(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 January 2001 (25.01.2001)

PCT

(10) International Publication Number
WO 01/05431 A1

(51) International Patent Classification[7]: A61K 47/32

(21) International Application Number: PCT/US00/18948

(22) International Filing Date: 12 July 2000 (12.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/353,549 14 July 1999 (14.07.1999) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 09/353,549 (CIP)
Filed on 14 July 1999 (14.07.1999)

(71) Applicant *(for all designated States except US)*: **SCHERING-PLOUGH LTD.** [CH/CH]; Toepferstrasse 5, CH-6004 Lucerne (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **GAO, Rong** [US/US]; 2 Clinton Avenue, Edison, NJ 08820 (US). **SHAO, Zezhi, Jesse** [US/US]; 68 Patriot Hill Drive, Basking Ridge, NJ 07920 (US). **FAN, Allan, Chor-Lun** [US/US]; 31 Timber Drive, Berkeley Heights, NJ 07922 (US). **WITCHEY-LAKSHMANAN, Leonore, Catherine** [US/US]; 21 Boxwood Road, Piscataway, NJ 08854 (US). **STEWART, Daniel, Charles** [US/US]; Apartment 6D, 100 Park Boulevard, Cherry Hill, NJ 08034 (US).

(74) Agents: **KUTZENCO, Allan, N.** et al.; Schering-Plough Corporation, Patent Department, K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, US, UZ, VN, YU, ZA.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

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.

WO 01/05431 A1

(54) Title: TASTE MASKING OF ORAL QUINOLONE LIQUID PREPARATIONS USING ION EXCHANGE RESINS

(57) Abstract: The invention relates to the formulation of oral liquid products of quinolones or derivatives thereof using ion exchange resins, such as methacrylic acid polymer crosslinked with divinylbenzene, as the carrier, thereby eliminating the extreme bitterness of the quinolones oral liquid formulation.

TASTE MASKING OF ORAL QUINOLONE LIQUID PREPARATIONS USING ION EXCHANGE RESINS

BACKGROUND OF THE INVENTION

1. Field Of The Invention

The present invention relates to the formulation of oral liquid preparations of quinolones or derivatives thereof using ion exchange resins, such as a methacrylic acid polymer crosslinked with divinylbenzene, as the carrier. The formation of a quinolone-resin complex (resinate) eliminates the extreme bitterness of the quinolones to make the liquid oral dosage form palatable.

2. Description Of Related Art

Quinolone antibiotics are widely used in the treatment of common infections. The current quinolone products on the market, including orbifloxacin, and ciprofloxacin, are administered as tablets or capsules. Since quinolones have an extremely bitter taste, development of palatable liquid oral dosage forms has always been challenging. Liquid oral dosage forms are useful for patients having difficulty swallowing capsules or tablets. The Journal of Pharm. Sciences, vol 60, No 10, pp 1523-1527 (Oct 1971) discloses polycarboxylic acid ion exchange resins as adsorbates for masking the bad taste of ephedrine, dextromethorphan,

pseudoephedrine, and methapyrilene; EPO 225615, published June 16, 1987, discloses liquid pharmaceutical compositions containing dextrometorphan, ion exchange resin (preferably a cationic resin) and acceptable pharmaceutical carriers, sweetners and formulation aids. Taste is not an issue. US 4,808,411 issued February 28, 1989 discloses antibiotic polymer compositions containing acrylic acid polymers and erythromycin. Said compositions can be prepared as liquids and are effective in masking the taste of the erythromycin antibiotic; US 5,152,986, issued October 6, 1992, discloses pharmaceutical compositions containing quinolone carboxylic acid derivatives (such as ciprofloxacin) and ion exchange resins (preferably cationic) which mask the bad taste of the quinolone in animal feeds. Said compositions are in solid form and paste form; EPO 622083, published November 11, 1994, discloses a solid pharmaceutical preparation containing any number of therapeutic agents, such as β-lactam antibiotics, antihistamines, bronchodilators and antiinflammatories, and cationic or anionic ion exchange resins which decrease the unpleasant taste and odor of the therapeutic agent.

There is still a need in the art for oral liquid quinolone preparations with acceptable taste. Applicants have satisfied this need in the art by preparing liquid quinolone preparations with acceptable taste.

DEFINITIONS AND USAGES OF TERMS

The term "pharmaceutical composition", as used herein, means a combination comprised of a safe and effective amount of the quinolone compound active ingredient, or mixtures thereof, and pharmaceutically-acceptable excipients.

The term "pharmaceutically acceptable excipients", as used herein, means any physiologically inert, pharmacologically inactive material known to one skilled in the art, which is compatible with the physical and chemical characteristics of the particular quinolone compound active ingredient selected for use. Pharmaceutically-acceptable excipients include, but are not limited to, polymers, resins, plasticizers, fillers, binders, lubricants, glidants, disintegrants, solvents, co-solvents, buffer systems, surfactants, preservatives, sweetening agents, flavoring agents, pharmaceutical grade dyes or pigments, and viscosity agents.

The term "ion exchange resin", as used herein, means anionic or cationic ion exchange resins.

The term " oral dosage form", as used herein, means any pharmaceutical composition intended to be systemically administered to an individual by delivering said composition to the gastrointestinal tract of an individual, via the mouth of said individual. Oral dosage forms include, tablets, coated or non-coated; liquids, such as solutions and suspensions; or capsules, coated or non-coated.

All percentages are on a weight percent basis unless otherwise indicated.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to an aqueous pharmaceutical composition comprising:

a. 0.01% to 30% by weight of a quinolone compound or derivative thereof;

b. 0.01% to 60% by weight of an ion exchange resin;

c. pharmaceutically acceptable excipients to equal 100%.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to an aqueous pharmaceutical composition comprising:

a. 0.01% to 30% by weight of a quinolone compound or derivative thereof;

b. 0.01% to 60% by weight of an ion exchange resin;

c. pharmaceutically acceptable excipients to equal 100%.

Quinolones and Derivatives Thereof Useful in the Practice of the Present Invention

Quinolones and derivatives thereof useful in the practice of the present invention include, but are not limited to, orbifloxacin, ciprofloxacin, danofloxacin, enoxacin, grepafloxacin, levofloxacin,lomefloxacin, nalidixic acid, norfloxacin, ofloxacin,sparfloxacin, and trovafloxacin mesylate. The preferred quinolone is orbifloxacin available from Schering Plough, Kenilworth, NJ as ORBAX®. Other quinolones useful in the practice of the present invention are described in WO 96/16055 published May 30, 1996; US 5,104,868 issued April 14, 1992;

US 5,496,947 issued March 5, 1996; US 5,498,615 issued March 12, 1996; US 5,770,597 issued June 23,1998; US 5,840,333 issued November 24, 1998; US 5,672,600 issued September 30, 1997; US 5,491,139 issued February 13, 1996; US 5,530,116 issued June 25, 1996; and US 5,646,163 issued July 8, 1997, all incorporated by reference herein.

The quinolone compounds useful in the practice of the present invention comprise from about 0.01% to about 30% by weight of the pharmaceutical compositions of the present invention. Preferably, the quinolone compounds useful in the practice of the present invention comprise from about 0.1 % to about 10% by weight of the pharmaceutical compositions of the present invention. More preferably, the quinolone compounds useful in the practice of the present invention comprise from about 0.5% to 5 % by weight of the pharmaceutical compositions of the present invention

Ion Exchange Resins Useful in the Practice of the Present Invention

Ion exchange resins useful in the practice of the present invention include, but are not limited to, anionic resins such as: DUOLITE® AP143/1083 (cholestyramine resin USP) and cationic resins such as: AMBERLITE® IRP-64 (a porous copolymers of methacrylic acid crosslinked with divinylbenzene), AMBERLITE® IRP-69 (Sodium polystyrene sulfonate USP) and AMBERLITE® IRP-88 (Polacrilin Potassium). AMBERLITE® IRP 64 is preferred resin. The DUOLITE® and AMBERLITE® resins are available from the Rohm and Haas Company, Philadelphia, PA. The DOWEX® resins, available from the Dow Chemical Company, Midland, MI are also useful in the practice of the present invention. Said DOWEX® resins are strong cationic

exchangers based upon polystyrenesulphonic acid with variable crosslinking (1-12% divinylbenzene) in a variety of particle sizes.

Further, said AMBERLITE® IRP 69 (sodium polystyrenesulfonate) is available commercially as a sodium salt. However, it is within the scope of the present invention to convert the sodium salt to other salt forms including, but not limited to, K and Li.

The ion exchange resins useful in the practice of the present invention comprise from about 0.01 % to about 60% by weight of the pharmaceutical compositions of the present invention. Preferably the ion exchange resins useful in the practice of the present invention comprise from about 0.2 % to about 20% by weight of the pharmaceutical compositions of the present invention. More preferably, the ion exchange resins useful in the practice of the present invention comprise from about 0.5% to 15% by weight of the pharmaceutical compositions of the present invention

Pharmaceutically Acceptable Excipients Useful in the Practice of the Present Invention

As stated hereinabove, pharmaceutically-acceptable excipients include, but are not limited to, resins, fillers, binders, lubricants, solvents, glidants, disintegrants, co-solvents, surfactants, preservatives, sweetener agents, flavoring agents, buffer systems, pharmaceutical-grade dyes or pigments, and viscosity agents.

The preferred solvent is water.

Flavoring agents among those useful herein include those described in *Remington's Pharmaceutical Sciences,* 18th Edition, Mack Publishing Company, 1990, pp. 1288-1300, incorporated by reference herein. The pharmaceutical compositions suitable for use herein generally contain from 0-5% flavoring agents.

Preferred co-solvents include, but are not limited to, ethanol, glycerin, propylene glycol, polyethylene glycols. The pharmaceutical compositions of the present invention include from 0.01 % to 30% co-solvents.

Preferred buffer systems include, but are not limited to, NaOH, acetic, boric, carbonic, phosphoric, succinic, malaic, tartaric, citric, benzoic, lactic, glyceric, gluconic, glutaric and glutamic acids and their sodium, potassium and ammonium salts. The pharmaceutical composition of the present invention generally contain from 0.1 % to 20% buffer systems.

Preferred surfactants include, but are not limited to, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene monoalkyl ethers, sucrose monoesters and lanolin esters and ethers, alkyl sulfate salts, sodim, potassium, and ammonium salts of fatty acids.

Preferred preservatives include, but are not limited to, phenol, alkyl esters of parahydroxybenzoic acid, sorbic acid, and methylparaben, o-phenylphenol benzoic acid and the salts thereof, chlorobutanol, benzyl alcohol, thimerosal, phenylmercuric acetate and nitrate, nitromersol, benzalkonium chloride, cetylpyridinium chloride, methyl paraben, and propyl paraben. Particularly preferred is sorbic acid. The

compositions of the present invention generally include from 0.01 % to 5% preservatives.

Preferred sweeteners include, but are not limited to, sucrose, glucose, saccharin, sorbitol, malt extract syrup, mannitol, and aspartame. Particularly preferred is malt extract syrup. Sweeteners such as sucrose, glucose, saccharin and sorbitol are generally used at levels of 0.1% to 10%. Sweeteners such as malt extract syrup are generally used at levels of 10% to 75%.

Preferred viscosity agents include, but are not limited to, methylcellulose, sodium carboxymethylcellulose, hydroxypropyl-methylcellulose, hydroxypropylcellulose, sodium alginate, carbomer, povidone, acacia, guar gum, xanthan gum and tragacanth. Particularly preferred are methylcellulose, carbomer, xanthan gum, guar gum, povidone, sodium carboxymethylcellulose, and magnesium aluminum silicate. Compositions of the present invention include 0.1% to 5% viscosity agents.

The compositions of the present invention may optionally contain lactose, mannitol, sorbitol, tribasic calcium phosphate, dibasic calcium phosphate, compressible sugar, starch, calcium sulfate, dextro and microcrystalline cellulose, magnesium stearate, stearic acid, talc, colloidal silicon dioxide, starch, sodium starch glycolate, crospovidone, croscarmelose sodium, and microcrystalline cellulose, acacia, tragacanth, hydroxypropylcellulose, pregelantinized starch, gelatin, povidone, ethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and methylcellulose.

Preparing the Compositions of the Present Invention

The compositions of the present invention are prepared according to methods known to those skilled in the art. Basically, the preparation procedure involves dissolving the quinolone in an aqueous media followed by the addition of an ion exchange resin to form a drug/resin complex. The complex can be suspended directly into suitable vehicles with flavor agents such as, but not limited to, a syrup base (malt extract) with the aid of an anticaking agent such as, but not limited to, colloidal silicone dioxide and a preservative, such as, but not limited to, sorbic acid.

The drug/resin complex can also be isolated and dried for later usage. This would be advantageous when reconstitution in the pharmacy is desired or very bitter drugs are being employed. Specifically, the quinolone and ion exchange resin complex can be blended with, for example, lactose, magnesium stearate, silicon dioxide, talc, microcrystalline cellulose or gelatin, to prepare a powder that can be shipped to the pharmacy and reconstituted into a palatable oral liquid dosage form by the pharmacist. For very bitter drugs, the drug/resin complex can be isolated, for example, by rinsing with deionized water, from uncomplexed (or free) drug. The isolated and dried powder will contain substantially only drug/resin complex. This isolated, purer drug/resin complex (substantially devoid of free drug) can be formulated into an oral liquid preparation that contains little to no amount of the bitter free drug.

The following nonlimiting Examples 1 & 2 illustrate the compositions of the present invention. Said Examples are prepared on a weight to volume (w/v) basis.

Example 1

Purified water, USP pure - 33.75%
Orbifloxacin - 2%
Lactic Acid, USP to pH 4.5
Sodium Polystyrene Sulfonate ion exchange resin (USP) - 12%
Malt Extract - 65%
Propylene Glycol - 2.5%
Sorbic Acid - 0.1%
Purified water, USP Pure to equal 100%

The general procedure for preparing the composition described in Example 1 is as follows:

1) Charge orbifloxacin into water and mix well.

2) Add Lactic acid and adjust pH to 4.5

3) Charge sodium polystyrene sulfonate resin and mix well to form a slurry .

4) Charge malt extract syrup to slurry and mix well.

5) Dissolve sorbic acid in propylene glycol and charge it into slurry formed in steps 3 and 4.

6) Add water to equal 100%, weight to volume.

Example 2

Purified Water, USP - 45%
Orbifloxacin - 3%
Lactic Acid to pH, 4.5
AMBERLITE IRP-64 - 15%
50% w/w NaOH to pH 5.5
Sorbic Acid - 0.1%
Propylene Glycol - 10%
Colloidal Silicon Dioxide - 1.5%
Malt Extract to equal 100%

The general procedure for preparing the composition described in Example 2 is as follows:

1) Charge orbifloxacin into water and mix well.

2) Add Lactic acid to adjust pH to 4.5

3) Charge Amberlite® IRP-64 and mix well to form a slurry .

4) Adjust pH to 5.5 by adding 50% w/w NaOH.

5) Dissolve sorbic acid in propylene glycol and add it to the pH adjusted slurry.

6) Add colloidal silicon dioxide and mix well.

7) Add malt extract syrup to equal 100%, weight to volume.

WHAT IS CLAIMED IS:

1. An aqueous pharmaceutical composition comprising:

a. 0.01% to 30% by weight of a quinolone compound or derivative thereof;

b. 0.01% to 60% by weight of an ion exchange resin;

c. pharmaceutically acceptable excipients to equal 100%.

2. An aqueous pharmaceutical composition according to Claim 1, wherein said quinolone compound or derivative thereof is orbifloxacin.

3. An aqueous pharmaceutical composition according to Claim 1, wherein said ion exchange resin is cationic.

4. An aqueous pharmaceutical composition according to Claim 3, wherein said cationic ion exchange resin is a methacrylic acid polymer crosslinked with divinylbenezene.

5. An aqueous pharmaceutical composition according to Claim 3, wherein said orbifloxacin compound is from 0.5 - 5% by weight of said pharmaceutical composition.

6. An aqueous pharmaceutical composition according to Claim 4, wherein said methacrylic acid polymer crosslinked with divinylbenzene is from 0.5 - 15% by weight of said pharmaceutical composition.

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/US 00/18948

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

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

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 152 986 A (LANGE PETER M ET AL) 6 October 1992 (1992-10-06) cited in the application column 1, line 22 - line 24 column 1, line 30 -column 2, line 62 column 2, line 67 -column 3, line 14 column 3, line 32 - line 40 column 3, line 58 - line 60 column 4, line 55 - line 60 column 4, line 64 column 5, line 1 - line 4 column 5, line 16 - line 22 column 5, line 53 - line 61; claims; example 3 --- -/--	1,3

[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

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 November 2000	08/11/2000

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	Marttin, E

1

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

INTERNATIONAL SEARCH REPORT

Intern ıal Application No
PCT/US 00/18948

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 05816 A (ALCON LAB INC) 1 April 1993 (1993-04-01) page 1, paragraph 1; claims; example 1 page 1, line 27 -page 2, line 5 page 3, paragraph 1 page 3, paragraph 3 -page 4, last paragraph ---	1,3
X	US 5 275 820 A (CHANG NIENYUAN J) 4 January 1994 (1994-01-04) column 1, line 15 - line 21 column 4, line 13 - line 18 column 4, line 55 - line 59 column 5, line 31 - line 34 column 6, line 11 - line 57 column 7, line 22 column 9, line 16 - line 23; claims 11,15,16,19 ---	1,3
A	US 5 032 393 A (DOUGLAS STEPHEN J ET AL) 16 July 1991 (1991-07-16) column 1, line 47 - line 51 column 1, line 58 - line 62 column 2, line 10 - line 23 column 2, line 42 - line 47 column 2, line 58 - last line column 3, line 52 - line 56 column 3, line 67 -column 4, line 4; claims; examples B,8,9 -----	1-6

1

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Interr nal Application No
PCT/US 00/18948

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5152986 A	06-10-1992	DE 3719764 A	22-12-1988
		AT 68694 T	15-11-1991
		AU 599239 B	12-07-1990
		AU 1764388 A	15-12-1988
		BR 8802853 A	03-01-1989
		CA 1318078 A	18-05-1993
		CN 88103473 A,B	28-12-1988
		CN 1108968 A	27-09-1995
		CZ 8804096 A	15-12-1994
		DD 271061 A	23-08-1989
		DE 3865748 A	28-11-1991
		DK 170573 B	30-10-1995
		EP 0295495 A	21-12-1988
		ES 2040290 T	01-04-1995
		FI 882747 A,B,	14-12-1988
		GR 3002988 T	25-01-1993
		HU 48234 A,B	29-05-1989
		IE 60209 B	15-06-1994
		IL 86697 A	15-07-1992
		JP 1004625 A	09-01-1989
		JP 2572815 B	16-01-1997
		KR 9514238 B	23-11-1995
		MX 168987 B	16-06-1993
		NZ 224975 A	26-07-1990
		PL 273001 A	24-07-1989
		PT 87647 A,B	01-07-1988
		SK 409688 A	09-07-1997
		SU 1828394 A	15-07-1993
		ZA 8804154 A	29-03-1989
WO 9305816 A	01-04-1993	AT 162081 T	15-01-1998
		AU 2672892 A	27-04-1993
		DE 69224071 D	19-02-1998
		DE 69224071 T	07-05-1998
		DK 604570 T	14-09-1998
		EP 0604570 A	06-07-1994
		ES 2111083 T	01-03-1998
		GR 3026209 T	29-05-1998
		US 5679336 A	21-10-1997
US 5275820 A	04-01-1994	AU 9130691 A	17-08-1992
		EP 0564537 A	13-10-1993
		JP 6504051 T	12-05-1994
		WO 9211871 A	23-07-1992
US 5032393 A	16-07-1991	AT 401614 B	25-10-1996
		AT 112089 A	15-03-1996
		AU 624613 B	18-06-1992
		AU 3461789 A	16-11-1989
		BE 1002159 A	14-08-1990
		CA 1337272 A	10-10-1995
		CH 679011 A	13-12-1991
		CN 1037651 A,B	06-12-1989
		CY 1781 A	20-10-1995
		DE 3915347 A	16-11-1989
		DK 229489 A	12-11-1989
		ES 2011573 A	16-01-1990
		FI 892248 A,B,	12-11-1989

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern ıal Application No
PCT/US 00/18948

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5032393 A		FR	2631232 A	17-11-1989
		GB	2218333 A,B	15-11-1989
		GR	89100314 A,B	12-03-1990
		HK	45094 A	13-05-1994
		HR	940626 A	28-02-1997
		HU	50036 A	28-12-1989
		HU	204994 B	30-03-1992
		HU	9500512 A	30-10-1995
		IE	60722 B	10-08-1994
		IL	90245 A	12-04-1994
		IT	1232831 B	05-03-1992
		JP	2111719 A	24-04-1990
		JP	2944678 B	06-09-1999
		LU	87515 A	12-06-1990
		MX	15983 A,B	01-10-1993
		NL	8901188 A	01-12-1989
		NO	175131 B	30-05-1994
		NZ	229064 A	23-12-1991
		PH	27612 A	31-08-1993
		PL	279377 A	22-01-1990
		PT	90523 A,B	30-11-1989
		SE	508343 C	28-09-1998
		SE	8901671 A	12-11-1989
		SG	48194 G	25-11-1994
		RU	2033155 C	20-04-1995
		US	5219563 A	15-06-1993
		YU	97189 A	30-06-1990
		ZA	8903463 A	28-03-1990