PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
A61K 45/06, 33/08	A1	WO 94/03209
		(43) International Publication Date: 17 February 1994 (17.02.94)

(21) International Application Number: PCT/US93/06725

(22) International Filing Date: 19 July 1993 (19.07.93)

(30) Priority data:
921,880 29 July 1992 (29.07.92) US

(60) Parent Application or Grant
(63) Related by Continuation
US 921,880 (CIP)
Filed on 29 July 1992 (29.07.92)

(71) Applicants *(for all designated States except US):* MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MCNEIL-PPC, INC. [US/US]; Van Liew Avenue, Milltown, NJ 08850 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only) :* SIMS, Robert, T. [US/US]; 5080 Anderson Road, Holicong, PA 18928 (US). SLIVKA, William [US/US]; 9425 Meadowbrook Lane, Philadelphia, PA 19118 (US). GATES, Thomas, N. [US/US]; 132 Sandywood Drive, Doylestown, PA 18901 (US).

(74) Agent: WINOKUR, Melvin; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(81) Designated States: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: DEXIBUPROFEN/ANTACID/SIMETHICONE COMBINATIONS

(57) Abstract

This invention relates to pharmaceutical compositions for use in the treatment of pain and inflammation and in the relief of indigestion, sour stomach, heartburn und other gastrointestinal disorders in mammals, including humans, by administering compositions comprising (i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and (ii) an amount effective in the treatment of acid indigestion, sour stomach, heartburn, and other gastrointestinal disorders of an antacid; and (iii) simethicone.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**FR**	France	**MR**	Mauritania
AU	Australia	**GA**	Gabon	**MW**	Malawi
BB	Barbados	**GB**	United Kingdom	**NE**	Niger
BE	Belgium	**GN**	Guinea	**NL**	Netherlands
BF	Burkina Faso	**GR**	Greece	**NO**	Norway
BG	Bulgaria	**HU**	Hungary	**NZ**	New Zealand
BJ	Benin	**IE**	Ireland	**PL**	Poland
BR	Brazil	**IT**	Italy	**PT**	Portugal
BY	Belarus	**JP**	Japan	**RO**	Romania
CA	Canada	**KP**	Democratic People's Republic of Korea	**RU**	Russian Federation
CF	Central African Republic			**SD**	Sudan
CG	Congo	**KR**	Republic of Korea	**SE**	Sweden
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovak Republic
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LU**	Luxembourg	**TD**	Chad
CS	Czechoslovakia	**LV**	Latvia	**TG**	Togo
CZ	Czech Republic	**MC**	Monaco	**UA**	Ukraine
DE	Germany	**MG**	Madagascar	**US**	United States of America
DK	Denmark	**ML**	Mali	**UZ**	Uzbekistan
ES	Spain	**MN**	Mongolia	**VN**	Viet Nam
FI	Finland				

TITLE OF THE INVENTION

DEXIBUPROFEN/ANTACID/SIMETHICONE COMBINATIONS

BACKGROUND OF THE INVENTION

The non-steroidal anti-inflammatory drugs (NSAID) have been utilized in the treatment of pain/inflammation and a number of other symptoms including stiffness that are associated with painful conditions affecting muscles, bones, and joints. NSAIDs have been prescribed to relieve back pain, gout, menstrual pain, headaches, mild pain following surgery, and pain from soft tissue injuries such as sprains and strains. NSAIDs are within the broader class of non-narcotic analgesics which also includes aspirin and acetaminophen. Non-narcotic analgesics are considered to exert their effect by blocking the production of prostaglandins at the site of pain, irritation or injury so that the pain signal does not reach the brain.

Ibuprofen (2-(4-isobutylphenyl)propionic acid) is a well known and commonly employed NSAID. Recently, it has been found that a faster onset of pain relief and an enhanced analgesic response can be obtained by the utilization of the single enantiomer (S)-ibuprofen (also known as (+)-ibuprofen or dexibuprofen) rather than the racemic mixture of ibuprofen. See U.S. Patent 4,877,620.

Antacids are commonly prescribed to treat excess acid buildup in the stomach, duodenum or esophagus. Damage to the mucus lining surrounding these tissues may occur which also enables destructive action of the stomach acids on the underlying tissue. Commonly known antacids include aluminum hydroxide, calcium carbonate, magnesium hydroxide and sodium bicarbonate. Simethicone may optionally be used to treat flatulence.

Combinations of ibuprofen with antacids and simethicone have been disclosed. EPO App. No. 0 465 235 A1 discloses a combination of ibuprofen and an antacid and optionally simethicone. It is known that the potential of most NSAIDs to irritate the stomach is less that of an analgesic such as aspirin. There is a need to employ a compound with faster acting and enhanced analgesic capability such as (S)-ibuprofen lysinate substantially free of (R)-ibuprofen in combination with an antacid to treat and prevent the pain and discomfort associated with headaches, indigestion, sour stomach, heartburn or other gastrointestinal disorders. The present invention provides both faster onset and enhanced relief of aches and pains associated with the head and stomach to provide broad and concurrent symptomatic relief.

DETAILED DESCRIPTION OF THE INVENTION

This invention claims pharmaceutical compositions for use in the treatment of pain and inflammation and the treatment of mild stomach and esophagus disorders. The composition comprises:
(i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from
(S)-ibuprofen-(S)-lysine and
(S)-ibuprofen-(R)-lysine; and
(ii) an amount effective in the treatment of indigestion, sour stomach, heartburn, and other gastrointestinal disorders of at least one antacid; and
(iii) an amount effective in the treatment of flatulence of simethicone.

This invention is also directed to a method of treating pain and inflammation and concurrently treating indigestion, sour stomach, heartburn, and other gastrointestinal disorders in mammals, including humans, in need thereof, comprising administering to such organism:

(i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from
(S)-ibuprofen-(S)-lysine and
(S)-ibuprofen-(R)-lysine; and
(ii) an amount effective in the treatment of indigestion, sour stomach, heartburn, and other gastrointestinal disorders of at lease one antacid; and
(iii) an amount effective in the treatment of flatulence of simethicone.

This invention is further directed to a method of eliciting an onset hastened and enhanced response for the treatment of pain and inflammation and the treatment of gastrointestinal or esophagus disorders in mammals, including humans, in need thereof, comprising administering to such organism:
(i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and
(S)-ibuprofen-(R)-lysine; and
(ii) an amount effective in the treatment of indigestion, sour stomach, heartburn, and other gastrointestinal disorders of at least one antacid; and
(iii) an amount effective in the treatment of flatulence of simethicone.

Substantially free of (R)-ibuprofen means that the ratio of (S)-ibuprofen to (R)-ibuprofen is at least 90:10.

Salts of (S)-ibuprofen include pharmaceutically acceptable salts such as alkali metals (sodium or potassium), alkaline earth metals (calcium), or salts with other metals such as magnesium, aluminum, iron, zinc, copper, nickel or cobalt.

Pharmaceutically acceptable salts of (S)-ibuprofen further include the amino acid salts, particularly the basic amino acids such as lysine or arginine. Specifically included within the composition of the instant invention is (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine.

The term mammals or mammalian organism

includes but is not limited to man, dog, cat, horse and cow.

The term treatment encompasses the complete range of therapeutically positive effects associated with pharmaceutical medication including reduction of, alleviation of and relief from the symptoms or illness which affect the organism.

(S)-ibuprofen may be prepared following the procedures disclosed in U.S. Patent 4,877,620. Metal salts of ibuprofen may be obtained by contacting a hydroxide, or carbonate with ibuprofen. Amino acid salts of ibuprofen may be obtained by contacting an amino acid in solution with ibuprofen. U.S. Patent No. 4,994,604 describes a process for the formation and resolution of (S)-ibuprofen-(S)-lysine that employs preferential crystallization to separate a pair of diastereomeric salts, (S)-ibuprofen-(S)-lysine and (R)-ibuprofen-(S)-lysine. The basic procedure involves (a) contacting (R),(S)-ibuprofen and (S)-lysine in an aqueous-organic solvent mixture; (b) separating any suspended solid from the mixture; and (c) cooling the clear mixture until the mixture is supersaturated with respect to each of the (S)-ibuprofen-(S)-lysine and (R)-ibuprofen-(S)-lysine salts; (d) contacting the supersaturated mixture with a slurry of (S)-ibuprofen-(S)-lysine in an aqueous-organic solvent; and (e) separating the formed crystalline (S)-ibuprofen-(S)-lysine.

Specifically, the racemic ibuprofen starting material is mixed with an organic solvent that is miscible with water. The (S)-lysine is mixed with water and the ibuprofen and lysine solutions are combined.

The mixture is agitated for a time period sufficient to crystallize all the salts, if any, in excess of the solubility limit. The suspended salts are separated to obtain a clear mother liquor which is generally saturated with respect to the diastereomeric salts (S)-ibuprofen-(S)-lysine and (R)-ibuprofen-(S)-lysine. Filtration may be employed to effect the separation. The liquor is then cooled to a temperature at which it is supersaturated with respect to each of the diastereomeric salts. It is preferred that the liquor be cooled to the point at which maximum supersaturation is obtained with respect to each salt without nucleation of either crystallizable species. Typically the temperature of the mother liquor must be lowered by about 5°C to reach maximum supersaturation without precipitation of either salt. However, the degree of cooling will depend on the particular solvent composition. The supersaturated liquor is then passed into a vessel containing a slurry of (S)-ibuprofen-(S)-lysine, hereafter referred to as the (S,S) salt, in the same solvent system employed above for the mixture of racemic ibuprofen and (S)-lysine. In the presence of the (S,S) salt crystals acting as a seed, the supersaturation of the (S,S)-salt in the feed liquor is released by the growth of further crystals of the (S,S)-salt. Conversely, there is little or no change in the (R)-ibuprofen-(S)-lysine supersaturation because the growth rate of the (R,S) crystals is essentially zero in the absence of any initial (R,S) salt seed. The (S,S) crystals are then separated by filtration or centrifugation and washed with aqueous-organic solvent to yield (S)-ibuprofen-(S)-lysine of purity approximating 98%.

The pharmaceutical compositions of the present invention are useful in the rapid and enhanced treatment of pain and inflammation and in the treatment of various mild gastrointestinal disorders including indigestion, sour stomach, and heartburn and flatulence. In particular, the (S)-ibuprofen-(S)-lysinate combined with an antacid such as aluminum hydroxide/magnesium hydroxide containing an anti-foaming agent such as simethicone is useful for the treatment of pain, inflammation, and the various gastrointestinal disorders such as indigestion, sour stomach, or heartburn and flatulence. The utilization of (S)-ibuprofen-(S)-lysine in an analgesic/antacid/simethicone combination offers significant advantages over the combination of racemic ibuprofen or (S)-ibuprofen and an antacid.

The lysine salt of (S)-ibuprofen provides a faster onset of pain and inflammation relief and an enhanced degree of relief compared to racemic ibuprofen. These benefits contribute to overall enhanced and faster relief of symptoms associated with headaches and other aches and pains that often accompany gastrointestinal disorders when the (S)-ibuprofen lysinate is combined with an antacid and simethicone.

The absence or reduction of (R)-ibuprofen also provides significant benefits. The allergic contraindications sometimes associated with ibuprofen administration are absent or reduced in a (R)-ibuprofen-free or substantially-free composition. An additional advantage may be that less metabolic energy will be used to convert the

inactive (R)-ibuprofen to the active (S)-ibuprofen. In addition, a reduced burden may be placed on the urogenital system since administration of the pure (S)-ibuprofen salt eliminates the need to excrete the (R)-ibuprofen or its metabolites. The absence of the (R)-enantiomer also reduces or eliminates the incorporation of this molecule into fatty tissue. The renal burden and renal toxicities sometimes associated with racemic ibuprofen therapy may be reduced or eliminated in a (S)-ibuprofen salt composition that is substantially free of the (R) enantiomer.

Antacids are well known in the treatment of ulcers and other gastrointestinal disorders and may be used in combination with (S)-ibuprofen salts. Antacids used for the treatment of gastrointestinal pain and discomfort fall into four major groups: aluminum compounds; magnesium compounds, calcium buffers, or sodium buffers. Antacids are used to neutralize stomach or gastrointestinal acids and to relieve associated pain and discomfort. Antacids are well tolerated and thus advantageously may be used in the present invention in combination with (S)-ibuprofen. A rapid acting and faster onset analgesic such as (S)-ibuprofen-(S)-lysinate with a potent or mild antacid provides a combination which simaltaneously and selectively provides relief from headaches, pain, inflammation, and discomfort and injury to the stomach, esophagus, or duodenum from excess production of gastric acid.

The absence of inactive enantiomers, particularly (R)-ibuprofen provides for significant size and weight advantages in a combination dosage

form, particularly a sustained release dosage from. Where a sustained release dosage of ibuprofen may have required 800 to 1000 mg, the employment of (S)-ibuprofen reduces the weight to 400 to 500 mg, and provides for a more practical size tablet for an ibuprofen/antacid combination.

An effective amount of an (S)-ibuprofen salt for use in a unit dose composition of this invention may range from 50-800 mg (S)-ibuprofen salt. The preferred amount of (S)-ibuprofen is about 100 to 400 mg. The amount of a salt such as (S)-ibuprofen-(S)-lysinate is determined based on the amount of (S)-ibuprofen contained therein.

The antacid employed herein may be selected from any of the commercially available or known antacids or combinations thereof such as aluminum hydroxide, calcium carbonate, magnesium hydroxide or sodium bicarbonate. The combination of aluminum hydroxide/magnesium hydroxide is advantageously used in the present invention in combination with (S)-ibuprofen-(S)-lysine. The amount of the antacid used in the present invention in humans may range from 5 mg to 1500 mg depending upon the specific antacid employed. When the composition is administered in the form of a tablet or capsule, the amount of antacid may vary from about 20 to 1,500 mg per tablet/capsule. When the composition is administered in the form of an elixir, syrup or suspension the amount of the antacid may vary from about 5 mg to 150 mg per mL of composition. Advantageously, the composition if in tablet or capsule form contains about 200-400 mg aluminum hydroxide, 200-400 mg magnesium hydroxide,

and 1-40 mg of simethicone and is administered in combination with 100 to 400 mg of (S)-ibuprofen. More advantageously, the ratio of magnesium hydroxide to aluminum hydroxide in the above composition is 1:1. A composition in elixir, syrup or suspension form advantageously comprises aluminum hydroxide in the amount of about 40-80 mg per ml of liquid and simethicone in the amount of about 4 to 8 mg. The combination claimed in the instant invention is advantageously administered orally.

Additional foaming agents besides simethicone may also be added to the composition of the instant invention. Foaming agents act to relieve symptoms associated with excess gas that often accompany gastrointestinal disturbance. Foaming agents such as sodium alginate may be added to create a foam that acts as a physical barrier to block stomach acids from backing up into the esophagus thereby preventing heartburn. The composition of the instant invention may further comprise an anti-ulcerative agent such as sucralfate, misoprostol and the like. The composition of the instant invention may also further comprise a pro-motility agent to improve gastro/esophageal peristalsis and relieve the symptoms of indigestion. Such a pro-motility agent is selected from metoclopramide hydrochloride, cisapride and the like.

The present composition may be administered in the form of tablets, caplets, gelcaps, capsules, elixirs, syrups, or suspensions. For oral administration, the active ingredients may be admixed with a pharmaceutically acceptable diluent such as lactose, starch, sucrose, cellulose, magnesium

stearate, dicalcium phosphate, calcium sulfate, mannitol, and, in a liquid composition, ethyl alcohol. Acceptable binders such as PVP, starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes, may also be admixed with the active components. Where necessary, lubricants such as magnesium stearic acid talc, boric acid, sodium benzoate, sodium acetate and sodium chloride, and disintegrators such as docusate sodium, sodium starch glycolate or cross-linked PVP may also be included.

The active components may also be formulated in sustained release formulations. These formulations may be employed in oral, dermal, rectal or vaginal administrations. Such sustained release formulations also include layered formulations which provide for distinct release ratio and thus may be more effective in allowing for short and long term relief

The following examples illustrate the compositions of the present invention and as such are not to be considered as limiting the invention set forth in the claims.

EXAMPLE 1

(S)-Ibuprofen lysinate/antacid Tablet

(S)-ibuprofen-(S)-lysine	342 mg
Aluminum Hydroxide	250 mg
Magnesium Hydroxide	250 mg
PVP	15 mg
Avicel PH101	40 mg
Magnesium Stearate	4 mg

EXAMPLE 2

(S)-Ibuprofen lysinate/antacid/anti-gas Tablet

(S)-ibuprofen-(S)-lysine	342 mg
Aluminum Hydroxide	250 mg
Magnesium Hydroxide	250 mg
PVP	15 mg
Avicel PH101	40 mg
Magnesium Stearate	4 mg
Simethicone	30 mg

EXAMPLE 3

(s)-Ibuprofen lysinate/antacid Sustained Release

(S)-ibuprofen-(S)-lysine	400 mg
Aluminum Hydroxide	250 mg
Magnesium Hydroxide	250 mg
PVP	30 mg
Avicel PH101	80 mg
Magnesium Stearate	8 mg
Methocel E10MCR	66 mg
Methocel K100MLV	200 mg

EXAMPLE 4

(S)-Ibuprofen/antacid/anti-gas Sustained Release

(S)-ibuprofen-(S)-lysine	400 mg
Aluminum Hydroxide	250 mg
Magnesium Hydroxide	250 mg
PVP	30 mg
Avicel PH101	80 mg
Magnesium Stearate	8 mg
Methocel E10MCR	66 mg
Methocel K100MLV	200 mg
Simethicone	30 mg

EXAMPLE 5

(S)-Ibuprofen-(S)-lysine/Antacid Solution

(S)-ibuprofen-(S)-lysine	342 mg
Aluminum Hydroxide	300 mg
g.s. syrup	5 ml

EXAMPLE 6

(S)-Ibuprofen-(S)-lysine/Antacid/Anti-Gas Solution

(S)-ibuprofen-(S)-lysine	342 mg
Aluminum Hydroxide	250 mg
Magnesium Hydroxide	250 mg
g.s. syrup	5 ml
Simethicone	30 mg

EXAMPLE 7

(S)-Ibuprofen-(S)-lysine/Antacid/Anti-Gas Solution

(S)-ibuprofen-(S)-lysine	342 mg
Aluminum Hydroxide	200 mg
Magnesium Hydroxide	200 mg
g.s. syrup	5 ml
Simethicone	30 mg

EXAMPLE 8

(s)-Ibuprofen-(S)-lysine/Antacid/Anti-Gas Solution

(S)-ibuprofen-(S)-lysine	342 mg
Aluminum Hydroxide	400 mg
Magnesium Hydroxide	400 mg
g.s. syrup	5 ml
Simethicone	30 mg

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for use in the treatment of pain and inflammation and the treatment of gastrointestinal disorders such as indigestion, sour stomach and heartburn in mammals, including humans comprising:
(i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and
(ii) an amount effective in the treatment of indigestion, sour stomach, heartburn, and other gastrointestinal disorders of at least one antacid; and
(iii) an amount effective in the treatment of flatulence of simethicone.

2. The composition according to Claim 1 comprising at least 50 mg of the salt of (S)-ibuprofen.

3. A composition of Claim 1 wherein the antacid is selected from; aluminum hydroxide, magnesium hydroxide, sodium bicarbonate, calcium carbonate, magnesium carbonate, magnesium oxide, magnesium trisilicate or combinations thereof.

4. The composition of Claim 3 wherein the antacid is aluminum hydroxide in combination with magnesium hydroxide.

5. The composition of Claim 4 wherein the antacid is aluminum hydroxide/magnesium hydroxide in a ratio of 1:1.

6. A method of treating pain and inflammation and the treating gastrointestinal disorders such as indigestion, sour stomach and heartburn, in a mammalian organism in need of such treatment, comprising administering to such organism:

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen, or a salt thereof, substantially free of (R)-ibuprofen;

(ii) an amount effective in the treatment of gastrointestinal disorders or associated symptoms of at least one of the antacids.

(iii) an amount effective in the relief of flatulence of simethicone.

7. A method according to Claim 6 wherein the composition administered to a mammalian organism in need thereof comprises:

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen-(S)-lysine;

(ii) an amount effective in the neutralization of gastric acid of an antacid;

(iii) an amount effective in the treatment of flatulence of simethicone.

8. A method of eliciting an onset enhanced and hastened response for the treatment of pain and inflammation and the treatment of gastrointestinal disorders such as indigestion, sour stomach and heartburn in a mammaliam organism in need of such treatment, comprising administering to such organism;

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen, or a salt thereof, substantially free of (R)-ibuprofen;

(ii) an amount effective in the treatment of gastrointestinal disorders or associated symptoms of at least one of the antacids;

(iii) an amount effective in the treatment of flatulence of simethicone.

9. A method according to Claim 8 wherein the composition administered to a mammalian organism in need thereof comprises:

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen-(S)-lysine;

(ii) an amount effective in the neutralization of gastric acid of a combination of magnesium hydroxide/aluminum hydroxide in a ratio of 1:1;

(iii) an amount effective in the treatment of flatulence of simethicone.

10. A method of reducing the side effects associated with the administration of a racemic ibuprofen/antacid combination which comprises the administration of (S)-ibuprofen, or a salt thereof, substantially free of (R)-ibuprofen, and at least one of the antacids and simethicone.

11. A method according to Claim 10 wherein the composition administrered to a mammalian organism in need thereof comprises:

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen-(S)-lysine;

(ii) an amount effective in the neutralization of gastric acid of an antacid;

(iii) an amount effective in the treatment of flatulence of simethicone.

12. A method of reducing the size and weight of a pharmaceutically effective amount of a racemic ibuprofen/antacid combination dosage form which comprises combining (S)-ibuprofen, or a salt thereof, substantially free of (R)-ibuprofen and at least one of the antacids and simethicone.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/06725

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 45/06; A61K 33/08
US CL :562/496 514/820; 424/690; 424/692

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)

U.S. :

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online; APS; Derwent

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,994,604 (Tung et al.) 19 February 1991. See entire document.	1, 2
Y	EP, A, 0,465,235 (GOLDMAN) 08 January 1992. See entire document.	1 to 12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search 30 JULY 1993	Date of mailing of the international search report 15 OCT 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer PHYLLIS SPIVACK Telephone No. (703) 308-0135

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