



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 7/16	A1	(11) International Publication Number: WO 00/28952 (43) International Publication Date: 25 May 2000 (25.05.00)
(21) International Application Number: PCT/GB99/03779 (22) International Filing Date: 12 November 1999 (12.11.99) (30) Priority Data: 60/108,212 12 November 1998 (12.11.98) US 09/434,334 4 November 1999 (04.11.99) US (71) Applicant (for all designated States except US): BLOCK DRUG COMPANY, INC. [US/US]; 257 Cornelison Av- enue, Jersey City, NJ 07302-3198 (US). (71) Applicant (for SD only): WHALLEY, Kevin [GB/GB]; 57-60 Lincoln's Inn Fields, London WC2A 3LS (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): BILALI, Essat [US/US]; 270 6th Street, Palisade Park, NJ 07650 (US). (74) Agent: ABLEWHITE, Alan, James; Marks & Clerk, 57-60 Lincoln's Inn Fields, London WC2A 3LS (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, 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 <i>With international search report.</i>
(54) Title: FLAVOUR BLEND FOR MASKING UNPLEASANT TASTE OF ZINC COMPOUNDS (57) Abstract A synergistic flavouring combination of at least a flavouring oil and lauryl alcohol for use in an orally administered formulation which contains an ionisable zinc compound having an undesirable taste. The flavouring combination is unexpectedly effective in masking the unpleasant taste or aftertaste of zinc.		

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.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Flavour Blend For Masking Unpleasant Taste Of Zinc Compounds

BACKGROUND OF THE INVENTION

1. Field of Invention. This invention relates to a flavouring method and flavour composition for masking flavour and taste of compositions for oral absorption and administration by humans which contain zinc compounds.
2. General background. The value of the element zinc is well-established. Zinc has a vital role in a number of pharmaceutical formulations. Zinc deficiency is an important feature of many cases of sickle cell anaemia characterised by growth retardation and hypogonadism, and zinc appears to have an antisickling effect. Zinc has also been shown to be beneficial in the relief of acute inflammatory conditions associated with rheumatoid arthritis. Use of zinc gluconate and zinc acetate has been described as a method for reducing duration of common cold symptoms. Zinc oxides are used in a number of dental products such as dentifrices, denture adhesives, dental fillings, dental cements, and dental impression materials. Zinc salts are generally reported to enhance activity of triclosan and cationic anti-microbials in dentifrices and mouthwashes. Zinc chloride has been recognised as possessing anti-odour properties in oral health care products. Zinc citrates are useful in reducing dental calculus formation.

In recent years, formulations for oral administration and /or absorption such as tablets, powders, lozenges, syrups, sprays, dentifrices, mouthwashes, etc. have been formulated containing a zinc component. One of the major drawbacks of the incorporation of zinc compounds into various orally absorbed or administered products has been the characteristic bitterness of zinc that is experienced as soon as the zinc compound is released and proceeds to break down in the mouth. A variety of formulations and methods have been prepared and attempted to lessen or mask entirely the bitter taste and aftertaste of zinc compounds.

US Pat. Nos. 4,684,528 and 4,758,439 disclose the formulation of zinc compounds with glycine and certain other amino acids to reduce the unpalatable and undesirable aftertaste of prior zinc formulations. US Patent No. 5,095,035 teaches masking

compositions which contain zinc acetate with the addition of extramolar citric acid. US Patent No. 5,002,970 discloses that ionisable zinc compounds can be masked with anethole to eliminate or reduce the taste and after taste of zinc. US Patent No. 5,766,622 teaches the use of phosphorylated amino acid in oral compositions to inhibit bitter and/or metallic taste from a pharmaceutical active component. US Patent No. 5,817,295 discloses a tripartite blend of peppermint oils that provides for a pleasant tasting mouthwash and masking the bitter taste of essential oils used for antimicrobial efficacy in the mouthwash.

There is still a need for a new way to eliminate the objectionable taste and after taste of zinc compounds using new technologies.

SUMMARY OF THE INVENTION

The present invention relates to an orally administered formulation comprising about 0.1 to 25 wt. % of an ionisable zinc compound having an undesirable taste, and a synergistic flavouring combination of at least a flavouring oil and lauryl alcohol in an amount effective to mask the undesirable taste of said ionisable zinc compound.

The invention also provides a method for improving the taste of an orally administered formulation containing about 0.1 to 25 wt. % of an ionisable zinc compound with undesirable taste, by mixing into said formulation a synergistic flavouring combination of at least a flavouring oil and lauryl alcohol in an amount effective to mask the undesirable taste of said ionisable zinc.

DESCRIPTION OF THE INVENTION

The present invention provides an orally administered formulation containing an ionisable zinc compound with undesirable taste, but without the unpleasant metallic taste of zinc. The formulation can be in the form of foods, pharmaceuticals, toiletries, etc. The formulation contains an ionisable zinc compound and a carrier medium making up the balance.

Zinc Compounds. The orally administered formulations may contain one or more ionisable zinc compounds depending on the application. Zinc compounds include both inorganic and organic zinc salts and, in particular, salts such as the halides, nitrates, sulfates, chromates, silicates, and compounds comprising complexes of these materials constituting the inorganic salts contemplated herein. Organic salts of zinc include but not limited zinc

gluconate, zinc formate, zinc succinate, zinc aspartate and the like. Particular zinc halides include zinc chloride, zinc bromide, zinc fluoride, and mixtures.

In terms of specific applications, typical zinc compounds used in dental formulations include such materials as zinc oxide for use in inhibiting bacterial attack in dentifrices. Zinc oxide is also used as a binding materials in denture adhesives. Zinc chloride and zinc citrate are used as anti-odour ingredients in dental formulations. Zinc acetate and hydroxide is used for their anti-plaque properties. Zinc citrate, polyphosphates such as disodium ethane-1-hydroxy-1, 1-diphosphonate (EHDP), pyrophosphate, tetrametaphosphate, metaphosphate and orthophosphate salts of zinc for tartar removal effects in dentifrices. Zinc glycerophosphate, zinc phenolsulfonate, zinc fluorosilicate, zinc fluorozirconate are known for their astringent and deodorant capabilities. Zinc citrate is preferred for dental formulations. Zinc acetate and zinc gluconate are favoured in compositions for treating common colds.

In general, the concentration of zinc compounds in orally administered formulations varies from about 0.1 to 15 wt. %. The concentration can range up to as much as 25% depending on the particular formulation in which the zinc compound is incorporated. A more preferred amount is about 0.2 to 2 wt. %. A most preferred amount is from about 0.5 to 2 wt. %.

Flavouring / masking components: The taste masking / flavouring combination of the present invention is made up of a mixture of flavouring oils and lauryl alcohol.

For the purpose of this invention, flavouring oils used herein refer to both entire essential oils and the aroma chemicals making up the essential oils. Essential oils are predominately volatile materials from botanical sources. The most widely used process for the isolation of essential oils is steam distillation of plant matter, although dry distillation and solvent extraction are also used. Essential oils are generally recognised as safe compositions that can be included in ingested materials. Aroma chemicals refer to chemicals which may be synthetic or natural, derived from essential oils, i.e., derived from plants by distillation, expression, or extraction, and which usually carry the flavour of the plant from which they are derived.

Although the invention is not limited to the specific essential oils listed individually in this specification, a number of important essential oils include spearmint oil; peppermint oil; wintergreen oil; lavender oil; sassafras oil; ginger oil; clove oil; sage oil; basil oil; eucalyptus

oil; laurel oil; mayonara oil; cinnamon oil; camomile oil; thyme oil; citrus oils such as lemon oil, orange oil, grapefruit oil, tangerine oil; oil of anise; camphor oil; and the like.

Aroma chemicals include but not limited to anethole, carvone, cintronellal, camphor, linalool, menthol, menthone, thymol, and the like.

It has been found that in an orally administered formulation of the claimed invention, the additional presence of lauryl alcohol in combination with a mixture of flavouring oils as a flavouring composition, enhances the organoleptic properties, imparts freshness in the mouth and masks the unpleasant taste and aftertaste of the zinc compound in the formulation. The flavouring oils appear to be operating in synergistic combination, perhaps with the lauryl alcohol or perhaps because of the ability of various components of the flavouring oils themselves to inhibit different biological pathways associated with bioavailability.

The individual flavouring oils can be mixed and matched as desired to provide the intended flavour in the orally administered composition. The concentrations of the individual components can therefore vary quite widely. It is preferred, nevertheless, that the flavouring oils in total will be about 80 - 99.5 wt. % of the synergistic taste masking / flavouring combination, and most preferred about 95 - 99%. The lauryl alcohol makes up the rest of the masking / flavouring combination.

In general, the synergistic taste masking / flavouring combination is present in an amount of about 0.1 to 5 wt. % of the orally administered formulation. A preferred amount is about 0.1-3% wt. %. A most preferred amount is from about 0.1 to 2 wt. %.

Carriers & Other Ingredients: The carriers vary according to the applications. In toothpastes it is desirable to employ thickening agents such as hydroxyethylcellulose and water-soluble salts of cellulose ethers, including sodium carboxymethyl cellulose and sodium carboxymethylhydroxyethyl cellulose; or natural gums, including gum karaya, gum arabic, and gum tragacanth. Also, colloidal magnesium aluminium silicate or finely divided silica can be used as part of the thickening agent to improve the texture of the product. Thickening agents are used at levels of from 0.1% to 5.0% of the toothpaste composition. It is also desirable to include a humectant material in toothpastes. Suitable materials for this purpose include glycerine, sorbitol, and other edible polyhydric alcohols or mixtures thereof. These materials can comprise from about 1% to about 50% of the toothpaste composition. Dentifrices normally also contain sweetening agents. Suitable sweetening agents for use in dentifrices include for example saccharin, dextrose and levulose. The sweetening agents are

used at levels of from about 0.05% to about 2%. In addition to the aforementioned typical components of a toothpaste, water usually comprises the balance of the toothpaste, and is usually present at levels up to about 50%.

Mouthwashes generally comprise a water/ethyl alcohol solution and optionally other ingredients such as sweeteners, and humectants such as those mentioned above for dentifrices. The alcohols provide an antibacterial effect and help the solubility of the flavouring oils. Optionally, mouthwashes also contain sudsing agents. Humectants such as glycerine and sorbitol give a moist and sweet feel in the mouth and are desirably also present. While these materials are not always essential, they are useful to help solubilise and enhance the flavouring oils, and aid in making the product sweet, smoother and imparting body. Antibacterial agents are sometimes incorporated into mouthwashes or dentifrices at levels from about 0.01% to about 2.0%. Generally, mouthwashes suitable for use as carriers herein contain: 5% to 40% ethyl alcohol; 0% to 20%, preferably 5% to 20%, glycerine or other humectant; 0% to 12%, preferably 0.1% to 12%, sudsing agent, 0% to 0.5%, preferably 0.05% to 0.5%, sweetening agent such as saccharin; and 0% to 0.3%, preferably 0.05% to 2% of the flavouring / masking components of the present invention; and the balance, water with colorants or dyes if desired.

Chewing gum suitable for use as a carrier herein comprises a gum base and flavouring materials such as those mentioned above for dentifrices. The flavouring materials are present at a level of 0.01% to about 2.0% of the final chewing gum composition. The gum base is a chewable plastic gum material such as natural rubber, chicle, polyvinyl acetate, ester gum, coumarone resin, and paraffin wax. The gum base is typically made from a mixture of two or more plastic gum materials to achieve a preferred degree of plasticity for chewing. Optionally, corn syrup is added as a softener and binder for the chewing gum and sugar is optionally added as a sweetener and adding nuance to the flavour. A typical chewing gum suitable as a carrier herein comprises 15% to 30% gum base, 15% to 20% corn syrup, 50% to 65% sugar, 1% of zinc gluconate trihydrate, and 0.05% to 1.5% of the flavouring / masking composition of the invention.

Lozenges suitable as carriers herein comprise a hard sugar candy base and one or more flavouring oils. Optionally, lozenges can contain various other materials. A typical lozenge suitable as a carrier in this invention is a hard candy comprised of a hard candy base containing 0.05% to 1.5 wt. % of the flavouring / masking components and about 1 wt. % of

zinc acetate dihydrate. The hard candy base is a solidified solution of amorphous sugar which is generally formed from a sugar solution which has been cooked at high temperature so as to remove nearly all of the moisture. The taste masking / flavouring materials are added before the moisture is removed.

The orally administered compositions of the present invention can also optionally contain additional therapeutic materials including for example, water-soluble fluoride such as sodium fluoride and stannous fluoride.

Preparations: The orally administered compositions of the present invention without the metallic zinc taste can be prepared by any convenient method. The individual components of the synergistic masking / flavouring composition can be added separately as separate components to the orally administered compositions, but it is generally preferred to prepare the masking / flavouring composition separately and thereafter combine it with the orally administered compositions.

The orally administered compositions of the present invention can be in solid forms such as tablets, lozenges and powders; chewable forms such as chewing gums and soft candies; paste and gel forms such as dentifrices; liquids such as syrups, mouthwashes, and sprays. Flavoured lozenges with zinc compounds can be prepared by mixing the masking components of the present invention with the carriers and other ingredients, then by direct compression of the ingredients.

When the compositions are applied to or in contact with oral and oral pharyngeal membranes of a human, they are palatable and without undesirable taste or unpleasant metallic taste of zinc compounds. The flavours produced are truer, smoother, and better in taste than formulations without the masking/flavouring components of the present invention. In order to further illustrate the present invention, examples are set forth below. All parts and percentages are by weight and all temperatures in degrees in centigrade unless otherwise indicated.

Various flavouring compositions were prepared by mixing the components (in wt. %) set forth in Table 1 that follows:

TABLE 1

Ingredient	Example 1	Compare 1	Example 2	Compare 2
1-Menthol	31.3	13.9	9	35.4
Peppermint Oil	24.3	27.8	54	25.3
1-Carvone	21.5	17.6	-	29.3
Spearmint Oil 50/50	18.0	32.4	17	5
Anethole	3.5	8.3	-	4
Lauryl Alcohol, C-12	1.4	-	-	1
Optiacool A	-	-	20	-

The flavour compositions were combined into a dentifrice composition containing the following components, shown in Table 2 below:

TABLE 2

Ingredients	Parts By Weight
Sorbitol Solution	27
Glycerine	10
Amorphous Silica	10
Cocamidopropyl Betaine	4
KCl	3.75
Zinc Citrate	2
Colloidal Silica	1.7
Sodium Carboxymethyl Cellulose	1.6
Flavour Blend	1
Titanium Dioxide	0.5
Carboxymethyl Cellulose	0.4
Sodium Saccharine	0.4
Sodium Fluoride	0.3
Trisodium Phosphate	0.2
Water	Qs to 100

In blind taste tests, it is found that the dentifrice compositions containing the masking / flavouring compositions in the Examples exhibit "good tasting" properties and without any trace of the unpleasant metallic taste of zinc compounds.

Various changes and modifications can be made in the products of the present invention without departing from the spirit and scope thereof. The various embodiments which were disclosed herein were for the purpose of further illustrating the invention but were not intended to limit it.

CLAIMS:

1. An orally administered formulation that releases zinc ions to the oral and oral pharyngeal mucous membranes of a human comprising a suitable carrier and uniformly contained in said formulation:
 - about 0.1 to 25 wt. % of an ionisable zinc compound having an undesirable taste;
 - a synergistic flavouring combination of at least a flavouring oil and lauryl alcohol in an amount effective to mask the undesirable taste of said ionisable zinc compound.
2. The orally administered formulation of claim 1, wherein the lauryl alcohol is present in an amount of about 0.5-20 wt. % of the synergistic flavouring combination.
3. The orally administered formulation of claim 1 or claim 2, wherein said at least a flavouring oil is selected from the group consisting of: peppermint oil, spearmint oil, carvone, anethole and mixtures thereof.
4. The orally administered formulation of any one of claims 1 to 3, wherein said ionisable zinc compound is selected from the group consisting of: zinc oxide, zinc citrate, zinc chloride, zinc acetate, zinc hydroxide, zinc fluorosilicate, zinc fluoroaluminumate, zinc acetate, zinc gluconate and mixtures thereof.
5. The orally administered formulation of claim 4, wherein said ionisable zinc compound is zinc citrate.
6. The orally administered formulation of any one of claims 1 to 5, in the form of a dentifrice.
7. The orally administered formulation of any one of claims 1 to 5, in the form of a lozenge.
8. The orally administered formulation of any one of claims 1 to 5, in the form of a mouth rinse.

9. The orally administered formulation of any one of claims 1 to 5, in the form of a chewable tablet.
10. The orally administered formulation of any one of claims 1 to 5, in the form of a syrup.
11. The orally administered formulation of any one of claims 1 to 5, selected from the group consisting of foods, pharmaceuticals, and mixtures thereof.
12. A method for improving the taste of an orally administered formulation, which formulation includes about 0.1 to 25 wt. % of an ionisable zinc compound having an undesirable taste, said method comprising mixing a synergistic flavouring combination of at least a flavouring oil and lauryl alcohol in an amount effective to mask the undesirable taste of said ionisable zinc.
13. The method of claim 12, wherein the lauryl alcohol is present in an amount of about 0.5-20 wt. % of the synergistic flavouring combination.
14. The method of claim 12 or claim 13, wherein said flavouring oil is selected from the group consisting of: peppermint oil, spearmint oil, carvone, anethole and mixtures thereof.
15. The method of any one of claims 12 to 14, wherein said ionisable zinc compound is selected from the group consisting of: zinc oxide, zinc citrate, zinc chloride, zinc acetate, zinc hydroxide, zinc fluorosilicate, zinc fluorozirconate, zinc acetate, zinc gluconate and mixtures thereof.
16. The method of any one of claims 12 to 15, wherein said orally administered formulation is selected from the group consisting of foods, pharmaceuticals, and mixtures thereof.
17. A preformulation consisting essentially of about 80 - 99.5 wt. % of at least a flavouring oil and about 0.5 to 20 wt. % lauryl alcohol, wherein said preformulation when

uniformly mixed in an orally administered formulation containing about 0.1 to 25 wt. % of an ionisable zinc compound with undesirable taste, masks the undesirable taste of said ionisable zinc compound.

18. The preformulation of claim 17, wherein said flavouring oil is selected from the group consisting of: peppermint oil, spearmint oil, carvone, anethole and mixtures thereof.

19. The preformulation of claim 17 or claim 18, wherein said orally administered formulation is selected from the group consisting of foods, pharmaceuticals, and mixtures thereof.

20. The preformulation of any one of claims 17 to 19, wherein said ionisable zinc compound is selected from the group consisting of: zinc oxide, zinc citrate, zinc chloride, zinc acetate, zinc hydroxide, zinc fluorosilicate, zinc fluorozirconate, zinc acetate, zinc gluconate and mixtures thereof.

INTERNATIONAL SEARCH REPORT

Inter. Appl. No.

PCT/GB 99/03779

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K7/16

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 049 671 A (BIOSYSTEMS RESEARCH INC) 14 April 1982 (1982-04-14) page 7, line 27 - line 33 page 11, line 12 - line 16; example 24.3 page 11, line 28 - line 34; claims 1-3,5,6,8,9,11	1-16
Y	US 4 758 439 A (GODFREY JOHN C) 19 July 1988 (1988-07-19) cited in the application claims 3,5-7; examples 8-21	1-6,9-16
Y	US 5 002 970 A (EBY III GEORGE A) 26 March 1991 (1991-03-26) cited in the application claims 1-3,5; examples 1-7,9-13	1-4,7-9, 16
	-/--	



Further documents are listed in the continuation of box C.



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

14 January 2000

Date of mailing of the international search report

24/01/2000

Name and mailing address of the ISA

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

Authorized officer

Minas, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/03779

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 012, no. 297 (C-519), 12 August 1988 (1988-08-12) & JP 63 066115 A (LION CORP), 24 March 1988 (1988-03-24) abstract ---	1-20
A	PATENT ABSTRACTS OF JAPAN vol. 008, no. 218 (C-245), 4 October 1984 (1984-10-04) & JP 59 101418 A (RAION KK), 12 June 1984 (1984-06-12) abstract ---	1-20
A	GB 1 055 854 A (HOFFMANN-LA ROCHE & CO., AG) 18 January 1967 (1967-01-18) page 2, line 46 - line 51 page 2, line 79 - line 80; claims 1,4 -----	1-20

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 99/03779

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0049671 A	14-04-1982	AU 542977 B	28-03-1985
		AU 7553081 A	05-01-1984
		BR 8106432 A	22-06-1982
		CA 1170664 A	10-07-1984
		CA 1193611 A	17-09-1985
		DK 441481 A	08-04-1982
		ES 506066 A	16-08-1982
		FI 813110 A	08-04-1982
		GR 75340 A	13-07-1984
		IN 157474 A	05-04-1986
		JP 57091948 A	08-06-1982
		NO 813385 A	13-04-1982
		NZ 198418 A	24-08-1984
		PH 17352 A	01-08-1984
		PT 73780 A, B	01-11-1981
		RO 83310 A	12-04-1984
		US RE32909 E	18-04-1989
		ZA 8106894 A	29-09-1982
		AU 7552981 A	09-09-1982
		FI 813111 A	09-04-1982
		GR 75341 A	13-07-1984
		JP 57095909 A	15-06-1982
		NZ 198416 A	31-07-1984
		PT 73781 A, B	01-11-1981
		ZA 8106893 A	29-09-1982
		US 4404146 A	13-09-1983
		US 4407818 A	04-10-1983
US 4758439 A	19-07-1988	US 4684528 A	04-08-1987
		CA 1243952 A	01-11-1988
		DE 3587766 D	07-04-1994
		DE 3587766 T	14-07-1994
		EP 0183840 A	11-06-1986
		GB 2179536 A, B	11-03-1987
		WO 8600004 A	03-01-1987
US 5002970 A	26-03-1991	US 4956385 A	11-09-1990
		US 5409905 A	25-04-1995
		US 5286748 A	15-02-1990
		US 4503070 A	05-03-1985
		US 5095035 A	10-03-1992
		US RE33465 E	27-11-1990
JP 63066115 A	24-03-1988	JP 8016049 B	21-02-1996
JP 59101418 A	12-06-1984	JP 1835498 C	11-04-1994
		JP 3043246 B	01-07-1991
GB 1055854 A		BE 664197 A	22-11-1965
		DE 1467938 A	13-03-1969
		DK 119079 B	09-11-1970
		FR 1455118 A	29-12-1966
		IL 23502 A	29-01-1969
		NL 6505953 A	23-11-1965
		SE 330955 B	07-12-1970
		US 3466362 A	09-09-1969