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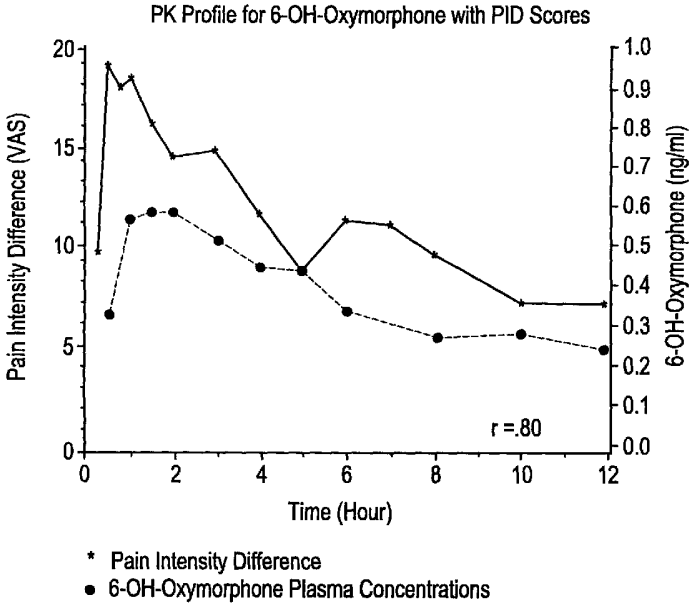
[Continued on next page]

(54) Title: PARENTERAL ADMINISTRATION OF 6-HYDROXY-OXYMORPHONE FOR USE AS AN ANALGESIC



(57) Abstract: In a method of treating pain a patient is administered a pharmaceutical composition of 6-hydroxy oxymorphone in an amount sufficient to induce analgesia. In one embodiment,the pharmaceutical composition is administered parenterally, preferably by injection and intravenous drip. To achieve the desired analgesic effect, blood plasma levels of 6-hydroxy oxymorphone are raised to at least approximately 0.05 ng/mL during treatment. Administration of compositions containing 6-hidroxy oxymorphone, and one or more carriers, diluents, and excipients in an amount sufficient to induce analgesia is also contemplated.

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ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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PARENTERAL ADMINISTRATION OF 6-HYDROXY-OXYMORPHONE FOR USE AS AN ANALGESIC

This application relates to provisional patent application serial nos. 60/329,445 filed October 15, 2001, 60/329,432 filed October 15, 2001, 60/303,357 filed July 6, 2001, and 60/329,444 filed October 15, 2001.

Background

Field of Invention

The invention relates to methods for alleviating pain. More particularly, the invention relates to methods for alleviating pain by administering 6-hydroxy oxymorphone. Most particularly, the invention relates to methods of inducing analgesia by increasing blood plasma levels of 6-hydroxy oxymorphone.

Summary of the Invention

The present invention provides methods for treating pain by administration of a pharmaceutical composition comprising 6-hydroxy oxymorphone in an amount sufficient to induce analgesia. In one embodiment, the pharmaceutical composition is administered parenterally, preferably by injection and intravenous drip. To achieve the desired analgesic effect, blood plasma levels of 6-hydroxy oxymorphone are raised to at least approximately 0.05 ng/mL. Methods for administering compositions comprising 6-hydroxy oxymorphone, and one or more carriers, diluents, and excipients in an amount sufficient to induce analgesia are also provided.

Brief Description of the Drawings

Fig. 1 is a pharmacokinetic profile for 6-hydroxy oxymorphone with PID scores.

Fig. 2 is a pharmacokinetic profile for oxymorphone with PID scores.

Fig. 3 is a pharmacokinetic profile for 6-hydroxy oxymorphone with categorical pain scores.

Fig. 4 is a pharmacokinetic profile for oxymorphone with categorical pain scores.

Detailed Description

The methods described herein provide for the direct administration of a pharmaceutical composition containing 6-hydroxy oxymorphone as an active ingredient. In a preferred embodiment the composition comprising 6-hydroxy oxymorphone alone (excepting, of course, carriers, diluents, and other excipients), In other embodiments, 6-hydorxy oxymorphone may be combined with other opioids or other pharmaceutical agents. For example compositions comprising both 6-hydroxy oxymorphone and its parent, oxymorphone.

In separate studies, blood plasma levels and indications of pain relief were recorded over a 12 hour period. Figs. 1-4 show graphical representation of the data combining the two studies such that the effect of blood plasma levels on pain can be evaluated.

The administration of oxymorphone yields blood plasma levels of oxymorphone and one of its metabolites, 6-hydroxy oxymorphone. Oxymorphone levels peak within 2 hours, fall slightly, and plateau. Interestingly, the level spikes again at 4-6 hours from administration. After this time, oxymorphone levels again drop and eventually fall to levels near the earlier plateau.

Like oxymorphone, 6-hydroxy oxymorphone blood plasma levels peak within 2 hours after administration. After the initial peak, however, a more or less steady decline in the 6-hydroxy oxymorphone's plasma levels is observed.

Comparing these levels to the pain profiles, a correlation between the 6-hydroxy oxymorphone blood plasma levels and pain relief can be seen. The pain levels nearly mirror the 6-hydroxy oxymorphone levels, with substantial rises in relief near the spikes associated with oxymorphone blood levels. Thus, pain relief can be achieved through administration of 6-hydroxy oxymorphone alone.

In addition to the pharmacokinetic studies, binding studies have been conducted to compare the binding affinity of 6-hydroxy oxymorphone to that of oxymorphone. The results are reported in TABLE 1. These results clearly indicate that 6-hydroxy oxymorphone has great binding affinity for the δ, κ and μ, receptor cites, comparable to the binding affinity of its parent. The inventors believe that by virtue of this binding

affinity, 6-hydroxy oxymorphone has similar analgesic effects to its parent, oxymorphone.

TABLE 1: ASSAY REPORT

	6-HYDROXY OXYMORPHONE		OXYMORPHONE	
	10nm 1.0 E-8	**10μm 1.0 E-5**	**10nm 1.0 E-8**	**10μm 1.0 E-5**
Opiate, Delta 1	-4.12%	90.48%	-18.26%	89.03%
Opiate, Delta 2 (Human Recombinant)	7.19%	55.45%	7.76%	72.74%
Opiate, Kappa (Human Recombinant)	2.45%	62.47%	10.35%	89.41%
Opiate, Mu (Human Recombinant)	63.16%	99.91%	85.42%	100.39%

Accordingly, methods of administering the metabolite, 6-hydroxy oxymorphone, directly have been developed. It is believed that the β isomer has greater efficacy in the treatment of pain, but this disclosure is not limited to use of that isomer alone. Pharmaceutical compositions containing either 6-α-hydroxy oxymorphone, 6-β-hydroxy oxymorphone, or mixtures thereof can be used in the invention.

Parenteral administration of 6-hydroxy oxymorphone ensures immediate release into the blood stream and the quickest route to pain relief. Administration of a composition containing 6-hydroxy oxymorphone by injection, IV drip, or other means is most effective. Regardless of the actual route of administration, an amount of 6-hydroxy oxymorphone sufficient to induce analgesia will be supplied. Blood plasma levels of 6-

hydroxy oxymorphone must be raised to levels sufficient to induce the desired level of analgesia.

The amount administered will be dependent upon normal criteria such as patient weight, intensity of pain, and other factors. Based on the pharmacokinetic studies blood plasma levels around at least 0.05 ng/mL will provide some analgesia. The upper plasma level limit will be ultimately established by safety concerns. Over-dosing of any opioid, including 6-hydroxy oxymorphone, can lead to respiratory failure and other undesirable side effects, and can even result in death. Preferably, the blood plasma level of 6-hydroxy oxymorphone will be raised to at least 0.075 ng/mL. Subsequent doses may be required to maintain these blood levels.

The preferred administration is of 6-hydroxy oxymorphone with appropriate carriers and excipients as will be readily apparent to those skilled in the art. The resulting blood plasma in these preferred administrations will therefore be substantially free of oxymorphone.

The above description encompasses some preferred embodiments of the invention. This disclosure is merely illustrative in nature and is not intended to limit the following claims.

CLAIMS

What is claimed is:

1. A method of treating pain comprising:

administering parenterally to a patient a pharmaceutical composition comprising 6-hydroxy oxymorphone in an amount sufficient to induce analgesia.

2. The method of claim 1 wherein said pharmaceutical composition is administered by injection or IV drip.

3. The method of claim 1 wherein said administration is sufficient to raise blood plasma levels of 6-hydroxy oxymorphone to at least about 0.05 ng/mL.

4. The method of claim 1 wherein said administration is sufficient to raise blood plasma levels of 6-hydroxy oxymorphone to at least about 0.075 ng/mL.

5. A method of treating pain comprising about parenterally administering to a patient a pharmaceutical composition comprising 6-hydroxy oxymorphone, and one or more carriers, diluents, and excipients in an amount sufficient to induce analgesia.

6. A pharmaceutical comprising 6-hydroxy oxymorphone in a solution for parenteral delivery to animals, including humans.

7. A method of treating pain comprising:

parenterally administering to a patient a pharmaceutical composition comprising 6-hydroxy oxymorphone and oxymorphone in an amount sufficient to induce analgesia.

FIG. 1

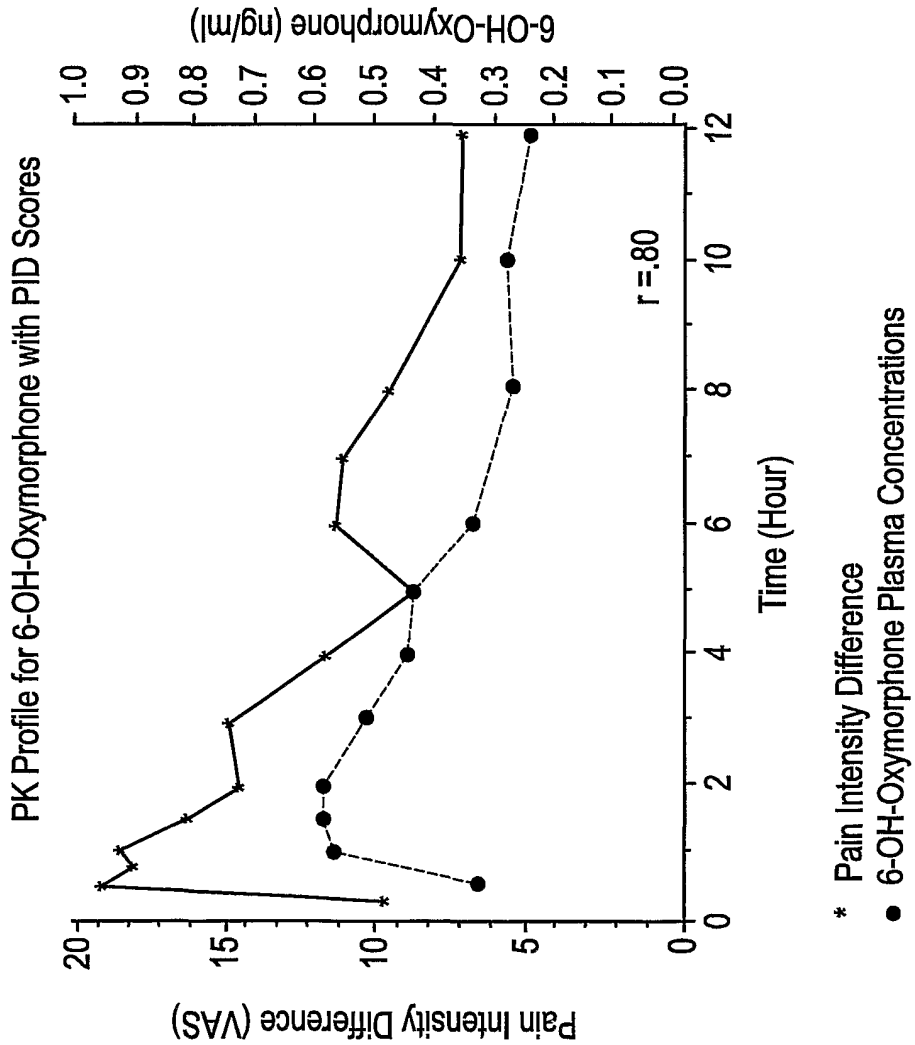

PK Profile for 6-OH-Oxymorphone with PID Scores
Pain Intensity Difference (VAS)
6-OH-Oxymorphone (ng/ml)
Time (Hour)
r =.80
* Pain Intensity Difference
● 6-OH-Oxymorphone Plasma Concentrations

FIG. 2

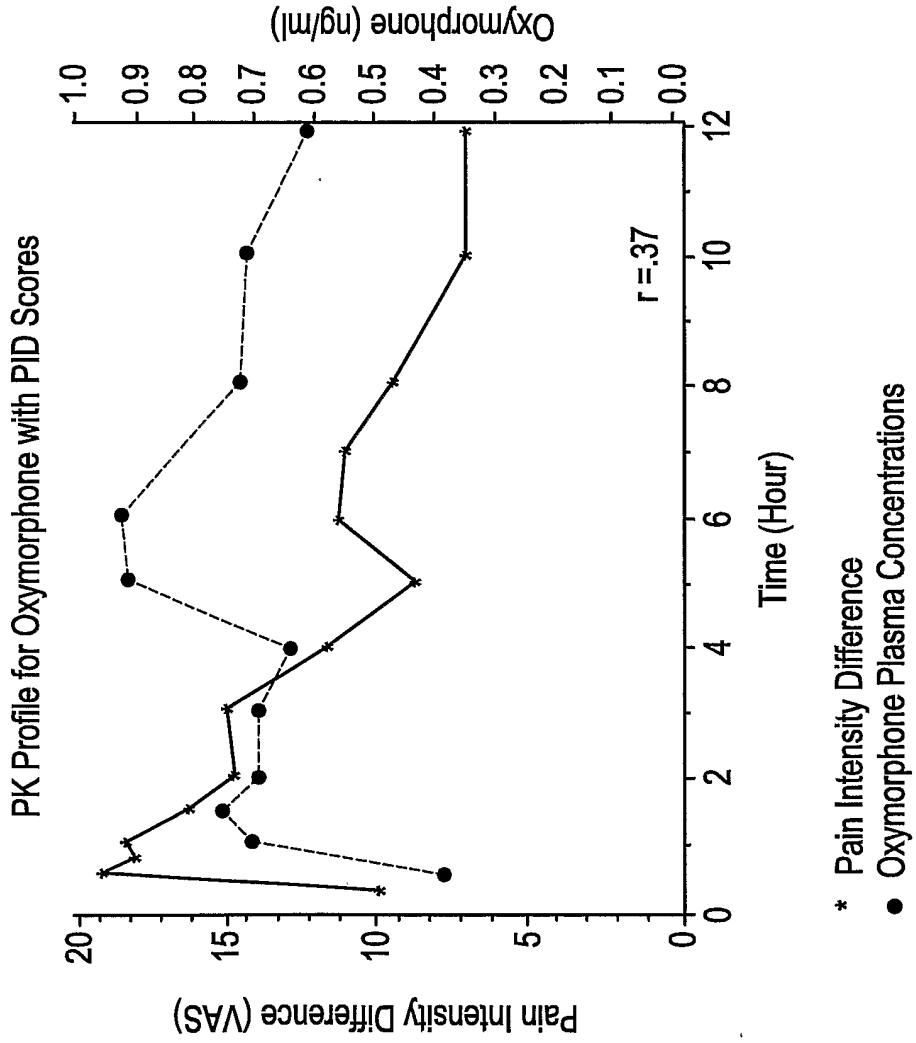

PK Profile for Oxymorphone with PID Scores
Pain Intensity Difference (VAS)
Oxymorphone (ng/ml)
Time (Hour)
r =.37
* Pain Intensity Difference
● Oxymorphone Plasma Concentrations

FIG. 3

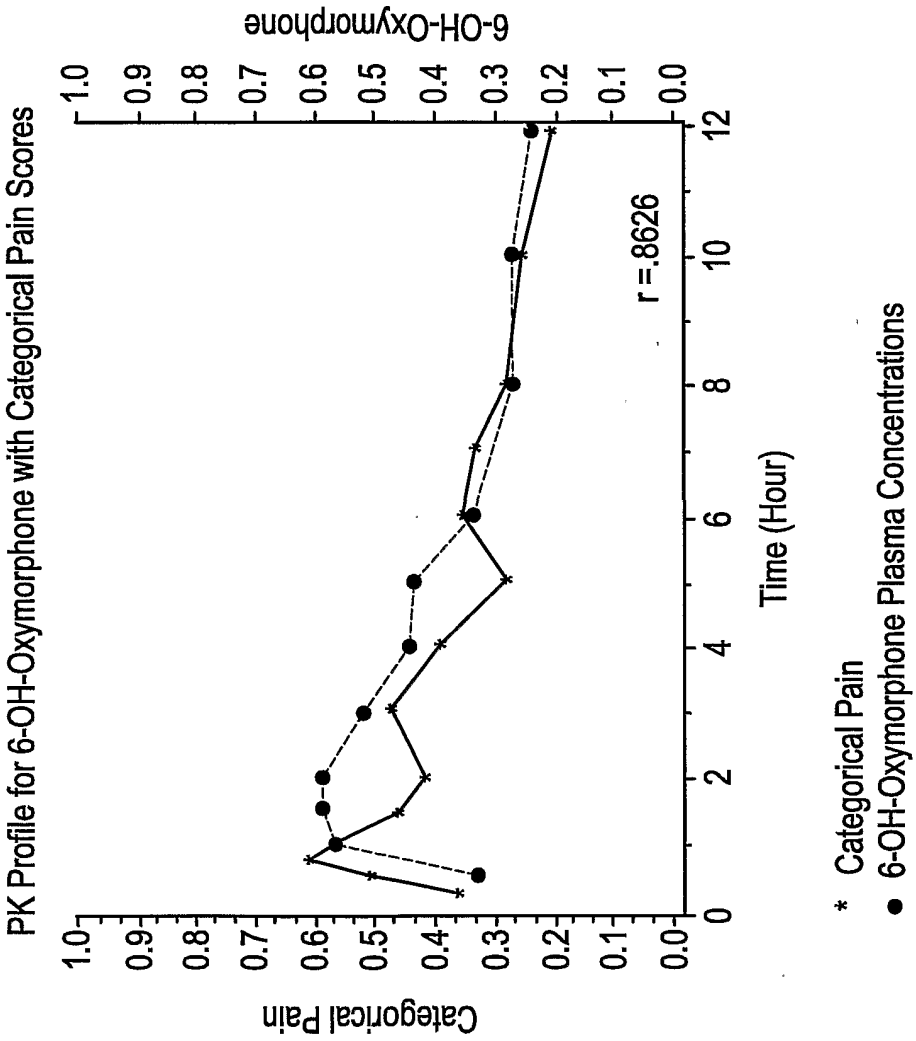
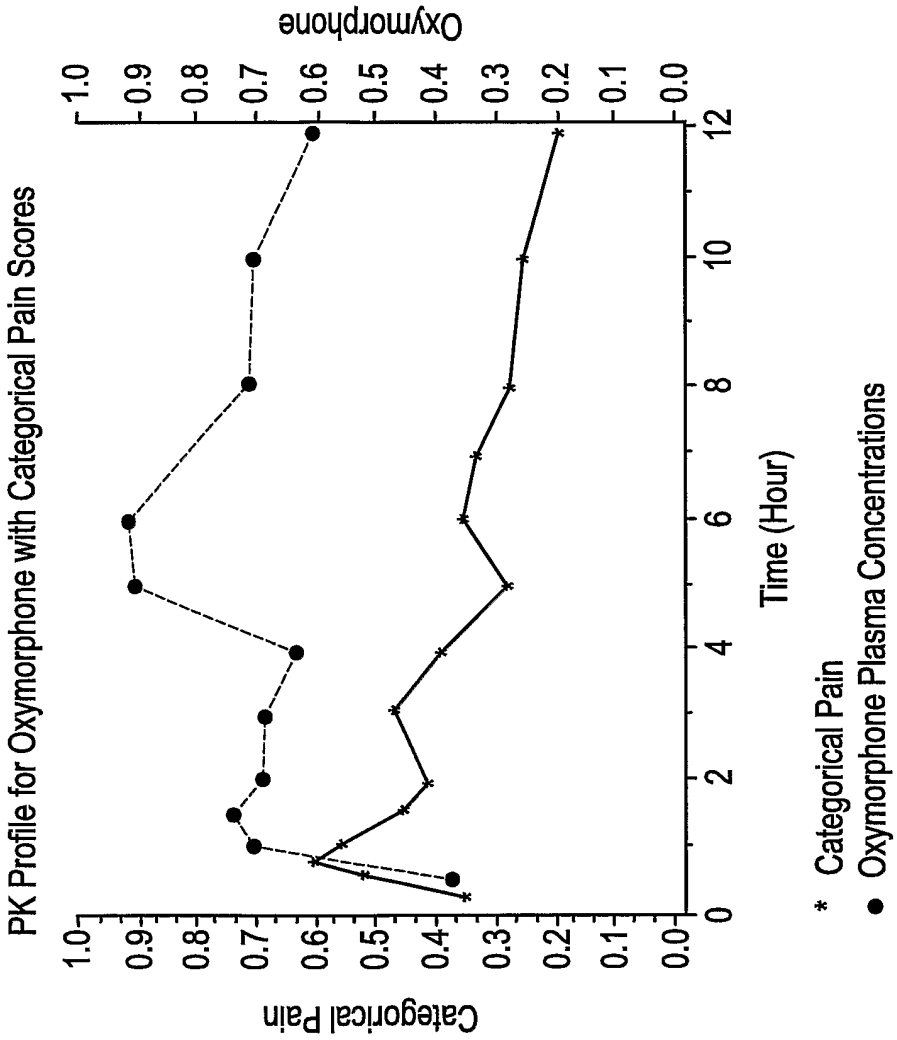

PK Profile for 6-OH-Oxymorphone with Categorical Pain Scores
Categorical Pain
6-OH-Oxymorphone
Time (Hour)
r = .8626
* Categorical Pain
● 6-OH-Oxymorphone Plasma Concentrations

FIG. 4


PK Profile for Oxymorphone with Categorical Pain Scores
Categorical Pain
Oxymorphone
Time (Hour)
* Categorical Pain
● Oxymorphone Plasma Concentrations
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
0
2
4
6
8
10
12

INTERNATIONAL SEARCH REPORT

In ional Application No
PCT/US 02/21398

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/485 A61K9/00 A61P25/04

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, CHEM ABS Data, EMBASE, SCISEARCH, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CONE, EDWARD J.: "General procedure for the isolation and identification of 6-.alpha.- and 6-.beta.-hydroxy metabolites of narcotic agonists and antagonists with a hydromorphone structure" J. CHROMATOGR. (1976), 129, 355-61, XP001106444 page 356; table 1 page 357, paragraph SECOND page 361 ---	1-7
Y	US 6 166 211 A (DRUMMOND JR SPENCER ET AL) 26 December 2000 (2000-12-26) column 2 --- -/--	1-7

[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)

"O" document referring to an oral disclosure, use, exhibition or other means

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"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
23 October 2002	06/11/2002

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	Brunnauer, H

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

INTERNATIONAL SEARCH REPORT

Ir ional Application No
PCT/US 02/21398

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	CONE E J ET AL: "Oxymorphone metabolism and urinary excretion in human, rat, guinea pig, rabbit, and dog." DRUG METABOLISM AND DISPOSITION, (1983 SEP-OCT) 11 (5) 446-50., XP001106446 abstract page 446, right-hand column	1-7
Y	US 4 844 907 A (ELGER GORDON A ET AL) 4 July 1989 (1989-07-04) claims 1,2	1-7
Y	US 5 629 011 A (ILLUM LISBETH) 13 May 1997 (1997-05-13) claims 1,9	1-7
Y	US 4 366 159 A (MAGRUDER MICHAEL R) 28 December 1982 (1982-12-28) column 3, line 35-37 - line 55-59	1-7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/21398

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 1-5 and 7 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 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 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

In ional Application No
PCT/US 02/21398

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