

666306

AUSTRALIA  
PATENTS ACT 1990  
NOTICE OF ENTITLEMENT

We, **SmithKline Beecham Corporation**, the applicant/Nominated Person in respect of Application No. 17464/92 state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person derives title to the invention from the inventors by assignment.

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 is the assignee of the applicants in respect of 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 FOURTEENTH day of OCTOBER 1993



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

(DCC ref: 1620178)



AU9217464

(12) PATENT ABRIDGMENT (11) Document No. AU-B-17464/92  
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 666306

- (54) Title  
CONDITION-CONTROLLED DENTIFRICE COMPOSITION
- International Patent Classification(s)  
(51)<sup>5</sup> A61K 007/22 A61K 007/18
- (21) Application No. : 17464/92 (22) Application Date : 07.04.92
- (87) PCT Publication Number : WO92/18096
- (30) Priority Data
- (31) Number (32) Date (33) Country  
683149 10.04.91 US UNITED STATES OF AMERICA
- (43) Publication Date : 17.11.92
- (44) Publication Date of Accepted Application : 08.02.96
- (71) Applicant(s)  
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- (56) Prior Art Documents  
US 4188372  
US 4205061  
US 4273759
- (57) Claim

1. A dentifrice for reducing plaque formation and treating gingivitis on teeth and soft tissue which has a pH between 6 and 8 comprising:

- (a) a quaternary ammonium cationic antibacterial agent in an amount between about 0.005 and 10% by weight;
- (b) at least one thickening agent which is not an anionic thickening agent;
- (c) at least one surfactant which is not an anionic surfactant; and
- (d) an abrasive selected from the group consisting of calcium carbonate, dicalcium phosphate and calcium pyrophosphate.

OPI DATE 17/11/92 APPLN. ID 17464/92  
AOJP DATE 24/12/92 PCT NUMBER PCT/US92/02918



AU9217464

INTERNATIONAL PUBLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                            |
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| <b>(51) International Patent Classification 5 :</b><br><b>A61K 7/16, 7/18, 7/22</b>                                                                                                                                                                                                                                                                                                                                                                                                                                             |  | <b>A1</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <b>(11) International Publication Number:</b> <b>WO 92/18096</b><br><b>(43) International Publication Date:</b> 29 October 1992 (29.10.92) |
| <b>(21) International Application Number:</b> PCT/US92/02918<br><b>(22) International Filing Date:</b> 7 April 1992 (07.04.92)<br><b>(30) Priority data:</b><br>683,149 10 April 1991 (10.04.91) US<br><b>(60) Parent Application or Grant</b><br><b>(63) Related by Continuation</b><br>US 683,149 (CON)<br>Filed on 10 April 1991 (10.04.91)<br><b>(71) Applicant (for all designated States except US):</b> SMITH-KLINE BEECHAM CORPORATION [US/US]; 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US). |  | <b>(72) Inventors; and</b><br><b>(75) Inventors/Applicants (for US only) :</b> GALLOPO, Andrew, Robert [US/US]; 133 Wessington Avenue, Garfield, NJ 07026 (US). IBRAHIM, Nader, I. [US/US]; 18 Nancy Terrace, Hackettstown, NJ 07840 (US). MAZZANO-BILE, Salvatore [US/US]; 246 Crocker Place, Haworth, NJ 07641 (US).<br><b>(74) Agents:</b> KANAGY, James, M. et al.; SmithKline Beecham Corporation, Corporate Patents - U.S. (UW2220), 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).<br><b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US.<br><br><b>Published</b><br><i>With international search report.</i><br><i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |                                                                                                                                            |
| <b>666306</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                            |
| <b>(54) Title:</b> QUATERNARY AMMONIUM ANTIBACTERIAL DENTIFRICES WITH SELECTED CALCIUM ABRASIVES                                                                                                                                                                                                                                                                                                                                                                                                                                |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                            |
| <b>(57) Abstract</b><br><br>Dentifrices containing selected abrasives which are compatible with quaternary ammonium cationic antibacterial agents are disclosed herein.                                                                                                                                                                                                                                                                                                                                                         |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                            |

QUATERNARY AMMONIUM ANTIBACTERIAL DENTIFRICES WITH  
SELECTED CALCIUM ABRASIVES

Background Of The Invention

The present invention relates to a dentifrice  
5 comprising a cationic antibacterial agent useful in the  
prophylaxis and/or treatment of periodontal disease,  
calculus and caries and selected abrasives. A new  
thickening agent comprising a soluble alkali metal  
pyrophosphate and a calcium salt is also disclosed.

10 The use of antibacterial agents, including cationic  
antibacterial agents, in oral hygiene compositions has  
been widely advocated as a means of reducing the bacterial  
plaque population and this may be beneficial in the  
treatment of periodontal disease, calculus and/or caries.

15 While mouthwashes containing cationic antibacterial  
agents are available, these suffer the disadvantage that  
the cationic antibacterial agents tend to leave a brown  
stain due to interaction of the agents with plaque. Such  
a drawback may be, in principle, minimized by using the  
20 antibacterial agent in a dentifrice, so that the abrasive  
included therein removes the stained plaque. In practice  
however there are found to be severe problems in providing  
a useful formulation because of the intrinsic  
incompatibility of the cationic antibacterial agents with  
25 many of the other conventional elements of a dentifrice  
formulation, which incompatibility drastically reduces the  
bio-availability of the cationic agent. In addition, the  
cationic antibacterial agents often have a bitter taste  
which needs to be masked to provide a product which is  
30 acceptable to the consumer.

It has now been discovered that the problem of bio-  
availability may be overcome or at least mitigated by the  
use of certain abrasives in combination with cationic  
antibacterial agents in dentifrices. Also, the thickening

agents preferably based on a pyrophosphate and a calcium salt make it possible to eliminate all or essentially all of certain thickening agents such as non-abrasive silica gels which may reduce CPC availability.

5                   Summary of the Invention

Accordingly, the present invention provides a dentifrice for reducing plaque formation and treating gingivitis on teeth and soft tissue which has a pH between 6 and 8 comprising:

- 10           (a) a quaternary ammonium cationic antibacterial agent in an amount between about 0.005 and 10% by weight;
- (b) at least one thickening agent which is not an anionic thickening agent;
- 15           (c) at least one surfactant which is not an anionic surfactant; and
- (d) an abrasive selected from the group consisting of calcium carbonate, dicalcium phosphate and calcium pyrophosphate.

20           Optionally a humectant, an anti-caries agent, flavoring agents and other excipients necessary or useful in formulating and using a dentifrice can be included in these compositions.

25                   Specific Embodiments

             These dentifrice may be substantially solid, pasty or liquid in character such as is found in a tooth powder, a dental tablet or a toothpaste or dental cream. These

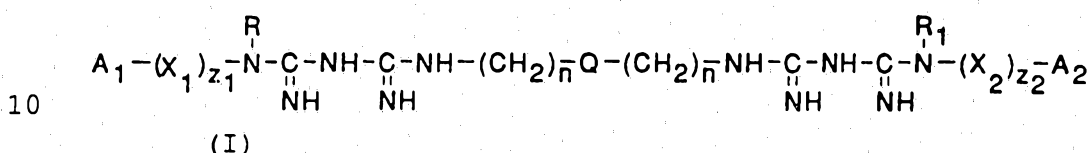
30           compositions typically will have a pH similar to that of the oral cavity, but may be formulated so as to be either

(v) bispyridine derivatives such as octenidine  
(N,N'[1,10-decanediyl-di-1(4H)-pyridinyl-4-  
ylidene]bis(1-octanamine dihydrochloride); and

(vi) biguanides including:

5 (a) mono-biguanides such as *p*-chlorobenzyl biguanide,  
and N'-(4-chlorobenzyl)-N''-(2,4-  
dichlorobenzyl)biguanide.

(b) bis-biguanides of the general formula (I):



wherein:

15  $A_1$  and  $A_2$  are independently a phenyl group  
optionally substituted by (C<sub>1-4</sub>)alkyl, (C<sub>1-4</sub>)alkoxy,  
nitro, halogen, C<sub>1-12</sub>)alkyl group, or (C<sub>4-12</sub>)alicyclic;

$X_1$  and  $X_2$  are independently (C<sub>1-3</sub>)alkylene;

$R$  and  $R^1$  are independently hydrogen, (C<sub>1-12</sub>)alkyl, or aryl(C<sub>1-6</sub>)alkyl;

20  $Z_1$  and  $Z_2$  are independently 0 or 1;

$Q$  is CH<sub>2</sub>, oxygen, sulfur, or aryl;

$n$  in each (CH<sub>2</sub>) <sub>$n$</sub>  group is independently is an  
integer from 1 to 12 but the total of both  $n$  groups may  
not exceed 12;

25 aryl is phenyl, naphthyl or another aromatic  
ring; and orally acceptable acid addition salts thereof.  
Preferred compounds are chlorhexidine and alexidine.

(c) poly(biguanides) such as polyhexamethylene biguanide  
hydrochloride.

30 An amount sufficient of the cationic antibacterial  
agent to usefully reduce plaque formation and treat  
gingivitis will be one in the range of about 0.005 to 10%

acidic or alkaline. Buffers may be added to maintain pH if desired. ~~A preferred~~<sup>The</sup> pH range for these toothpastes is between 6 and 8.

5     Suitable cationic antibacterial agents for use in dentifrices of the invention include:

- 10     (i) quaternary ammonium compounds, for instance those in which one or two of the substituents on the quaternary nitrogen has between 8 and 20, preferably 10 and 18 carbon atoms and is preferably an alkyl group, which may optionally be interrupted by an amide, ester, oxygen, sulphur, or heterocyclic ring. The remaining nitrogen substituents will have a lower number of carbon atoms, for instance between 1 and 7, and are preferably alkyl, for instance methyl or ethyl, or benzyl. The anion will be an orally acceptable salt forming group. Examples of such compounds including benzalkonium, chloride, dodecyl trimethyl ammonium chloride, benzyl dimethyl stearyl ammonium chloride, and cetyl trimethyl ammonium bromide, benzethonium chloride (diisobutyl phenoxyethoxyethyl dimethylbenzyl ammonium chloride), and methyl benzethonium chloride;
- 15     (ii) pyridinium and isoquinolinium compounds, exemplified by hexadecylpyridinium chloride, cetyl pyridinium chloride, and alkyl isoquinolinium bromide;
- 20     (iii) pyrimidine derivatives such as hexetidine (5-amino-1,3-bis(2-ethylhexyl)-5-methylhexahydropyrimidine);
- 25     (IV) amidine derivatives such as hexamidine isethionate (4,4'-diamidino- $\alpha,\omega$ -diphenoxyhexane isothionate);
- 30

weight/weight (w/w), preferably 0.005 to 5%, more preferably 0.005 to 2.5% and most preferably 1.0% w/w.

Any thickening agent may be used so long as it is not an anionic thickening agent. More specifically, nonionic and cationic thickening agents are preferred for use in this invention.

Suitable nonionic thickening agents include (C<sub>2-6</sub>)alkylene oxide modified (C<sub>1-6</sub>)alkylcellulose ethers, for instance hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and mixtures thereof.

Suitable cationic thickening agents include quaternary cellulose derivatives such as the products supplied by Amerchol Europe under the trademark LR 30M and JR 30M, cationic guar gum derivatives such as the products supplied by Celanese under the trademark Jaguar C17 (guar hydroxypropyltrimmonium chloride), or a copolymer of a diallyl ammonium chloride and acrylic acid such as the product supplied by Merck and Co. under the trademark 'Merquat 280' (CFTA approved name polyquaterinium 22). Other thickening agents which may be employed include polyvinylpyrrolidone, starch and certain non-abrasive silica gels such as those sold by Huber under the trade name Zeofree, and other silica thickening agents.

Advantageously thickening agent are present in the range 0.01 to 30%, preferably 0.1 to 15%.

The preferred thickening agents of this invention may be prepared by combining a soluble or sparingly soluble alkali metal pyrophosphate with an insoluble or essentially insoluble calcium salt and thereby creating in situ material which thickens dentifrices. Useful soluble alkali metal pyrophosphates are, for example, tetrasodium and tetrapotassium pyrophosphate or combinations thereof. Calcium salts which can be used in combination with the

those pyrophosphates are, for example,  $\text{CaCO}_3$ ,  $\text{CaHPO}_4$  and the like. Useful concentrations of the soluble pyrophosphate range up to about 10.0% of the composition by weight, preferably up to about 8% by weight. As for  
5 the calcium salt, it is expected that some amount in the range of up to 3.0%, preferably 0.5 to 2.6 % by weight, will impart a thickening affect to a dentifrices. If a calcium salt is used as the abrasive, thickening is achieved without reducing the abrasive characteristics of  
10 the formulation by increasing the amount of that abrasive salt by several percentage points, for example 1 to 2%.

Any surfactant may be used in this invention so long as it is not anionic. For example nonionic, cationic and amphoteric surfactants may be used in these dentifrices.

15 Suitable nonionic surfactant include polyethoxylated sorbitol monoesters (for instance, 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  
20 'Plutonic' by BASF-Wyandotte); condensates of propylene glycol and polyethoxylated hydrogenated castor oil (for instance, cremophors).

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

30 Useful cationic surfactants may be, for example, cocamidopropyl PG dimonium chloride phosphate (Monaquat PTC) and lauramidopropyl PG dimonium chloride phosphate (Monaquat PTL).

These dentifrices contain abrasives, also called polishing materials. For the purposes of this invention, essentially insoluble abrasives are to be used. The term insoluble is defined with reference to both the confected  
5 dentifrices and its use in the oral cavity.

Examples of such abrasives are certain phosphates such as dicalcium phosphate dihydrate, anhydrous dicalcium phosphate and calcium pyrophosphate, certain carbonates such as calcium carbonate, and mixtures thereof. Preferred  
10 abrasives include dicalcium phosphate, particularly the dihydrate, calcium pyrophosphate and calcium carbonate.

Most if not all of the abrasives listed above are available from commercial sources, or they can be prepared by means known in the art. For instance, dicalcium phosphate in  
15 the preferred dihydrate form is readily available from many commercial sources. Likewise calcium pyrophosphate and calcium carbonate are commercially available. It is understood that any chosen abrasive will be sufficiently pure so as to meet the health and regulatory standards for  
20 dentifrices.

Abrasives are generally present in amounts ranging from about 5% to about 95% by weight of the oral preparation. Preferably, they will be present in amounts ranging from about 5% to about 75% in toothpaste, and from about 10% to  
25 about 95% in tooth powder.

In certain forms of this invention a fluoride-providing compound is present in the oral preparation. These compounds may be slightly soluble in water or may be

fully water-soluble. They are characterized by their ability to release fluoride ions in water and by substantial freedom from reaction with other compounds of the oral preparation. Among these materials are inorganic fluoride salts, such as soluble alkali metal, alkaline earth metal and heavy metal salts, for example, sodium fluoride, potassium fluoride, ammonium fluoride, lead fluoride, a copper fluoride such as cuprous fluoride, zinc fluoride, a tin fluoride such as stannic fluoride or stannous chlorofluoride, barium fluoride, sodium fluorosilicate, ammonium fluorosilicate, sodium fluorozirconate, sodium monofluorophosphate, aluminum mono- and difluorophosphate, and fluorinated sodium calcium pyrophosphate. Alkali metal and tin fluorides, such as sodium and stannous fluorides, sodium monofluorophosphate and mixtures thereof, are preferred.

The amount of the fluoride-providing compound is dependent to some extent upon the type of compound, its solubility and the type of oral preparation, but it must be a nontoxic amount. In a solid oral preparation, such as a toothpaste or tooth powder, an amount of such compound which releases a maximum of 1% by weight of the preparation is considered satisfactory. Any suitable minimum amount of such compound may be used, but it is preferable to employ sufficient compound to release from 0.005% to 2%, and preferably about 0.1% of fluoride ion. Typically, in the cases of alkali metal fluorides and stannous fluoride, the component is present in an amount up to 4% by weight, based on the weight of the preparation, and preferably in the range of from 0.05% to 2%. In the case of sodium monofluorophosphate (MFP), the compound may be present in an amount up to 7.6% by weight more typically 0.76%.

Optionally, anti-calculus agents may be incorporated into these compositions. For example certain pyrophosphates have been found to be useful in reducing calculus formation. There are numerous publications and patents describing pyrophosphate-based anti-calculus compositions and their use in the oral cavity. For example see U.S. patent 3,515,772 which describes the use of certain alkali metal pyrophosphates, particularly di alkali and tetra-alkali metal pyrophosphate salts of  $P_2O_7^{4-}$

4. The tetrapotassium and tetrasodium forms are most frequently used in dentifrices as anticalculus agent. This U.S. patent is incorporated herein by reference as if set out in full in this writing. Other phosphates, including hexametaphosphates, tripolyphosphates and other polyphosphates, usually in the form of an alkali metal salt, have been proposed or are being used in dentifrices as anticalculus agents. It is expected that one or more of these agents can be usefully incorporated into the compositions of this invention.

In preparing tooth powders, it is usually sufficient to admix mechanically, e.g., by milling, the various solid ingredients in appropriate quantities and particle sizes.

With regard to pastes the liquid vehicle may comprise water, and usually a humectant, typically in an amount ranging from about 10% to about 90% by weight of the preparation. Glycerin, sorbitol, or polyethylene glycol are examples of useful humectants. Particularly advantageous liquid ingredients comprise mixtures of water, glycerine or sorbitol.

Various other ingredients such as preservatives, dyes and other coloring agents, flavorings, sweeteners, anti-staining agents, desensitizing agents and the like may be added to these dentifrices. Such additives are frequently

used in dentifrices and are therefore well known in the art.

It will be understood that these dentifrices are to be sold or otherwise distributed in suitably labelled packages. Toothpastes are packaged in tubes or squeezable tubes (aluminum or plastic) or containers or in a rigid tube with some expelling device for delivering the paste, such as a pump. Powders normally are prepared in cans or bottles with a removable top or some means whereby the powder can be dispensed by inverting and shaking or by introducing a spoon or other device for removing a portion of the powder. Liquid formulations can be packaged in capped tubes or bottles and be dispensed by squeezing, mechanical means; pre-pressurized containers may also used with liquid formulations.

This invention is further illustrated by the following examples. These examples are only intended to illustrate the invention not to limit its scope or practice in any manner or form. Formulations are given on a weight/weight basis.

#### Examples 1

##### CPC/Dicalcium Phosphate Abrasive Toothpaste

An example of a toothpaste where the abrasive is dicalcium phosphate dihydrate is set out below. Table I lists the ingredients for the paste, which was tested for the availability of the cationic antibacterial by extracting the water solubles, then looking at the amount of recovered antibacterial via instrumental analyses such as an HPLC-bases assay and microbiological assay.

Table 1

| <u>Ingredients</u>           | <u>Percent by Weight/Weight</u> |
|------------------------------|---------------------------------|
| Glycerin                     | 7.000                           |
| Methocel KI5M <sup>1</sup>   | 0.500                           |
| Na MFP                       | 0.836                           |
| Na Saccharin                 | 0.246                           |
| Sorbitol                     | 3.550                           |
| CaHPO <sub>4</sub> Dihydrate | 40.000                          |
| TiO <sub>2</sub>             | 0.956                           |
| Flavor                       | 0.800                           |
| Deionized Water              | 36.012                          |
| Pluronic F127                | 9.000                           |
| CPC <sup>2</sup>             | 1.000                           |
|                              | 100.000                         |

A paste suitable for use as a dentifrice using these materials was prepared as follows: The glycerin and Methocel were mixed together. Then the sodium monofluorophosphate and sodium saccharin were dissolved in a portion of the water and added to the first mix. Sorbitol (Sorbo) was then added, followed by a mix of the dicalcium phosphate dihydrate and titanium dioxide. Flavoring was then added after which a mixture of the remaining water, Pluronics and CPC was mixed into the earlier prepared mixture.

#### Example 2

##### CPC/Alumina Abrasive Toothpaste

A toothpaste with alumina as the abrasive and CPC as the cationic antibacterial agent was prepared. Table II sets out the ingredients and their relative amounts.

<sup>1</sup> Hydroxyethylpropylcellulose, Dow Chemical Co.

<sup>2</sup> Cetylpyridinium chloride.

Table II

| Ingredients                 | Percent by Weight/Weight |
|-----------------------------|--------------------------|
| Glycerin                    | 20.000                   |
| Natrosol 250 H <sup>3</sup> | 1.000                    |
| Na MFP                      | 0.836                    |
| Na Saccharin                | 0.246                    |
| Alumina                     | 14.000                   |
| Zeofree 153 <sup>4</sup>    | 10.000                   |
| TiO <sub>2</sub>            | 0.956                    |
| PEG 400                     | 3.000                    |
| Flavor                      | 0.800                    |
| Deionized Water             | 46.162                   |
| Pluronic F-87               | 1.000                    |
| Pluronic F-127              | 1.000                    |
| CPC                         | 1.000                    |
|                             | 100.00%                  |

5 The paste was prepared by first combining glycerin and the Natrosol 250H in a portion of the water. To this was added a mix of water, the sodium monofluorophosphate and sodium saccharin. Then alumina, Zeofree 153 and titanium  
10 dioxide was combined and added to the existing mixture. A mix of the remaining glycerin and PEG 400 was added followed by the flavoring agent. Finally the rest of the water mixed with the Pluronic and CPC was added with  
mixing to form a toothpaste.

### Example 3

#### 15 CPC/Alumina Toothpaste with Pyrophosphates

A paste with pyrophosphates for tartar removal was prepared with the CPC/alumina paste of Example 2. Table III recites the ingredients and amounts contained in this preparation.

20

<sup>3</sup> Hydroxyethyl cellulose, Aqualon.

<sup>4</sup> Thickening silica, Huber.

Table III

| <u>Ingredients</u> | <u>Percent by Weight/Weight</u> |
|--------------------|---------------------------------|
| Na MFP             | 0.836                           |
| Na Saccharin       | 0.246                           |
| $K_4P_2O_7$        | 4.000                           |
| $Na_4P_2O_7$       | 1.810                           |
| Alumina            | 14.000                          |
| Zeofree 153        | 10.000                          |
| $TiO_2$            | 0.956                           |
| Glycerin           | 20.000                          |
| PEG 400            | 3.000                           |
| Flavor             | 0.800                           |
| Deionized Water    | 40.352                          |
| Pluronic F-127     | 1.000                           |
| Pluronic F-87      | 1.000                           |
| CPC                | 1.000                           |
|                    | 100.000                         |

5 A paste was prepared from these materials in the manner described in Example 2.

Example 4

CPC/Calcium Pyrophosphate Toothpaste

10 Toothpastes with calcium pyrophosphate as the abrasive were prepared. Table V gives a representative example of the ingredients which were used to prepare such pastes.

Table IV

| Ingredients                                   | Percent by<br>Weight/Weight |
|-----------------------------------------------|-----------------------------|
| K <sub>4</sub> P <sub>2</sub> O <sub>7</sub>  | 5.000                       |
| Na <sub>4</sub> P <sub>2</sub> O <sub>7</sub> | 1.810                       |
| Na MFP                                        | 0.836                       |
| Na Saccharin                                  | 0.246                       |
| CaHPO <sub>4</sub>                            | 2.300                       |
| Glycerin                                      | 22.000                      |
| Natrosol 250H                                 | 0.600                       |
| Calcium pyrophosphate                         | 40.000                      |
| TiO <sub>2</sub>                              | 0.956                       |
| Flavor                                        | 0.800                       |
| Pluronic F-127                                | 1.000                       |
| Pluronic F-87                                 | 1.000                       |
| CPC                                           | 1.000                       |
| Deionized Water                               | quo 100%                    |

In making up a paste, a portion of the water was used to dissolve up the pyrophosphates, sodium monofluorophosphate and sodium saccharin. Then the dicalcium phosphate was added to that mix. Subsequently, a portion of the glycerin and Natrosol 250H were combined and mixed in with earlier mixture. A mix of calcium pyrophosphate and titanium dioxide was then prepared and incorporated into the earlier mix. The remaining glycerin was then added, followed by the flavoring agent. Finally, a mixture of water, pluronics and CPC was prepared and mixed in with the previously described mixture to form the paste.

#### Example 5

##### CPC/Calcium Carbonate Toothpaste

Toothpastes with calcium carbonate as the abrasive were prepared. Table IV gives a representative example of the ingredients where used to prepare such pastes.

Table V

| <u>Ingredients</u> | <u>Percent by Weight/Weight</u> |
|--------------------|---------------------------------|
| Natrosol 250 H     | 1.500                           |
| Na MFP             | 0.836                           |
| Na Saccharin       | 0.246                           |
| Zeofree 153        | 5.000                           |
| Glycerin           | 22.000                          |
| CaCO <sub>3</sub>  | 35.000                          |
| TiO <sub>2</sub>   | 0.956                           |
| Flavor             | 0.800                           |
| Pluronic F-127     | 1.000                           |
| Pluronic F-87      | 1.000                           |
| CPC                | 1.000                           |
| Deionized Water    | quo 100%                        |

Here, qs refers to a quantity sufficient to make 100%.

- 5 The order of mixing was as follows: Part of the glycerin, part of the water and Natrosol 250H were combined. To this was added a mixture comprising water, sodium monofluorophosphate and sodium saccharin. Calcium carbonate was added to this mixture. The remaining
- 10 glycerin was then added followed by a mixture of the Zeofree and the titanium dioxide. Flavoring was added followed by a mix of the Pluronics and CPC.

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  
5 stated integer or group of integers but not the exclusion of any other integer or group of integers.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A dentifrice for reducing plaque formation and treating gingivitis on teeth and soft tissue which has a pH  
5 between 6 and 8 comprising:

- (a) a quaternary ammonium cationic antibacterial agent in an amount between about 0.005 and 10% by weight;
- 10 (b) at least one thickening agent which is not an anionic thickening agent;
- (c) at least one surfactant which is not an anionic surfactant; and
- 15 (d) an abrasive selected from the group consisting of calcium carbonate, dicalcium phosphate and calcium pyrophosphate.

2. The dentifrice of claim 1 where the abrasive is dicalcium phosphate or the dihydrate thereof which is present in an amount between about 5% to about 75% (w/w).  
20

3. The dentifrice of claim 1 or claim 2 where the quaternary ammonium compound is present in an amount between about 0.005 to 5% (w/w).

25 4. The dentifrice of claim 3 where the quaternary ammonium compound is cetylpyridinium chloride.

30 5. The dentifrice of claim 4 where the dicalcium phosphate is the dihydrate and is present in about 40% (w/w) and the cetylpyridinium chloride in about 1.0% (w/w) and which contains a fluoride-providing compound and an anticalculus agent.

35 6. The dentifrice of claim 1 where the abrasive is calcium pyrophosphate which is present in an amount between about 10% to about 75% (w/w).

7. The dentifrice of claim 6 where the quaternary ammonium compound is present in an amount between about 0.005 to 5% (w/w).

5 8. The dentifrice of claim 7 where the quaternary ammonium compound is cetylpyridinium chloride.

9. The dentifrice of claim 8 where the pyrophosphate is present in an amount of about 40% (w/w), the  
10 cetylpyridinium chloride in about 1.0% (w/w) and which contains an fluoride-providing compound and an anticalculus agent.

10. The dentifrice of claim 1 where the abrasive is  
15 calcium carbonate which is present in an amount between about 10% to about 75% (w/w).

11. The dentifrice of claim 10 where the quaternary ammonium compound is present in an amount between about 0.005  
20 to 5% (w/w).

12. The dentifrice of claim 11 where the quaternary ammonium compound is cetylpyridinium chloride.

25 13. The dentifrice of claim 12 where the calcium carbonate is present in an amount of about 40% (w/w), the cetylpyridinium chloride in about 1.0% (w/w) and which also contains a fluoride-providing compound and an anticalculus agent.

30 14. A dentifrice substantially as hereinbefore described with reference to the Examples.

DATED this 5th day of December, 1995

35 SmithKline Beecham Corporation

By Its Patent Attorneys

DAVIES COLLISON CAVE

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US92/02918

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(S) : A61K 7/16, A61K 7/18 A61K 7/22

US CL : 424/49 424/52 424/54 424/57

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)

U.S. : 424/49 424/52 424/54 424/57

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 practicable, search terms used)

Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|------------------------------------------------------------------------------------|-----------------------|
| X         | U.S.,A, 4,885,155 (Parran et al) 05 December 1989 See the entire document          | 1 to 17               |
| X         | U.S.,A, 4,822,599 (Mitra) 18 Apr 1989 See the entire document                      | 1 to 17               |
| X         | U.S.,A, 4,590,066 (Parran et al) 20 May 1986 See the entire document               | 1 to 17               |
| Y         | U.S.,A, 4,472,373 (Ryan) 18 Sept 1984 See col. 3, line 1 to 65                     | 1 to 12               |
| X         | U.S.,A, 4,273,759 (Gaffar et al) 16 June 1981 See the entire document              | 1 to 12               |
| Y         | U.S.,A, 4,205,061 (Vidra) 27 May 1980 See the entire document                      | 1 to 12               |
| Y         | U.S.,A, 4,188,372 (Gaffar) 12 Feb 1980 See the entire document                     | 1 to 12               |
| Y         | U.S.,A, 3,959,458 (Agricola et al) 25 May 1976 See the entire document             | 1 to 12               |

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

|                                                                                                                                                                         |                                                                                                                                                                                                                                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| * Special categories of cited documents:                                                                                                                                | *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                                              |
| *A* document defining the general state of the art which is not considered to be part of particular relevance                                                           | *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                                                                     |
| *E* earlier document published on or after the international filing date                                                                                                | *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 |
| *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) | *G* document member of the same patent family                                                                                                                                                                                                    |
| *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                                                                  |                                                                                                                                                                                                                                                  |

Date of the actual completion of the international search

28 JULY 1992

Date of mailing of the international search report

15 SEP 1992

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US92/02918

### B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS Terms: Cetylpyridinium/CLM and one of calcium carbonate, dicalcium phosphate or calcium pyrophosphate also:  
one of: calcium carbonate/CLM, dicalcium phosphate/CLM or calcium pyrophosphate/CLM and cetylpyridinium