662194

AUSTRALIA

PATENTS ACT 1990

NOTICE OF ENTITLEMENT

We, **SmithKline Beecham plc,** the applicant/Nominated Person in respect of Application No. 31663/93 state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person would, on the grant of a patent for the invention to the inventors, be entitled to have the patent assigned to the Nominated Person.

The Nominated Person is entitled to claim priority from the application listed in the declaration under Article 8 of the PCT because the Nominated Person made the application listed in the declaration under Article 8 of the PCT, and because that application was the first application made in a Convention country in respect of the invention.

DATED this FIFTEENTH day of JUNE 1994

.....

a member of the firm of DAVIES COLLISON CAVE for and on behalf of the applicant(s)

(DCC ref: 1668720)

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DENTIFRICE COMPOSITIONS

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(56) Prior Art Documents
US 5082653
WO 89/12399

(57) Claim

1. A dentifrice comprising from 0.001 to 5.0% of an antibacterial agent which consists essentially of a lanthocin antibacterial agent and an orally acceptable carrier or excipient which comprises an abrasive and does not have an anionic surfactant.

13. A method of preventing or treating plaque which method comprises applying an antiplaque effective amount of a composition as defined in any one of claims 1 to 12 to a patient in need thereof.

14. A process for preparing a dentifrice as defined in any one of claims 1 to 12 which process comprises admixing the ingredients thereof in the required pro[illegible]ions, in any order that is convenient and finally and if necessary adjusting the pH.

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(54) Title: DENTIFRICE COMPOSITIONS

(57) Abstract

The present invention provides for a dentifrice formulation comprising an antibacterially effect amount of a bacteriocin antibacterial agent and an orally acceptable carrier or excipient which composition does not contain an anionic surfactant. The present invention further comprises a method of reducing or preventing the formation of dental plaque, which method comprises applying an antiplaque effective amount of a composition according to the present invention to a patient in need thereof.

Dentifrice compositions.

This invention relates to oral hygiene compositions and in particular to dentifrices comprising particular antibacterial agents which compositions are useful in antiplaque therapy.

Oral hygiene compositions for use in antiplaque therapy generally comprise an antibacterial agent as the antiplaque agent. Antibacterial agents already used in various oral hygiene compositions include cationic antibacterial agents such as chlorhexidine digluconate and cetyl pyridinium chloride and non-cationic antibacterial agents such as triclosan.

Another class of antibacterial agents are the bacteriocins. These have been defined as proteinaceous substances produced by bacteria and which have antibacterial activity only against species closely related to the species of origin. More recently it has been found that, at least in certain instances, the spectrum of antibacterial activity may in fact be broader.

An example of a bacteriocin which has already found commercial application is nisin. This is a lanthocin, comprising the atypical amino acid lanthionine. Nisin is a polypeptide with antibacterial properties which is produced naturally by various strains of the bacterium *Streptococcus lactis*. It is also a naturally occurring preservative found in low concentration in milk and cheese. Nisin has recently been recognised by the FDA as a direct food ingredient. A summary of nisin's properties is to be found in Advances in Applied Microbiology 27 (1981), 85-123.

Recently, a purified form of nisin has been made available by Applied Microbiology Inc under the trade name AMBICIN N. It has been suggested for use in a variety of applications including oral care, as disclosed in PCT Application WO 89/12399 to Blackburn et al., and now in issued US Patent No. 5,135,910 for use in the oral cavity. US Patent 5,135, 910 specifically includes in the formulations of the lanthione antibacterial agents the use of all surfactants, including those which are anionic.

However, it has now been found that the bactericidal activity of the

bacteriocin derivatives, particularly nisin, is incompatible with anionic surfactants. As far as we are aware, no specific proposals for a dentifrice formulation have been proposed which has recognized this particular problem.

Accordingly, the present invention provides for a dentifrice comprising from 0.001 to 5.0% of an antibacterial agent which consists essentially of a lanthocin antibacterial agent and an orally acceptable carrier or excipient which comprises an abrasive and does not have an anionic surfactant.

We have found that bacteriocin antibacterial agents such as nisin are incompatible with conventional dentifrices bases that contain strong anionic surfactants, such as sodium lauryl sulphate and sodium N-methyl-N-cocyl laurate which are conventionally used in such bases. It is believed that the strong anionic surfactants reversibly inactivate or inhibit the bacteriocin antibacterial agents which tend to be positively charged. Care must therefore be exercised in selecting suitable surfactants for their compatibility with the antibacterial agent.

When used herein, in respect of a dentifrice ingredient, the term "compatible" is used to mean that the activity of the bacteriocin is not substantially compromised the presence of the ingredient. Suitably that activity in the presence of the ingredient should not be less than 40%, preferably less than 50%, advantageously less than 60% of that observed in the absence of the ingredient. This may be readily checked by bioassay, for instance the zone diffusion assay described in example 4.

Suitable bacteriocin antibacterial agents include nisin, gramicidin and tyrothricin and purified forms of bacteriocins such as AMBICIN N. Nisin and in particular the purified form thereof AMBICIN N are especially preferred.

The dentifrice comprises from 0.001 to 5.0%, preferably from 0.005 to 2.0%, advantageously from 0.02 to 1.0% of bacteriocin antibacterial agent by weight of the composition. In an alternative manner the level of bacteriocin agent needed is one which reaches a sufficient level in the oral cavity to inhibit the desired microorganisms. An effective level of a bacteriocin agent in the oral cavity, and more specifically nisin, to inhibit

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the desired organisms is a level of about 0.99 ppm.

When used herein, the term "orally acceptable carrier or excepient" includes the surfactant, thickening agent, humectant and abrasive, as well as other optional extras normally included in a dentifrice formulation.

Suitable surfactants for use in dentifrices according to the invention include, for instance, nonionic, cationic and amphoteric surfactants or mixtures thereof.

Suitable nonionic surfactants include, for example, polyethoxylated sorbitol esters, in particular polyethoxylated sorbitol monoesters, for instance, PEG(40) sorbitan diisostearate, and the products marketed under the trade name 'Tween" by ICI; polycondensates of ethylene oxide and propylene oxide (poloxamers), for instance the products marketed under the trade name 'Pluronic' by BASF-Wyandotte; condensates of propylene glycol; polyethoxylated hydrogenated castor oil, for instance, cremophors; and sorbitan fatty esters. It is further believed that certain nonionic "Tween" products may also have better compatability with nisin than other nonionic surfactants which appear to be due to impurities present in the product. Hence, use of purified products is preferable whereever possible. Alternatively, the use of a free radical scavenger, preferably methionine may be used to remove the detrimental effects of the impurities on the bacteriocin agents.

Suitable amphoteric surfactants include, for example, long chain imidazoline derivatives such as the product marketed under the trade name 'Miranol C2M' by Miranol; long chain alkyl betaines, such as the product marketed under the tradename 'Empigen BB' by Albright + Wilson, and long chain alkyl amidoalkyl betaines, such as cocamidopropylbetaine, and mixtures thereof.

Suitable cationic surfactants include the D,L-2-pyrrolidone-5-carboxylic acid salt of ethyl-N-cocoyl-L-arginate, marketed under the trade name CAE by Ajinomoto Co. Inc., cocamidopropyl PG dimonium chloride phosphate, available under the trade name MONAQUAT PTC from Mona Corpn., and lauramidopropyl PG dimonium chloride phosphate available

under the trade name MONAQUAT PTL from Mona Corpn..

Advantageously, the surfactant is present in the range 0.005 to 20%, preferably 0.1 to 10%, more preferably 0.1 to 5% by weight of the dentifrice.

Suitable thickening agents include, for instance, nonionic thickening agents such as, for example, (C_1-$_6$)alkylcellulose ethers, for instance methylcellulose; hydroxy(C_1-$_6$)alkylcellulose ethers, for instance hydroxyethylcellulose, hydroxypropylcellulose; (C_2-$_6$)alkylene oxide modified (C_1-$_6$)alkylcellulose ethers, for instance hydroxypropyl methylcellulose; and mixtures thereof. Other suitable thickening agents include natural and synthetic gums or gum like material such as Irish Moss, gum tragacanth, sodium carboxymethylcellulose, polyvinylpyrrolidone, starch and thickening silicas. Suitably the thickening agent has decreased numbers of anionic groups, such as a carboxy group, although carboxymethyl cellulose may be used. Preferably, the thicking agent is a methyl cellulose derivative such as hydroxyethyl cellulose, or hydroxyethyl methyl cellulose.

Advantageously the thickening agent is present in the range 0.01 to 30%, preferably 0.1 to 15%, more preferbly 1 to 5%, by weight of the composition.

Suitable humectants for use in compositions of the invention include for instance, glycerine, sorbitol, propylene glycol or polyethylene glycol, or mixtures thereof; which humectant may be present in the range from 5 to 70%, preferably 5 to 30%, more preferably 10 to 30% by weight of the dentifrice. Suitably, when the nonionic thickening agent is hydroxypropyl methylcellulose, the humectant is present in up to 30% by weight of the dentifrice.

Suitable abrasives for use in compositions of the present invention include calcium carbonate, calcium phosphates, calcium pyrophosphate, insoluble sodium metaphosphate, sodium aluminosilicate, alumina, hydrated alumina, zinc orthophosphate, plastics particles and silica, of which silica is preferred. Further preferred is the use of a "low anion" silica as is described in greater detail below.

Suitable silicas include natural amorphous silicas such as for instance diatomaceous each and synthetic amorphous silicas such as precipitated silicas and silica gels such as silica xerogels. Suitable silica xerogels are described in US 3,538,230. Suitable grades of precipitated silicas have BET surface areas in the range 20 to 300, preferably 20 to 100 m^2g and median agglomerate sizes in the range 2 to 50, preferably 5 to 30μ.

Suitable precipitated silicas and silica xerogels are those marketed by Degussa under the trade name SIDENT and by W R Grace Corporation. Davison Chemical Division under the trade name SYLOBLANC, respectively.

Advantageously, the silica is a "low anion" silica. As used herein, the term "low-anion" silicas refers to those in which anionic impurities such as sodium sulphate and sodium silicate which normally arise during the course of the manufacturing process are kept to a minium, through careful control of the manufacturing process. "Low anion" silicas suitably have less than 1%, preferably less than 0.5% advantageously less than 0.25% by weight of anionic impurities

Suitable such "low anion" silicas are described in EP 0 368 130 (Proctor & Gamble), EP 0 315 503 and EP 0 396 459 (Rhone-Poulenc) and WO 90/05113 (J.M. Huber Corp). Alternatively, grades of commercially available silica with ionic impurities may be rendered suitable by washing thereof with deionised water. Conductivity measurements on the water after washing may be used to monitor the efficacy of such washing. Suitably the conductivity of the water after washing is reduced to less than 200μSiemens/cm. Suitable "low anion" silicas include the grade RP93 available from Rhone-Poulenc.

Suitably, compositions will have from 5 to 80 %, preferably from 10 to 60 % by weight of the abrasive.

In a preferred aspect, compositions according to the present invention comprise a nonionic surfactant such as, for instance, a polycondensate of ethylene oxide and propylene oxide; a nonionic thickening agent such as, for instance, hydroxypropyl methylcellulose; a humectant such as, for

instance, glycerin; and an abrasive such as for instance a "low-anion" silica. In a second preferred aspect, a composition according to the present invention comprises a nonionic surfactant such as, for instance, a polycondensate of ethylene oxide and propylene oxide, a thickening agent such as sodium carboxymethyl cellulose (or hydroxy ethyl cellulose) optionally admixed with a thickening silica, a humectant such as sorbitol optionally admixed with glycerin and an abrasive such as a "low anion" silica.

Compositions according to the present invention may usefully comprise a fluoride ion source, to provide an anti-caries activity. A fluoride ion source is found to be compatible with the bacteriocin peptide antibacterial agent. Suitable fluoride ion sources include metal fluoride salts, for instance alkali metal fluoride salts such as sodium fluoride, amine fluoride salts, alkali metal monofluorophosphate salts such as sodium monofluorophosphate and amine monofluorophosphate salts. Suitably the fluoride ion source would, if present, be included to provide from 50 to 3500 ppm, preferably 100 to 2500 ppm of fluoride ions.

In addition to a humectant, compositions of the present invention may also contain further liquid such as, for instance, water, preferably deionised water.

The orally acceptable vehicle or carrier may also comprise further optional ingredients such as flavouring agents, sweetening agents, for example sodium saccharin, dyes, whitening agents, for example titanium dioxide, preservatives, antisensitivity agents such as stronium and potassium salts and anticalculus agents such as tetraalkali and dialkaliimetal pyrophosphate salts. It will be appreciated that in each instance, an optional ingredient, if included, will be compatible with the bacteriocin.

Dentifrices according to the present invention may be presented in any of the presentations as conventionally used in the art, for instance as toothpastes, toothpowders and gels.

Compositions according to the invention will have a pH which is orally acceptable and within which the antibacterial activity of the bactreiocin is not substantially compromised. Suitably, the pH is in the range 4 to 9.5,

preferably in the range 4 to 6.5, more preferably between 4 and 5.5 and most preferably 5 to 5.5.

Compositions according to the invention may be prepared by conventional processes comprising admixing the ingredients together in the appropriate relative amounts in any order that is convenient and finally and if necessary adjusting the pH to the desired value.

Compositions of the present invention are effective against oral plaque bacterial and as such will be of use in antiplaque therapy.

Accordingly, in a further aspect, the present invention also provides a method of reducing or preventing the formation of dental plaque, which method comprises applying an antiplaque effective amount of a composition according to the present invention to a patient in need thereof.

The invention will now be illustrated by reference to the following examples.

EXAMPLE 1

Toothpaste

AMBICIN N	0.50%
Glycerin	22.00
Hydroxypropyl methylcellulose	3.40
Titanium dioxide	1.00
Sodium saccharin	0.10
Poloxamer (Pluronic F108)	2.00
Flavour	1.00
Talin	0.02
Silica (RP93)	16.00
Deionised water	qs

EXAMPLE 2

Toothpaste

AMBICIN N	0.05%
Sorbitol (70% soln)	20.00
Glycerin	15.00
Sodium carboxymethyl cellulose	1.20
Sodium fluoride	0.23
Silica (RP 93)	16.00
Thickening silica (Sident 22)	5.00
Sodium saccharin	0.30
Poloxamer (Pluronic F108)	2.00
Deionised water	qs

EXAMPLE 3

Toothpaste

AMBICIN N	0.05%
Glycerin	22.00
Methocel K15 Premium	0.20
Methocel K100 Premium	3.20
Titanium dioxide	1.00
Sodium saccharin 30% soln.	0.33
Poloxamer (20% Pluronic F108 soln)	10.00
Sodium Fluoride	0.221
Flavour	1.00
5% Talin Solution	0.40
Silica (RP 93)	16.00
Deionised water	qs

The above noted example can be further prepared using Sodium carboxymethyl cellulose at 1.20 instead of the Methocel K15 Premium and Methocel K100 Premium.

Suitably the formulations of Examples 1 to 3 may also be prepared with increasing levels of nisin from 0.25%, 0.5%, 1.0 % and 2%, respectively.

EXAMPLE 4

Biological Data

The compatibility of AMBICIN N with various types of surfactants was examined in a simple *in vitro* assay of antibacterial activity.Using *M. luteus* as the test organism, the activity of AMBICIN N was determined in the presence and absence of a range of surfactants, using a conventional zone diffusion assay in agar agar. The surfactants examined are shown in the table below, along with an indication of which category they belong to. The results are also presented graphically in Figure 1. These show that whilst the antibacterial activity of AMBICIN N is substantailly diminished in the presence of an anionic surfactant such as sodium lauryl sulphate or sodium N-methyl-N-cocyl laurate, it is substantially maintained in the presence of a nonionic surfactant such as Pluronic F108, F127 and P87, Tween 80 and cremophor or as cationic surfactant such as CAE or an amphoteric surfactant such as Tegobetaine.

Table

Surfactant	Type	
Sodium lauryl sulphate	Anionic	
Adinol *CT95	Anionic	*Trade mark of Croda Chemicals Ltd.
Pluronic *F108	Nonionic	*Trade mark of BASF-Wyandotte
Pluronic *F127	Nonionic	*Trade mark of BASF-Wyandotte
Pluronic *P87	Nonionic	* Trade mark of BASF-Wyandotte
Tween *80	Nonionic	*Trade mark of ICI
Tegobataine *FU	Amphoteric	*Trade mark of Th. Goldschmidt Ltd.
CAE*	Cationic	*Trade mark of Ajinomoto Co Inc

EXAMPLE 7

Antibacterial spectrum of AMBICIN N

The antibacterial spectrum of activity of AMBICIN N (AMB N) was established by testing the compound against a range of orally important Gram negative and Gram positive bacteria in a conventional nominal inhibitory concentration (NIC) assay. The established antiplaque agents cetyl pyridinium chloride (CPC), chlorhexidine (CHX) and triclosan were included for comparison. The results are shown in the accompanying table. In all bar two instances, AMBICIN N has superior activity.

Table NIC data

Organism	CPC (ppm)	CHX (ppm)	Triclosan (ppm)	AMB N (ppm)
Strep.agalactiæ	0.78	0.41	4.96	0.22
Strep. sanguis	2.12	0.86	0.88	0.23
Strep.mutans	3.10	3.94	1.11	0.43
Strep. milleri	4.58	1.58	1.08	0.14
Strep. mitis	2.23	1.50	3.94	0.33
Strep mitior	1.22	4.55	4.23	0.05
Strep. salivarius	2.36	1.44	4.05	0.18
Strep.pyogenes	0.78	0.16	4.35	0.009
Staph.aureus	0.66	0.54	0.09	0.13
G.vaginalis	0.3	1.3	0.41	0.22
Lacto odontolyticus	0.83	1.88	7.49	0.02
Act. odontolyticus	1.23	3.37	3.02	0.12
Act. israelii	8.15	4.11	3.19	0.53
Act. naeslundii	4.61	2.01	1.98	>12.8
Act. actinomycetem	1.02	0.53	1.69	0.02
Fuso. nucleatum	0.82	0.64	1.6	0.048
Bact. intermedius	4.68	2.49	3.72	0.91
Peptostrepto. micros	4.96	8.46	6.76	>1.28
Porph. gingivalis	0.94	2.36	4.00	>1.28
Bact. ureolyticus	0.56	0.69	7.65	0.035
Candida albicans	1.39	1.71	1.00	>1.28
Candida kefyr	0.61	0.42	0.46	>1.28
Candida tropicalis	0.48	0.98	0.35	>1.28

EXAMPLE 6

Clinical data

In a double blind, crossover healthy volunteer study of 29 people, the toothpaste of example 1 containing AMBICIN N (0.05%) was found to give reductions in the aerobic, Steptococcal and anaerobic flora which were statistically significant compared to a similar placebo toothpaste from which AMBICIN N was omitted. The toothpastes were each used in a single brushing and the bacterial counts measured 15 minutes after brushing.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples are to be construed as merely illustrative and not a limitation on the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A dentifrice comprising from 0.001 to 5.0% of an antibacterial agent which consists essentially of a lanthocin antibacterial agent and an orally acceptable carrier or excipient which comprises an abrasive and does not have an anionic surfactant.

2. A dentifrice as claimed in claim 1 in which the lanthocin antibacterial agent is nisin.

3. A dentifrice as claimed in claim 2 in which nisin is provided as the product AMBICIN N.

4. A dentifrice as claimed in any one of claims 1 to 3 in which the orally acceptable carrier or excipient comprises a nonionic, a cationic or an amphoteric surfactant.

5. A dentifrice as claimed in claim 4 in which the surfactant is a poloxamer.

6. A dentifrice as claimed in any one of claims 1 to 5 in which the orally acceptable carrier or excipient comprises a thickening agent selected from a nonionic thickening agent or a natural or synthetic gum or gum-like material.

7. A dentifrice as claimed in claim 6 in which the thickening agent is hydroxypropyl methylcellulose or sodium carboxymethylcellulose.

8. A dentifrice as claimed in any one of claims 1 to 7 in which the abrasive is selected from calcium carbonate, calcium phosphates, calcium pyrophosphate, insoluble sodium metaphosphate, sodium aluminosilicate, hydrated alumina, zinc orthophophate, plastics particles and silica.

9. A dentifrice as claimed in claim 8 in which the abrasive is silica.

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10. A dentifrice as claimed in claim 9 in which the silica abrasive is a "low anion" silica abrasive.

11. A dentifrice as claimed in any one of claims 1 to 10 further comprising a fluoride ion source.

12. A dentifrice as claimed in any one of claims 1 to 11 which has a pH in the range of 4.5 to 9.

13. A method of preventing or treating plaque which method comprises applying an antiplaque effective amount of a composition as defined in any one of claims 1 to 12 to a patient in need thereof.

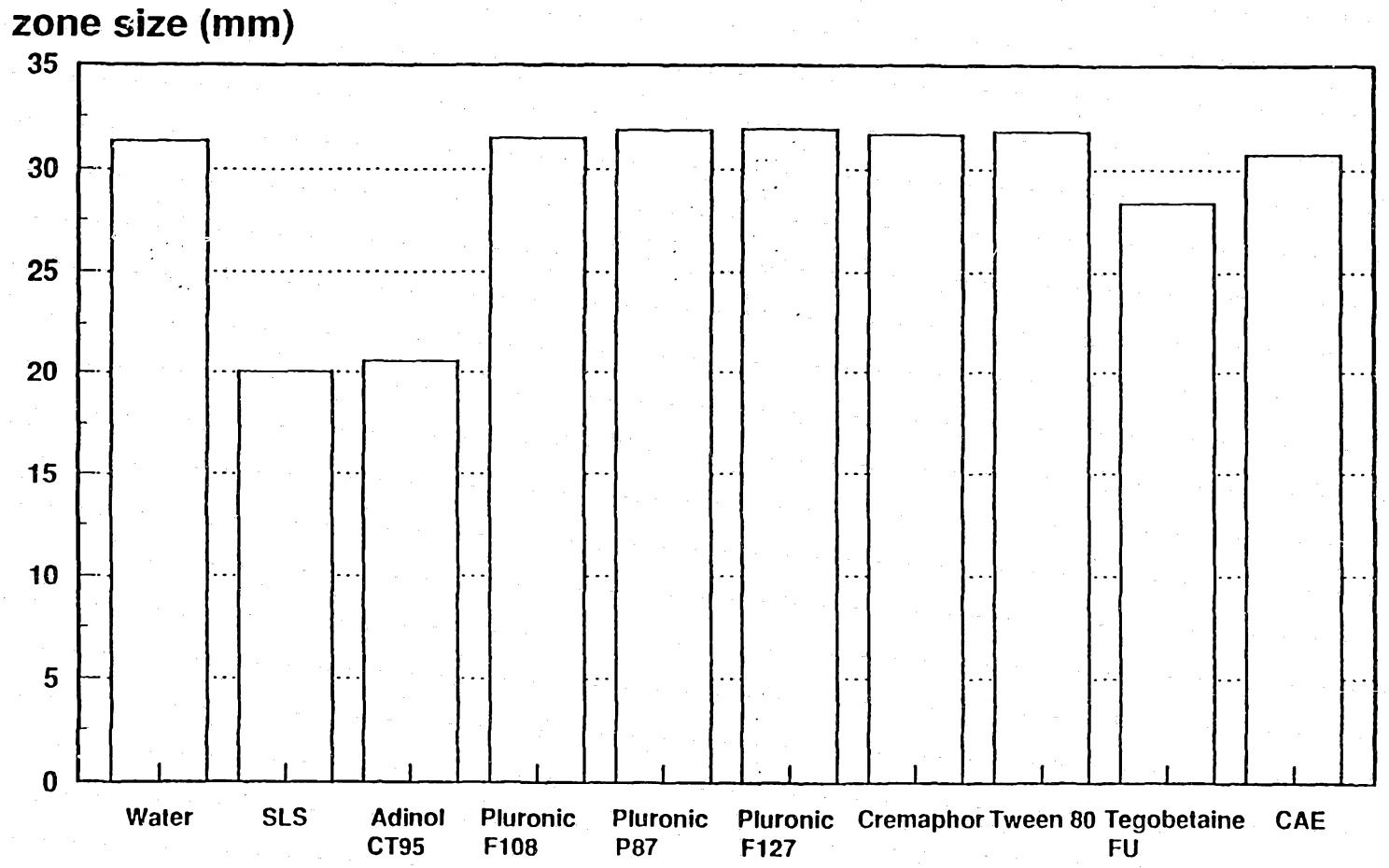
14. A process for preparing a dentifrice as defined in any one of claims 1 to 12 which process comprises admixing the ingredients thereof in the required proportions, in any order that is convenient and finally and if necessary adjusting the pH.

15. A dentifrice or a process for its preparation, substantially as described herein with reference to Examples 1 to 4.

DATED this 23rd day of June, 1995
SmithKline Beecham plc
By Its Patent Attorneys
DAVIES COLLISON CAVE

AUSTRALIAN PATENT OFFICE

COMPATIBILITY OF AMBICIN N WITH
TOOTHPASTE DETERGENTS/SURFACTANTS.



All components mixed with 1000ppm Ambicin N

FIGURE 1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/02348

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K7/16

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0 140 498 (LION CORPORATION) 8 May 1985 see claims 1,7-9,12-13; examples 14-15,8-10	1,4,6-8, 11,13-17
X	GB,A,2 160 771 (LION CORPORATION) 2 January 1986 see examples 14-15,8-10	1,4,6-8, 11,13-17
X	GB,A,710 129 (AMM-I-DENT) 9 June 1954 see page 1, line 66 - page 2, line 17 see page 2, line 86 - page 3, line 95	1-2,4,8, 13-17
X,P	US,A,5 082 653 (PAN ET AL.) 21 January 1992 see the whole document	1-2, 4-11, 13-17

-/--

° Special categories of cited documents :[10]

"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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29 MARCH 1993	22.04.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	FISCHER J.P.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	US,A,4 022 880 (VINSON ET AL.) 10 May 1977 see examples 20-21	1-2, 13-17
X	WO,A,8 912 399 (PUBLIC HEALTH RESEARCH INSTITUTE OF THE CITY OF NEW YORK) 28 December 1989 cited in the application see claims 1,2-4,710-12	1-2, 13-17
A	GB,A,1 063 787 (THE UPJOHN COMPANY) 30 March 1967 see the whole document	1-17
X	INT. J. CLIN. PHARM. RES. vol. 4, no. 8, 1988, pages 259 - 261 MATULA ET AL. 'SALIVARY LEVELS OF GRAMICIDIN AFTER USE A TYROTHRICIN-CONTAINING GARGLE/MOUTH-WASH AND TYROTHRICIN LOZENGES' see page 259 - page 261	1-2, 13-17

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9202348
SA 68531

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		JP-A-	60038329	27-02-85
		US-A-	4693888	15-09-87
GB-A-2160771	02-01-86	JP-A-	61012629	21-01-86
		CA-A-	1275380	23-10-90
		DE-A,C	3522898	02-01-86
		US-A-	4714612	22-12-87
GB-A-710129		None		
US-A-5082653	21-01-92	AU-A-	8869791	26-05-92
		EP-A-	0507921	14-10-92
		WO-A-	9207549	14-05-92
US-A-4022880	10-05-77	None		
WO-A-8912399	28-12-89	AU-B-	631803	10-12-92
		AU-A-	3843089	12-01-90
		EP-A-	0382814	22-08-90
		JP-T-	3500051	10-01-91
		US-A-	5135910	04-08-92
GB-A-1063787		BE-A-	649397	17-12-64
		FR-A-	1418050	
		NL-A-	6406899	18-12-64