatment with thromboxane A2 receptor antagonists.

The daily dosage may be provided in either a single or multiple regimen with the latter being generally preferred. These are simply guidelines since the actual dose must be
20 carefully selected and titrated by the attending physician based upon clinical factors unique to each patient. The optimal daily dose will be determined by methods known in the art and will be influenced by factors such as the age of the patient, the disease state, side effects associated with the particular agent being administered and other clinically relevant factors. In some cases, a patient may already be taking medications at the time that treatment with
25 the present combination is initiated. These other medications may be continued provided that no unacceptable adverse side effects are reported by the patient.

What is Claimed is:

1. A pharmaceutical composition in unit dose form, comprising:
 - (a) a COX-2 inhibitor; and
 - (b) a thromboxane A2 receptor antagonist;wherein said COX-2 inhibitor and said thromboxane A2 receptor antagonist are present in a therapeutically effective amount.
2. The pharmaceutical composition of claim 1, wherein said COX-2 inhibitor is selected from the group consisting of: celecoxib; rofecoxib; meloxicam; JTE-522; L-745,337; NS398; and pharmaceutically acceptable salts thereof.
3. The pharmaceutical composition of claim 2, wherein said COX-2 inhibitor is celecoxib, or a pharmaceutically acceptable salt thereof.
4. The pharmaceutical composition of claim 3, wherein said celecoxib is present in an amount of between 5 and 500 mg.
5. The pharmaceutical composition of claim 2, wherein said COX-2 inhibitor is rofecoxib, or a pharmaceutically acceptable salt thereof.
6. The pharmaceutical composition of claim 2, wherein said COX-2 inhibitor is meloxicam, or a pharmaceutical acceptable salt thereof.
7. The pharmaceutical composition of claim 2, wherein said COX-2 inhibitor is JTE-522, or a pharmaceutically acceptable salt thereof.
8. The pharmaceutical composition of either claim 1 or claim 2, wherein said thromboxane A2 receptor antagonist is a 7-oxabicycloheptane substituted prostaglandin analog; a benzenealkonic acid; or a benzenesulfonamide derivative.

9. The pharmaceutical composition of claim 8, wherein said thromboxane A2 receptor inhibitor is a 7-oxabicycloheptane substituted prostaglandin analog.
10. The pharmaceutical composition of claim 9, wherein said a 7-oxabicycloheptane substituted prostaglandin analog is ifetroban.
11. The pharmaceutical composition of claim 10, wherein said ifetroban is present in an amount of between 5 and 500 mg.
12. A therapeutic package for dispensing to a patient which comprises:
 - (a) one or more unit doses, each such unit dose comprising:
 - (i) a COX-2 inhibitor; and
 - (ii) a thromboxane A2 receptor antagonist;wherein said COX-2 inhibitor and said thromboxane A2 receptor antagonist are present in a therapeutically effective amount; and
 - (b) a finished pharmaceutical container therefor, said container enclosing said unit dose or unit doses, and further comprising labeling directed to the use of said package in the treatment of any condition responsive to a COX-2 inhibitor or a thromboxane A2 receptor antagonist.
13. The therapeutic package of claim 12, wherein said labeling is directed to the use of said package in the treatment of inflammation, pain or a cardiovascular condition.
14. The therapeutic package of claim 13, wherein said labeling is directed to the use of said package in the treatment of a cardiovascular condition selected from the group consisting of: arterial or venous thrombosis; angina; a transient ischemic attack; and hypertension.
15. The therapeutic package of claim 13, wherein said labeling is directed to the use of said package in the treatment of pain associated with headache, muscle pain or post-surgical pain.

16. The therapeutic package of claim 13, wherein said labeling is directed to the use of said package in the treatment of inflammation associated with arthritis.
17. The therapeutic package of claim 13, wherein said COX-2 inhibitor and said thromboxane A2 receptor antagonist are each present in an amount of between 5 and 500 mg.
18. A method of treating a patient for any condition responsive to a COX-2 inhibitor or a thromboxane A2 receptor antagonist, comprising administering to said patient the pharmaceutical composition of claim 1.
19. The method of claim 18, wherein said patient is treated for pain, inflammation or a cardiovascular condition.
20. The method of claim 19, wherein said patient is treated for a cardiovascular condition selected from the group consisting of: arterial or venous thrombosis; angina; a transient ischemic attack; and hypertension.
21. The method of claim 19, wherein said patient is treated for pain associated with headache, muscle pain or post-surgical pain.
22. The method of claim 19, wherein said patient is treated for inflammation associated with arthritis.
23. The method of any one of claims 18-22, wherein said thromboxane A2 receptor antagonist is ifetroban and wherein said COX-2 inhibitor and said ifetroban are each present in an amount of between 5 and 500 mg.
24. A method of treating a patient for any condition responsive to a COX-2 inhibitor or a thromboxane A2 receptor antagonist, comprising: administering to said patient in a co-timely manner:
 - (a) a COX-2 inhibitor; and
 - (b) a thromboxane A2 receptor antagonist;

wherein said COX-2 inhibitor and said thromboxane A2 receptor antagonist are administered in a therapeutically effective amount.

25. The method of claim 24, wherein said patient is treated for pain, inflammation or a cardiovascular condition.
26. The method of claim 24, wherein said patient is treated for a cardiovascular condition selected from the group consisting of: arterial or venous thrombosis; angina; a transient ischemic attack; and hypertension.
27. The method of claim 24, wherein said patient is treated for pain associated with headache, muscle pain or post-surgical pain.
28. The method of claim 24, wherein said patient is treated for inflammation associated with arthritis.
29. The method of any one of claims 24-28, wherein said thromboxane A2 receptor antagonist is ifetroban and wherein said COX-2 inhibitor and said ifetroban are each present in an amount of between 5 and 500 mg.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 03/02633

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K45/06 A61P9/10 A61P19/02 A61K31/42 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 A61P

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, MEDLINE, EMBASE, BIOSIS, CHEM ABS Data, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 87343 A (MERCK FROSST CANADA INC ;TURNER MERVYN (CA); RIENDEAU DENIS (CA);) 22 November 2001 (2001-11-22) page 3, line 1 - line 6 page 3, line 14 - line 15 page 4, line 22 - line 24 page 16, line 15 - line 18; examples 1-7 -----	1-29

☐ Further documents are listed in the continuation of box C.☒ 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)
- *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

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0187343	A	22-11-2001	AU 5997401 A	26-11-2001
			WO 0187343 A2	22-11-2001
			CA 2407469 A1	22-11-2001
			EP 1283723 A2	19-02-2003
			US 2002016342 A1	07-02-2002
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