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(71) Applicant *(for all designated States except US)*: **ALLERGAN, INC.** [US/US]; 2525 Dupont Drive, Irvine, CA 92612 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TIEN, Walter, L.** [US/US]; 17551 Friends Ct., Irvine, CA 92614 (US). **GRAHAM, Richard** [US/US]; 5066 Balsawood, Irvine, CA 92612 (US). **CHANG, James, N.** [US/US]; 36 Cervantes, Newport Beach, CA 92660 (US).

(74) Agents: **JOHNSON, Brent, A.** et al.; c/o Allergan, Inc., 2525 Dupont Drive, Irvine, CA 92612 (US).

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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING CYCLOSPORINS

(57) Abstract: A liquid comprising a therapeutically effective concentration of a cyclosparin and a vitamin E tocopherol polyethylene glycol succinate, wherein said liquid is an aqueous solution, and wherein no hydrophilic organic solvent is present at a concentration greater than half of that of the cyclosporin is also disclosed herein. A composition comprising a therapeutically effective concentration of cyclosporin A and an effective amount of a vitamin E tocopherol polyethylene glycol succinate, wherein said composition is an aqueous liquid solution which is intended for ophthalmic use, and wherein no hydrophilic organic solvent is present at a mass concentration greater than or equal to that of the cyclosporin, is disclosed herein. A composition comprising a therapeutically effective concentration of cyclosparin A and an effective amount of a vitamin E tocopherol polyethylene glycol succinate, wherein said composition is an aqueous liquid solution which is intended for parenteral use, and wherein no hydrophilic organic solvent is present at a mass concentration greater than or equal to that of the cyclosporin, is disclosed herein. Methods of treating diseases or conditions using said compositions, and medicarrients related thereto, are also disclosed herein.

PHARMACEUTICAL COMPOSITIONS COMPRISING CYCLOSPORINS

By Inventors

Walter L. Tien, Richard Graham, and James N. Chang

Field of the Invention

The present invention relates to pharmaceutical compositions. In particular, the present invention relates to compositions comprising cyclosporins.

Background of the Invention

Description of the Related Art

Dry eye disease is a general term for a variety of conditions characterized by abnormalities in the tear film, which affects three million people in the United States alone. Dry eye is characterized by symptoms such as a sandy-gritty feeling in the eye, burning, irritation, or a foreign-body sensation that worsens during the day. Patients suffering from dry eye disease complain of mild to severe symptoms, and those with severe symptoms may experience constant and disabling eye irritation, and develop ocular surface epithelial disease and sight-threatening sterile or microbial corneal ulceration.

Cyclosporins are a group of nonpolar cyclic oligopeptides with immunosuppressant, anti-inflammatory, and anti-parasitic properties. Cyclosporin A is a cyclosporin which is marketed in a topical ophthalmic emulsion formulation for the treatment of dry eye by Allergan, Inc. under the tradename Restasis®. The insolubility of cyclosporins in water is an ongoing problem in the formulation of these compounds.

WO0008085 discloses "a composition for oral administration comprising (i) an immunosuppressant, e.g. cyclosporin, (ii) tocopherol (Vitamin E), tocotrienol or a derivative thereof, (iii) a short chain phospholipid, and (iv) a non-ionic surfactant", and claims that "composition of the invention can provide for good solubility of the immunosuppressant, e.g. cyclosporin, in an excipient mixture as well as good dispersibility when placed in an aqueous environment".

U.S. Patent No. 5,798,333 discloses "pharmaceutical compositions which enable high concentrations of a cyclosporin and are water-soluble, such that the compositions will dissolve in aqueous media without precipitation of the cyclosporin. The compositions comprise a cyclosporin dissolved in tocophersolan and a hydrophilic organic solvent, preferably propylene glycol." The patent further discloses that "the solvent selected should be an efficient solvent for cyclosporin, and also a solvent for tocophersolan.

Preferred organic solvents meeting these criteria include but are not necessarily limited to propylene glycol and various monoalcohols, including ethanol, benzyl alcohol, hexanol, and phenethyl alcohol.

Most preferred is propylene glycol because it has low toxicity and low volatility in addition to being an efficient solvent for cyclosporin.

The amount of propylene glycol needed to provide a stable solution of cyclosporin and tocophersolan is about 1 g per g of cyclosporin. A suitable solution preconcentrate will thus consist of 1 part cyclosporin, 7.5 parts tocophersolan and 1 part propylene glycol. "

U.S. Patent Application Publication No. 20030108626, published on Jun. 12, 2003, and filed on Nov. 1, 2001, discloses "a method and composition for treating a dry eye condition by topically applying to the eye surfaces an emulsion...Includable in the mixture is a non-soluble therapeutic agent, such as cyclosporin which is effective against an eye disease and is delivered to the eye by the film".

BRIEF DESCRIPTION OF THE INVENTION

A liquid comprising a therapeutically effective concentration of a cyclosporin and a vitamin E tocopherol polyethylene glycol succinate, wherein said liquid is an aqueous solution, and wherein no hydrophilic organic solvent is present at a concentration greater than half of that of the cyclosporin is also disclosed herein.

A composition comprising a therapeutically effective concentration of cyclosporin A and an effective amount of a vitamin E tocopherol polyethylene glycol succinate, wherein said composition is an aqueous liquid solution which is intended for ophthalmic use, and wherein no hydrophilic organic solvent is present at a mass concentration greater than or equal to that of the cyclosporin, is disclosed herein.

A composition comprising a therapeutically effective concentration of cyclosporin A and an effective amount of a vitamin E tocopherol polyethylene glycol succinate, wherein said composition is an aqueous liquid solution which is intended for parenteral use, and wherein no hydrophilic organic solvent is present at a mass concentration greater than or equal to that of the cyclosporin, is disclosed herein.

Methods of treating diseases or conditions using said compositions, and medicaments related thereto, are also disclosed herein.

DETAILED DESCRIPTION OF THE INVENTION

The compositions disclosed herein are aqueous liquid solutions according to the meaning generally understood in the art.

The term "cyclosporin" refers to any cyclosporin compounds known in the art including cyclosporin A, cyclosporin B, cyclosporin C, cyclosporin D, and cyclosporin G. In certain compositions, the cyclosporin is cyclosporin A.

The term "vitamin E tocopherol polyethylene glycol succinate" refers to an ester compound or a mixture of compounds derived from succinic acid, polyethylene glycol, and tocopherol. The compounds are diesters of succinic

acid, where the two ester linkages occur to a phenolic hydroxyl group of the tocopherol and a hydroxyl group of polyethylene glycol. Polyethylene glycol is $HO(CH_2CH_2O)_nH$, otherwise known as polyethylene oxide. The term tocopherol refers to a naturally occurring form of vitamin E, and may refer to a single compound or a mixture. Examples of tocopherols include α-tocopherol, *dl*-α-tocopherol, β-tocopherol, γ-tocopherol, and δ-tocopherol. Polyethylene glycol is the well known polymer of ethylene glycol. One useful tocopherol which is conveniently obtained commercially is sold by Eastman Chemical as Vitamin E TPGS NF. The US Pharmacopeia has designated tocophersolan as the name for Vitamin E TPGS NF.

The term "hydrophilic organic solvent" refers to an organic compound which is an efficient solvent for cyclosporin, and also a solvent for tocophersolan. Examples of hydrophilic organic solvents include propylene glycol and water-soluble monoalcohols, including ethanol, benzyl alcohol, hexanol, and phenethyl alcohol. In certain compositions, no hydrophilic organic solvent is present at a mass concentration greater than or equal to that of the cyclosporin. In other words, there is a greater mass of the cyclosporin than any hydrophilic solvent which may be present in the solution. In other compositions, no hydrophilic organic solvent is present at a mass concentration greater than half of that of the cyclosporin.

Certain compositions contain essentially no hydrophilic organic solvent.

A therapeutically effective concentration of cyclosporin is a concentration useful to observe a therapeutic effect as compared to a placebo composition having the same composition sans cyclosporin, and can be determined by a person of ordinary skill in the art without undue experimentation. While not intending to limit the scope of the invention in any way, the water solubility of cyclosporin A is 0.0007% by weight, so the use of vitamin E tocopherol polyethylene glycol succinate in the composition is often useful when the cyclosporin concentration is 0.001% or greater. In other embodiments, the concentration of cyclosporin is greater than 0.01%. In other embodiments, the concentration of cyclosporin is greater than 0.02%. In other embodiments, the concentration of cyclosporin is at least 0.05%. For the

treatment of dry eye disease, a cyclosporin concentration of less than or equal to 1% is often adequate. In other words, in certain compositions, the concentration of the cyclosporin is at or below 1%. In other embodiments, the concentration of cyclosporin is at or below 0.2%. In other embodiments, the concentration of cyclosporin is at or below 0.15%. In other embodiments, the concentration of cyclosporin is about 0.05%. In other embodiments, the concentration of cyclosporin is about 0.1%.

An effective amount of vitamin E tocopherol polyethylene glycol succinate is the amount useful to enhance solubility of the cyclosporin, and will depend upon the amount and kind of cyclosporin used, as well as what other excipients may be present in the composition. While not intending to limit the scope of the invention in any way, in many cases a vitamin E tocopherol polyethylene glycol succinate concentration of at least 0.5% is useful. In other cases a vitamin E tocopherol polyethylene glycol succinate concentration of at least 1% is useful. In certain cases, the vitamin E tocopherol polyethylene glycol succinate concentration may be less than or equal to 5%. Often, a concentration of vitamin E tocopherol polyethylene glycol succinate which is at least 8 times the concentration of the cyclosporin is useful. In other cases, the concentration of vitamin E tocopherol polyethylene glycol succinate and the concentration of cyclosporin have a ratio of 10. In other cases the ratio may be even greater. In other words, there will be 10 mg of vitamin E tocopherol polyethylene glycol succinate for every 1 mg of cyclosporin in a given amount of solution, or in certain instances there may be even more than 10 mg of vitamin E tocopherol polyethylene glycol succinate for every mg of cyclosporin present in a given amount of solution. In certain compositions, the concentration of vitamin E tocopherol polyethylene glycol succinate is no more than 15 times the concentration of the cyclosporin.

A liquid which is intended for ophthalmic use is formulated such that it can be administered topically to the eye. The comfort should be maximized as much as possible, although sometimes formulation considerations may necessitate less than optimal comfort. In the case that comfort cannot be maximized, the liquid should be formulated such that the liquid is tolerable to

the patient for topical ophthalmic use. Additionally, an ophthalmically acceptable liquid may be packaged for single use, or contain a preservative to prevent contamination over multiple uses.

As is known in the art, buffers are commonly used to adjust the pH to a desirable range for ophthalmic use. Generally, a pH of around 5-8 is desired, however, this may need to be adjusted due to considerations such as the stability or solubility of the therapeutically active agent or other excipients. Many buffers including salts of inorganic acids such as phosphate, borate, and sulfate are known.

Another commonly used excipient in ophthalmic compositions is a viscosity-enhancing, or a thickening agent. Thickening agents may be used for a variety of reasons, ranging from improving the form of the formulation for convenient administration to improving the contact with the eye to improve bioavailability. The thickening agent may comprise a polymer containing hydrophilic groups such as monosaccharides, polysaccharides, ethylene oxide groups, hydroxyl groups, carboxylic acids or other charged functional groups. While not intending to limit the scope of the invention, some examples of useful thickening agents are sodium carboxymethylcellulose, hydroxypropylmethylcellulose, povidone, polyvinyl alcohol, and polyethylene glycol.

In ophthalmic solutions, tonicity agents may be used to adjust the composition of the formulation to the desired isotonic range. Tonicity agents are well known in the art and some examples include glycerin, mannitol, sorbitol, sodium chloride, and other electrolytes.

Preservatives may be used to prevent bacterial contamination in multiple-use ophthalmic preparations. Preservatives are well known in the art, and, while not intending to be limiting, examples include polyhexamethylenebiguanidine (PHMB), benzalkonium chloride (BAK), stabilized oxychloro complexes (otherwise known as Purite®), phenylmercuric acetate, chlorobutanol, benzyl alcohol, parabens, and thimerosal are examples of useful preservatives.

In ophthalmic compositions, a chelating agent may be used to enhance preservative effectiveness. Suitable chelating agents are those known in the art,

and, while not intending to be limiting, edetate (EDTA) salts like edetate disodium, edetate calcium disodium, edetate sodium, edetate trisodium, and edetate dipotassium are examples of useful chelating agents.

The compositions disclosed herein are useful in the treatment of dry eye disease, and in the preparation of medicaments for the treatment of dry eye disease. However, certain compositions disclosed herein are also useful for the treatment or prevention of other conditions or diseases which are related to immune response, inflammatory response, or parasitic or other infection.

The compositions disclosed herein are also useful for parenteral administration of a cyclosporin. A composition which is formulated for parenteral use is a composition which is formulated with the intention of administering the composition parenterally. Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. While not intending to limit the scope of the invention in any way, in addition to vitamin E tocopherol polyethylene glycol succinate, suitable excipients are, for example, saline, dextrose, buffering agents, and the like.

The best mode of making and using the present invention are described in the following examples. These examples are given only to provide direction and guidance in how to make and use the invention, and are not intended to limit the scope of the invention in any way.

Example 1

Formulations 1-4 in Table 1 below were prepared according to the following procedures.

Formulation 1 was prepared by adding 1 mg of cyclosporin into 100 μL of a 10% tocophersolan stock solution and then mixed until dissolved. To this clear solution is slowly added 890 μL of water to yield a clear solution containing 0.1% cyclosporin and 1% tocopehersolan.

Formulations 2 was prepared by adding 1 mg of cyclosporin into 10 μL polysorbate 80 and 10 μL of propylene glycol, and then mixed until dissolved. To this clear solution is slowly added 980 μL of water to yield a turbid solution containing 0.1% cyclosporin and 1% polysorabte 80 and 1% propylene glycol.

Formulation 3 was prepared by adding 1 mg of cyclosporin into 100 μL of a 10% polyoxy-40-stearate stock solution and then mixed until dissolved. To this clear solution is slowly added 890 μL of water to yield a turbid solution containing 0.1% cyclosporin and 1% polyoxy-40-stearate. This cloudy solution remained turbid even with the addition of 10 μL of propylene glycol.

Formulations 4 was prepared by adding 1 mg of cyclosporin into 10 μL polyethylene glycol 400 (PEG 400) and 10 μL of propylene glycol, and then mixed until dissolved. To this clear solution is slowly added 980 μL of water to yield a turbid solution containing 0.1% cyclosporin and 1% PEG 400 and 1% propylene glycol.

Table 1

Formulation	Cyclosporin concentration (%w/v)	Surfactant concentration (%w/v)	Type of Surfactant	Physical Appearance
1	0.1	1.0	Tocophersolan	Clear
2	0.1	1.0	Polysorbate 80	Precipitation
3	0.1	1.0	Polyoxyl-40-stearate	Precipitation
4	0.1	1.0	PEG400	Precipitation

While not intending to limit the scope of the invention in any way, or to be bound in any way by theory, Formulation 1, which uses a vitamin E tocopherol polyethylene glycol succinate is a clear solution, while the other formulations are not. In contrast to the formulation 1, the other formulations required propylene glycol as indicated in the procedures above. In addition to

being a superior surfactant, vitamin E tocopherol polyethylene glycol succinates are generally regarded in the art to have an excellent toxicology profile, and be generally less irritating than most other surfactants.

Example 2

A preserved cyclosporin solution appropriate for ophthalmic use (composition in Table 2) was prepared according to the following procedure. Cyclosporin (0.05 g) is dissolved in 5 mL of a 10% tocophersolan, 0.6% boric acid at pH 7.4 stock solution and then mixed until dissolved. To this clear solution was slowly added approximately 90 mL of a boric acid solution (boric acid stock solution; 0.6% boric acid adjusted to pH 7.4 with sodium hydroxide). The pH of this clear solution was confirmed to be 7.4, and then 0.455 mL of a Purite® stock solution (2.2%) was added. The clear solution was q.s. to 100 mL with the boric acid stock solution, and then sterile filtered.

Table 2

Ingredient	Amount or concentration (% w/v)
Cyclosporin A	0.05
Tocophersolan	0.5
Boric Acid	0.6
Purite® (stabilized oxychloro complex)	0.01
Sodium Hydroxide	pH adjusted to 7.3 – 7.5

Example 3

Dry eye is treated using the composition of Example 2. Relief of symptoms is experienced.

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Example 4

The composition of Example 2 is administered by intravenous injection to a patient receiving a kidney transplant. Rejection of the kidney by the patient is suppressed.

CLAIMS

What is claimed is:

1. A liquid comprising a therapeutically effective concentration of a cyclosporin and a vitamin E tocopherol polyethylene glycol succinate, wherein said liquid is an aqueous solution, and wherein no hydrophilic organic solvent is present at a mass concentration greater than half of that of the cyclosporin.

2. The liquid of claim 1 which contains essentially no hydrophilic organic solvent.

3. The liquid of claim 1 wherein the vitamin E tocopherol polyethylene glycol succinate is present at a concentration which is at least 8 times that of the cyclosporin, and wherein the vitamin E tocopherol polyethylene glycol succinate is present at a concentration which is no more than 15 times that of the cyclosporin.

4. The liquid of claim 1 wherein at least 10 mg of the vitamin E tocopherol polyethylene glycol succinate is present for every mg of the cyclosporin present in said solution.

5. The liquid of claim 1 wherein the vitamin E tocopherol polyethylene glycol succinate and the cyclosporin have a concentration ratio of about 10 to 1.

6. The liquid of claim 1 wherein vitamin E tocopherol polyethylene glycol succinate is present at a concentration that is no less than 0.5%, and wherein the vitamin E tocopherol polyethylene glycol succinate is present at a concentration that is no greater than 5%.

7. The liquid of claim 3 comprising about 0.1% cyclosporin A and about 1% vitamin E tocopherol polyethylene glycol succinate.

8. The liquid of claim 2 comprising cyclosporin A, wherein cyclosporin A is present at a concentration of at least 0.01%, and wherein cyclosporin A is not present at a concentration which is greater than 0.2%.

9. The liquid of claim 1 consisting essentially of a therapeutically effective concentration of cyclosporin A, an effective amount of a vitamin E tocopherol polyethylene glycol succinate, water, and an effective amount of one or any

combination of excipients selected from the group consisting of buffers, thickening agents, tonicity agents, preservatives, and chelating agents.

10. A composition comprising a therapeutically effective concentration of cyclosporin A and an effective amount of a vitamin E tocopherol polyethylene glycol succinate, wherein said composition is an aqueous liquid solution which is intended for ophthalmic use, and wherein no hydrophilic organic solvent is present at a mass concentration greater than or equal to that of cyclosporin A.

11. The composition of claim 10 wherein cyclosporin A is present at a concentration at or below 1%.

12. The composition of claim 10 wherein cyclosporin A is present at a concentration which is at least 0.02% and wherein cyclosporin A is present at a concentration which is less than or equal to 0.15%.

13. The composition of claim 12 comprising about 0.05% cyclosporin A.

14. The composition of claim 12 comprising about 0.1% cyclosporin A.

15. The composition of claim 14 comprising about 0.1% cyclosporin A and about 1% vitamin E tocopherol polyethylene glycol succinate.

16. A method of treating dry eye disease comprising administering to a patient an effective amount of a solution comprising cyclosporin A and an effective amount of a vitamin E tocopherol polyethylene glycol succinate, and wherein no hydrophilic organic solvent is present at a mass concentration greater than or equal to that of the cyclosporin in said solution.

17. The method of claim 16 comprising at least 0.001% cyclosporin A and wherein cyclosporin A is present at a concentration which is less than or equal to 1%.

18. The method of claim 16 wherein said solution comprises about 0.1% cyclosporin A and about 1% vitamin E tocopherol polyethylene glycol succinate.

19. The liquid of claim 1 which is intended for parenteral use.

20. The liquid of claim 1 which is intended for ophthalmic use.

21. The liquid of claim 20 comprising about 0.1% cyclosporin A and about 1% vitamin E tocopherol polyethylene glycol succinate.

22. A composition comprising a therapeutically effective concentration of cyclosporin A and an effective amount of a vitamin E tocopherol polyethylene glycol succinate, wherein said composition is an aqueous liquid solution which is intended for parenteral use, and wherein no hydrophilic organic solvent is present at a mass concentration greater than or equal to that of cyclosporin A.

23. The composition of claim 22 wherein cyclosporin A is present at a concentration which is at least 0.02% and wherein cyclosporin A is present at a concentration which is less than or equal to 0.15%.

24. The composition of claim 23 comprising about 0.1% cyclosporin A and about 1% vitamin E tocopherol polyethylene glycol succinate.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/08 A61K47/22 A61P27/04

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

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, BIOSIS, EMBASE, CHEM ABS Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 712 631 A (BIOGAL GYOGYSZERGYAR RT) 22 May 1996 (1996-05-22) example 10	1-9
X	US 5 891 845 A (MYERS ET AL) 6 April 1999 (1999-04-06) claims 1,9,20; examples 1,36,8	1-9
X	ISMAILOS G ET AL: "ENHANCEMENT OF CYCLOSPORIN A SOLUBILITY BY D-ALPHATOCOPHERYL-POLYETHY LENE-GLYCOL-1000 SUCCINATE (TPGS)" EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES, ELSEVIER, AMSTERDAM, NL, vol. 1, no. 5, 1 May 1994 (1994-05-01), pages 269-271, XP000196248 ISSN: 0928-0987 page 269, right-hand column, paragraph 3	1-9

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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

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/018025

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 839 342 A (KASWAN ET AL) 13 June 1989 (1989-06-13) the whole document	10-21
A	WO 89/01772 A (UNIVERSITY OF GEORGIA RESEARCH FOUNDATION, INC) 9 March 1989 (1989-03-09) the whole document	10-21
A	US 2004/014655 A1 (HEGEDUS LAJOS ET AL) 22 January 2004 (2004-01-22) claim 40	22-24
A	US 6 022 852 A (KLOKKERS ET AL) 8 February 2000 (2000-02-08) claims 1-6; example 5	22-24

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/018025

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0712631 A	22-05-1996	HU 215966 B1	28-07-1999
		AT 408945 B	25-04-2002
		AT 189395 A	15-09-2001
		AT 245994 T	15-08-2003
		CA 2145242 A1	22-05-1996
		CZ 9501054 A3	17-07-1996
		DE 19543271 A1	05-06-1996
		DE 69531389 D1	04-09-2003
		DE 69531389 T2	15-04-2004
		DK 712631 T3	27-10-2003
		EP 0712631 A2	22-05-1996
		ES 2202330 T3	01-04-2004
		GB 2295546 A ,B	05-06-1996
		HK 1016814 A1	21-07-2000
		IT MI952411 A1	21-05-1996
		PL 311430 A1	27-05-1996
		PT 712631 T	28-11-2003
		SI 9500350 A ,B	30-06-1996
		SK 54495 A3	05-02-1997
		US 5583105 A	10-12-1996
US 5891845 A	06-04-1999	AT 235235 T	15-04-2003
		AU 1301199 A	15-06-1999
		CA 2309836 A1	03-06-1999
		DE 69812690 D1	30-04-2003
		DE 69812690 T2	22-01-2004
		EP 1032373 A1	06-09-2000
		ES 2196621 T3	16-12-2003
		JP 2001523705 T	27-11-2001
		WO 9926607 A1	03-06-1999
US 4839342 A	13-06-1989	AT 109970 T	15-09-1994
		AU 620048 B2	13-02-1992
		AU 2421388 A	31-03-1989
		DE 3851152 D1	22-09-1994
		DK 54390 A	03-05-1990
		EP 0391909 A1	17-10-1990
		ES 2012116 A6	01-03-1990
		GR 88100578 A ,B	22-06-1989
		IE 65582 B1	01-11-1995
		JP 6067850 B	31-08-1994
		JP 3503159 T	18-07-1991
		KR 9203601 B1	04-05-1992
		PH 24814 A	30-10-1990
		WO 8901772 A1	09-03-1989
		US 5411952 A	02-05-1995
WO 8901772 A	09-03-1989	US 4839342 A	13-06-1989
		AT 109970 T	15-09-1994
		AU 620048 B2	13-02-1992
		AU 2421388 A	31-03-1989
		DE 3851152 D1	22-09-1994
		DK 54390 A	03-05-1990
		EP 0391909 A1	17-10-1990
		ES 2012116 A6	01-03-1990
		GR 88100578 A ,B	22-06-1989
		IE 65582 B1	01-11-1995
		JP 6067850 B	31-08-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/018025

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8901772 A		JP 3503159 T	18-07-1991
		KR 9203601 B1	04-05-1992
		PH 24814 A	30-10-1990
		WO 8901772 A1	09-03-1989
		US 5411952 A	02-05-1995
		CA 1335566 C	16-05-1995
US 2004014655 A1	22-01-2004	AT 230611 T	15-01-2003
		AU 734695 B2	21-06-2001
		AU 9362398 A	05-04-1999
		BG 104245 A	30-11-2000
		BR 9812469 A	05-02-2002
		CA 2269923 A1	25-03-1999
		CN 1270529 A ,C	18-10-2000
		DE 69810612 D1	13-02-2003
		DE 69810612 T2	02-10-2003
		DK 981375 T3	05-05-2003
		EA 4700 B1	24-06-2004
		EP 0981375 A1	01-03-2000
		ES 2187062 T3	16-05-2003
		HR 980499 A1	31-12-1999
		WO 9913914 A1	25-03-1999
		HU 9802107 A2	28-06-1999
		JP 2001508806 T	03-07-2001
		LT 2000018 A ,B	25-08-2000
		LV 12493 A ,B	20-06-2000
		NO 20001371 A	18-05-2000
		NZ 503302 A	31-08-2001
		PL 339369 A1	18-12-2000
		PT 981375 T	30-04-2003
		RO 118695 B1	30-09-2003
		SI 20189 A	31-10-2000
		SK 3292000 A3	14-08-2000
		TR 200001545 T2	23-10-2000
		TW 222365 B	21-10-2004
		US 6743826 B1	01-06-2004
		US 2005064028 A1	24-03-2005
		ZA 9808585 A	13-03-2000
US 6022852 A	08-02-2000	US 2001014665 A1	16-08-2001
		DE 10199039 I1	22-11-2001
		DE 59409377 D1	29-06-2000
		WO 9511039 A1	27-04-1995
		EP 0724452 A1	07-08-1996
		ES 2148345 T3	16-10-2000
		JP 3644543 B2	27-04-2005
		JP 9504012 T	22-04-1997