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 9/08, 9/10, 47/10 A61K 31/245	A1	WO 94/01087
		(43) International Publication Date: 20 January 1994 (20.01.94)

(21) International Application Number: PCT/SE93/00566

(22) International Filing Date: 24 June 1993 (24.06.93)

(30) Priority data:
9202128-6 9 July 1992 (09.07.92) SE

(71) Applicants: AKTIEBOLAGET ASTRA [SE/SE]; S-151 85 Södertälje (SE). THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION [US/US]; 1960 Kenny Road, Columbus, OH 43210-1063 (US).

(72) Inventors: BROBERG, Fredrik ; Landsortsgatan 20, S-619 00 Trosa (SE). BRODIN, Arne ; Kämpevägen 24, S-151 54 Södertälje (SE). RYDHAG, Lisbet ; PL 1570, Hälleberga, S-150 23 Enhörna (SE). FRANK, Sylvan, G. ; 1910 Wyandotte Rd, Columbus, OH 43212 (US).

(74) Agent: LINDEROTH, Margareta; Aktiebolaget Astra, Patent Department, S-151 85 Södertälje (SE).

(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN, 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: PRECIPITATION OF ONE OR MORE ACTIVE COMPOUNDS IN SITU

(57) Abstract

The present invention relates to an injectable solution for administration of one or more active compounds. According to the invention the active compound, which is in its neutral form, is solved in a biologically acceptable solvent whereby the active compound by administration precipitates, forming a solid phase of the solution in situ. Thus, said solution, which is easy to sterilize, is acting like a suspension when injected.

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

PRECIPITATION OF ONE OR MORE ACTIVE COMPOUNDS IN SITU

Field of the invention

The present invention is directed to an injectable solution for administration of one or more active compounds and a process for the preparation thereof.

Background of the invention

Sterile suspensions, i.e. formulations containing at least two phases, a solid and a liquid phase, are difficult to manufacture in large scale. Suspensions are by definition thermodynamically instable, and separation of the different phases will occur with time. Steam sterilization of such formulations often speeds up the separation. Aseptic preparation by filtration through a 0.2 μm filter is not applicable on suspensions. There are few suspension products on the market of this type. Novalucol® and Roxiam® are examples of mixtures for oral administration. Oil containing suspensions for injection are available for CNS indications. There is a need for an injectable suspension which can be sterilized either by steam sterilization or by filtration through a 0.2 μm filter.

Prior art

In NL 9000634 stable aqueous suspensions of water-soluble local anaesthetics and/or narcotic analgesics are disclosed where the local anaesthetics and/or narcotic analgesics have a specific particle diameter and said aqueous suspensions also containing a non-ionic surface-active agent. These suspensions are being sterilized by steam sterilization or with the aid of gammarays. When sterilized by

heating the suspended particles melt and wholly or partly flow together. To obtain the suspension again the residence is cooled down to a temperature below the freezing point of the aqueous medium while shaking. However, this is a complicated way of sterilizing, it takes time and it is not possible to control the sizes of the particles recovered.

Also in EP 197 308 a ready made suspension including a water insoluble local anesthetics for injection is disclosed. During steam sterilization of the suspension the same problem as mentioned above arises, i.e. the particles of the local anesthetic melts and have to be resuspended.

EP 213 851 discloses injectable semi-solid matrices, which mechanically hinder the release of the active compound. In fact, it is the matrice that will be degraded once injected. Also the formulation here is semi-solid and not solid.

It is well-known that solutions can be obtained by chelation with metal ions. This is disclosed in e.g. US 4 259 331. Here the mixed metal chelate releases an amount of active compound by injection. However it is desirable to prepare an injectable solution not including metal ions, but which solution still precipitates the active compound once injected.

Further in Dialog International Services, file 5:B10SIS, Benzon et al present a study concerning the effect of polyethylene glycol (PEG) on mammalian nerve impulses. PEG is a polymeric compound used as a vehicle for depot steroid preparations. According to the study,

PEG in a concentration of up to 40% does not cause neurolysis.

Another way of controlling postoperative pain is described by Cassuto et al in Anaesthesiology 895, 68, 1988, namely the administering of Xylocaine® spray, i.e. a solution if lidocaine base in ethanol, topically in surgical wounds of patients undergoing hermiorraphy.

Also in Acta Anaesthesiol Scand 112-114, 36, (1992) the use of the same lidocaine aerosol is described for post-operative pain following minor gynaecological laparotomy. The base form of lidocaine which is used in both these two studies is available in vivo, i.e. the solubility in the tissue fluids is high enough to give both sensory and motor block. This is also confirmed by the present invention. Xylocaine® spray used in the earlier studies contains, however, a number of additives, which should be avoided in wounds.

In J. Clin. Pharm. and Therap. 197-204, 15, 1990 and in a report called "Slow-release effect of pH-adjusted bupivacaine, in vitro demonstration" Bourqet et al and Bonhomme et al described studies of the slow-release effect of alkalinized bupivacaine hydrochloride solutions. Further, in Correspondance in Plast. Reconstr. Surg. 543, 84, 1989 and in Comment in Ann. R. Coll. Surg. Engl. 17, 72, 1989 the possibility to administer alkanized bupivacaine hydrochloride solutions topically to control post-operative pain has been pointed out.

Slow-release of analgetics have also been observed for base forms of analgetics such as nalbuphine in Drug Devel and Ind Pharm 67, 17,

1991, where it is described how suspensions of nalbuphine are prepared and injected. To be able to prepare an injectable suspension three suspending agents, methylcellulose, sodium carboxymethyl-cellulose, and PEG are added. However, these agents give possible side-effects and therefore a suspension containing as few auxiliaries as possible is desirable.

None of the prior art documents solves the problem how to prepare a stable injectable suspension of an active agent, where said suspension has the advantage that the effect thereof is much prolonged. According to present invention said problems can be solved.

Outline of the invention

It has been found that the difficulties of preparing sterile suspensions for injection can be avoided by preparing an injectable solution for administration of one or more active compounds solved in a biologically acceptable solvent whereby the active compound upon administration precipitates, due to changes of the conditions of solubility, i.e. the solid phase of the suspension is formed in situ. Sterilization of a solution can be performed by methods not applicable on suspensions namely by steam sterilization or by filtration through a 0.2 μm filter.

Another advantage with the present invention is that the active compound precipitates in situ, i.e. the solid phase might also act as a depot in the tissue, due to its solubility properities or the presence of other materials (excipients). Consequently, large doses of the active

compound can be administered in vivo, without obtaining severe toxic reactions. The present invention discloses an injectable solution where the active compound could be e.g. a local anaesthetic agent, an analgesic agent or a combination of these two agents giving both an analgesic and an anaesthetic effect, which sometimes is desirable. The active compound could also be a steroid or a drug for CNS indications.

The active compound is preferably a local anaesthetic agent such as lidocaine, prilocaine, mepivacaine, bupivacaine, ropivacaine or etidocaine but it can also be some other local anaesthetic agent. Most preferably the active compound is lidocaine.

The physico-chemical properities of the active compound, i.e. solubility, the influence of pH, salts and temperature on the solubility, are important parameters to control the precipitation of the active compound in situ.

The local anaesthetic agent used according to the present invention is in its neutral form which is less soluble than the hydrochloride form. It has been found that the neutral form of the anaesthetic agent enhances the duration of motor and sensory block compared to a solution of said anaestethic agent in hydrochloride form.

Since the neutral form is not soluble in water a lipophilic vehicle was determined which solves the active compound and thus made it suitable for injection. Upon administration this solution, i.e. the active compound and the vehicle, is changed due to changes of the conditions resulting in precipitation of the active compound. Thus the

injectable system acts as if it was a suspension. The neutral form is unchanged and can be e.g. the base form.

The optimal vehicle for a specific active compound according to present invention, is determined experimentally and the function confirmed in vivo. The physico-chemical properties of the active compound determines the solubility of the active compound. The lower limit of solubility is determined by the lowest effective concentration of the active compound (therapeutic concentration). The upper limit of the solubility should be equal to the desired amount of precipitated active compound.

The vehicles are biologically acceptable solvents and a mixture of one or more of water, an alcohol and a polyethylene glycol or another biologically acceptable solvent. Especially preferred vehicles according to the invention are:

a) ethanol, 99.5%
b) a mixture of ethanol and water
c) polyethylene glycol 300 (PEG 300)
d) a mixture of PEG 300 and ethanol
e) a mixture of PEG 300, ethanol and water
f) polyethylene glycol 400 (PEG 400)
g) a mixture of PEG 400 and ethanol
h) a mixture of PEG 400, ethanol and water
i) propylene glycol
j) a mixture of propylene glycol and water
k) a mixture of propylene glycol and ethanol
l) glycerol

m) a mixture of glycerol and ethanol or

n) a mixture of glycerol, ethanol and water

Most preferably the biologically acceptable solvent is

a) a mixture of ethanol and water

b) PEG 300 or

c) a mixture of PEG 400 and ethanol

According to an especially preferred embodiment of the invention the sterile injectable solution contains 5-80 w/w% of lidocaine solved in a mixture of 10-35 w/w% of ethanol and 2-65 w/w% of water.

According to a another preferred embodiment of the invention the sterile injectable solution contains 15-20 w/w% of lidocaine solved in 80-85 w/w% of PEG 300.

According to a further preferred embodiment of the invention the sterile injectable solution contains 5-20 w/w% of lidocaine solved in in a mixture of 2-10 w/w% of ethanol and 75-90 w/w% of PEG 400.

The injectable sterile solution according to present invention can be administered intramuscularly, epidurally, spinally, intratechally, rectally, topically, orally or in the lung.

The sterile injectable solution is prepared by mixing the specific active compound with the solvent in a flask. The flask is sealed and then shaken to solve the active compound. To completely solve the

active compound the flask is left in room temperature during maximum one day. After that the solution is sterilized either by steam sterilization or when prepared aseptically and filtered through a 0.2 μm filter.

The following examples illustrate the invention more in detail

Example 1

Lidocaine	5.0 % by weight
Ethanol, 99.5%	34.0 % by weight
Water	61.0 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above. A long duration of motor and sensory block was obtained when injected in vivo.

Example 2

Lidocaine	10.0 % by weight
Ethanol, 99.5%	36.0 % by weight
Water	54.0 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above. A long duration of motor and sensoric block was obtained when injected in vivo.

Example 3

Lidocaine	75.0 % by weight
Ethanol, 99.5%	20.0 % by weight
Water	5.0 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above.

Example 4

Lidocaine	80.0 % by weight
Ethanol, 99.5%	15.0 % by weight
Water	5.0 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above.

Example 5

Lidocaine	17.8 % by weight
PEG 300	82.2 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above.

Example 6

Lidocaine	17.8 % by weight
PEG 300	82.2 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above.

Example 7

Lidocaine	8.6 % by weight
Ethanol, 99.5%	3.4 % by weight
PEG 400	88.0 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above. A long duration of motor and sensoric block was obtained when injected in vivo.

Example 8

Lidocaine	17.4 % by weight
Ethanol, 99.5%	3.4 % by weight
PEG 400	79.2 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above. A long duration of motor and sensoric block was obtained when injected in vivo.

Example 9

Prilocaine	10.0 % by weight
Ethanol, 99.5 %	35.0 % by weight
Water	55.0 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above.

Example 10

Prilocaine	20.0 % by weight
PEG 300	80.0 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above.

Example 11

Prilocaine	10.0 % by weight
Ethanol, 99.5 %	5.0 % by weight
PEG 400	85.0 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above.

Example 12

Prilocaine	15.0 % by weight
Ethanol, 99.5 %	5.0 % by weight
PEG 400	85.0 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above.

Example 13

Mepivacaine	7.7 % by weight
Ethanol, 99.5 %	50.0 % by weight
Water	42.3 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above.

Example 14

Mepivacaine	10.0 % by weight
Ethanol, 99.5 %	60.0 % by weight
Water	30.0 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above.

Example 15

Bupivacaine	1.1 % by weight
Ethanol, 99.5 %	37.5 % by weight
PEG 400	30.0 % by weight
Water	31.5 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above.

Example 16

Bupivacaine	1.1 % by weight
Ethanol, 99.5 %	49.6 % by weight
PEG 400	49.3 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above.

Example 17

Ropivacaine	1.0 % by weight
Ethanol, 99.5 %	48.2 % by weight
PEG 400	50.8 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above.

Example 18

Ropivacaine	1.0 % by weight
Ethanol, 99.5 %	29.7 % by weight
PEG 400	69.3 % by weight

A sterile injectable solution was prepared in accordance with the general preparation procedure above.

Biological effect

Material and methods

Male guinea-pigs (Dunkin-Hartley, HB Sahlins Försöksdjursfarm, Malmö, Sweden), weighing 300-600 g, were used. The animals were housed 3 to a cage with free access to food and water.

Method 1

Sciatic nerve block. Male Guinea-pigs of the Dunkin-Hartley strain (291-563 g) were used according to a modification of the technique of Shackell described in Anesth. Analg. 20-22, 14 (1935). The hind leg was extended to the full length, and the landmark for needle insertion was located by palpation of the great trochanter of the femur head. This bony prominence together with the lateral aspect of the Os Coxa and adjacent tissues forms a well defined space in which the sciatic nerve is located. The **vehicle** with or without **local anaesthetic** was injected (0,2 ml) into this pocket. Frequency of block, time of onset, duration of motor block (hind limb paralysis) and sensory block (flexor reflex block) were measured. The period of motor block was defined as loss of weight support from the hind leg to the ability to walk. The sensory block was defined as onset of unresponsiveness to painful stimuli applied by pinching the foot-pads to the return of flexor reflex.

Results

The injectable solutions of lidocaine solved in mixtures of ethanol and water and the solutions of lidocaine solved in mixtures of ethanol and PEG 400 were compared to a reference solution containing 2 %, by weight of the water soluble lidocaine

hydrochloride, with regard to their ability to relieve postoperative pain. As seen from table 2, all these solutions according to the present invention giving longer durations of motor block and sensoric block compared to the reference solution.

Table 1 Compositions of injectable solutions of lidocaine

Sample No	Composition, g/100g					
	Lido-caine	Lido-caine HCl	Ethanol	PEG 400	Water	pH
I	5.0		34.0	-	61.0	9.5
II	10,0		36.0	-	54.0	10.3
III	8,6		3.4	88.0	-	9.2
IV	17,4		3.4	79.2	-	9.2
Ref.	-	2.0	-	-	98.0	6.8

Table 2. Durations, motor and sensoric block

Sample No.	Conc %	Motor block minutes	Freq.	Sensor block	Freq.
I	5.0	>96h	5/6	160 min n=1 >380>96h n=2 >96h n=2	5/6
II	10.0	>24h	3/3	>24h	3/3
III	8.6	>24h n=1 131.8 ± 9.5 n=5	6/6	121 ± 4.3	6/6
IV	17.4	>120<24h n=1 >72h n=2	3/3	>120<24h	3/3
Ref.	2.0	22.4 ± 3.5	6/6	13.5 ± 2	6/6

CLAIMS

1. Injectable solution for administration of one or more active compounds c h a r a c t e r i z e d in that the compound is solved in a biologically acceptable solvent which precipitates the active compounds upon injection whereby a solid phase of the solution is formed in situ.

2. Injectable solution according to claim 1 c h a r a c t e r i z e d in that the neutral form of the compound is solved in a biologically acceptable solvent which precipitates the active compound upon injection whereby a solid phase of the solution is formed in situ.

3. Injectable solution according to claim 1 c h a r a c t e r i z e d in that the said active compound is a local anaesthetic agent, and/or an analgesic, steroid or active on the central nervous system.

4. Injectable solution according to claim 3 c h a r a c t e r i z e d in that said active compound is a local anaesthetic agent such as lidocaine, prilocaine, mepivacaine, bupivacaine, ropivacaine or etidocaine.

5. Injectable solution according to claim 3 c h a r a c t e r i z e d in that said local anaesthetic agent is lidocaine.

6. Injectable solution according to claim 5 c h a r a c t e r i z e d in that the local anaesthetic agent is lidocaine in the form of its base.

7. Injectable solution according to claim 1 characterized in that said biologically acceptable solvent is a mixture of one or more of water, an alcohol and a polyethylene glycol.

8. Injectable solution according to claim 6 characterized in that said biologically acceptable solvent is

a) a mixture of ethanol and water

b) polyethylene glycol 300 (PEG 300)

c) a mixture of polyethylene glycol 400 (PEG 400) and ethanol

9. Injectable solution according to claim 1 characterized in that said injectable sterile solution contains 5-80 w/w% of lidocaine 10-35 w/w% of ethanol and 2-65 w/w% of water.

10. Injectable solution according to claim 1 characterized in that said injectable sterile solution contains 15-20 of lidocaine and 80-85 w/w% of PEG 300.

11. Injectable solution according to claim 1 characterized in that said injectable sterile solution contains 5-20 of lidocaine and 2-10 w/w% of ethanol and 75-90 w/w% of PEG 400.

12. Injectable solution according to claim 1 characterized in that said injectable sterile solution is administered intramuscularly, epidurally, spinally, intratechally, rectally, topically, orally or in the lung.

13. Process for the preparation of an injectable solution according to claim 1 c h a r a c t e r i z e d in that an amount of the specific active compound/compounds is mixed with said solvent in a flask which thereafter is sealed, shaken and left in room temperature during maximum one day, whereafter the solution is sterilized either by steam sterilization or prepared aseptically and filtered through a 0.2 μm filter.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00566

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 9/08, A61K 9/10, A61K 47/10, A61K 31/245
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)

IPC5: A61K

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

SE,DK,FI,NO classes as above

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

MEDLINE, BIOSIS, WPI, CLAIMS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4259331 (W.W. ARMSTRONG), 31 March 1981 (31.03.81), column 2, line 9 - line 46, claims	1-2,12-13
Y		1-13
	--	
Y	EP, A3, 0197308 (SHULMAN, MORTON), 15 October 1986 (15.10.86)	1-13
	--	
X	EP, A2, 0213851 (ELI LILLY AND COMPANY), 11 March 1987 (11.03.87), column 4, line 10 - line 14, claims	1-2,12-13
	--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family 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" erlier 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
14 October 1993	18 -10- 1993
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Jonny Brun Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00566

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Dialog International Services, file 5: BIOSIS, Dialog accession no. 5919483, BIOSIS accession no. 84052048, Benzon H T et al: "THE EFFECT OF POLYETHYLENE GLYCOL ON MAMMALIAN NERVE IMPULSES", ANESTH ANALG 66 (6), 1987, 553-559 -- --------	1-3,7-8, 12-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/08/93

International application No.
PCT/SE 93/00566

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4259331	31/03/81	AT-B- 370625	25/04/83
		AU-B- 517548	06/08/81
		AU-A- 5745480	23/10/80
		BE-A- 882788	15/10/80
		CA-A- 1135188	09/11/82
		CH-A- 644015	13/07/84
		DE-A,C- 3014223	23/10/80
		FR-A,B- 2454300	14/11/80
		GB-A,B- 2047097	26/11/80
		JP-C- 1285258	09/10/85
		JP-A- 55143910	10/11/80
		JP-B- 60005567	12/02/85
		LU-A- 82360	16/12/80
		NL-A- 8002176	20/10/80
		SE-B,C- 450624	13/07/87
		SE-A- 8002831	17/10/80
EP-A3- 0197308	15/10/86	CA-A- 1274472	25/09/90
		JP-A- 61212520	20/09/86
		US-A- 4599354	08/07/86
EP-A2- 0213851	11/03/87	SE-T3- 0213851	
		AU-B- 596806	17/05/90
		AU-A- 6119986	26/02/87
		CA-A- 1269933	05/06/90
		DE-A- 3684386	23/04/92
		JP-A- 62045538	27/02/87
		US-A- 4775659	04/10/88