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(21) International Application Number: PCT/SE98/02366 (22) International Filing Date: 17 December 1998 (17.12.98) (30) Priority Data: 9704789-8 19 December 1997 (19.12.97) SE (71) Applicant (for all designated States except US): DENTAL THERAPEUTICS AB [SE/SE]; Gillevägen 6, S-131 33 Nacka (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): BRÄNNSTRÖM, Martin [SE/SE]; Lagårdsvägen 7, S-131 50 Saltsjö-Duvnäs (SE). ORREBY, Kerstin [SE/SE]; Moränvägen 6, S-131 41 Nacka (SE). (74) Agents: KARLSSON, Leif et al.; L.A. Groth & Co. KB, P.O. Box 6107, S-102 32 Stockholm (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, 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> <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>
(54) Title: A PREPARATION FOR THE TREATMENT OF APHTAE (57) Abstract The present invention relates to a preparation for the treatment of aphtae, preferable aphtae stomatitis. The preparation includes: (a) 5.0 – 10.0 % by weight of orange interpenes; (b) 0.1 – 3.0 % by weight of glycyrrhizin; (c) 0.1 – 1.5 % by weight of xylitol; (d) 1.0 – 10.0 % by weight of cocoamphodiacetate. The inventive preparation is administered in the form of mouthwash, paste, tablets, capsules or chewing gum.		

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A PREPARATION FOR THE TREATMENT OF APHTAE

The present invention relates to a preparation for the treatment of recurrent aphtae (aphthous stomatitis).

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Aphtae in its different forms is both irritating and painful. The aphtae group includes both small and large ulcerations. The smaller ulcerations are the most frequent and manifest in the form of shallow ulcerations measuring up to 5 mm in size. These smaller forms of aphtae occur primarily in labial buccal mucosa and at the bottom of the mouth. They heal within the space of 10 to 14 days.

The larger forms of aphtae are more rare and of a more serious nature. They can exceed 1 cm in size and often leave a scar. It may take longer than 6 weeks for the larger forms to heal. Lips and the mucous membrane of the mouth are the most common points of attack.

The most serious form of aphtae is the herpetic form. Up to 100 ulcerations measuring about 2-3 mm can form simultaneously, and these ulcerations may grow into one another to form large irregular ulcerations.

The underlying causes of aphtae are many. Various attempts have been made to establish these causes and also to find methods of treatment. It has been assumed that the ulcerations occur as a result of an increase in the permeability of the protective epithelium layers, so as to enable bacteria to penetrate into the connective tissue, such that the epithelium layer will be in danger of disappearing and inflammation occurring. In its most serious forms, the condition can be partially disabling, where all movements associated with the mouth are extremely painful. No effective preventative measures or treatment agents have been developed.

The preparation according to the present invention has been found effective in the treatment of different forms of aphtae, particularly in the treatment of aphtae stomatitis.

Active substances included in the preparation are orange terpenes, cocoamphodiacetate, glycyrrhizin and xylitol.

The inventive preparation includes the following substances as active ingredients:

- a) 5.0 - 10.0 % by weight of orange terpenes
- b) 0.1 - 3.0 % by weight of glycyrrhizin
- c) 0.1 - 1.5 % by weight of xylitol
- d) 1.0 - 10.0 % by weight of cocoamphodiacetate

The preparation is used for the treatment of aphtae.

The inventive preparation may be administered in the form of mouthwash, paste, tablettes, capsules, or chewing gum.

According to another embodiment of the invention, the preparation for the treatment of aphtae includes the following substances, in addition to water:

- a) 5.0 - 10.0 % by weight of orange interpenes
- b) 0.1 - 3.0 % by weight of glycyrrhizin
- c) 0.1 - 1.5 % by weight of xylitol
- d) 1.0 - 10.0 % by weight of cocoamphodiacetate
- e) 1.0 - 10.0 % by weight of polyethylene (20) sorbitan monostearate
- f) 1.5 - 3.2 % by weight of carboxymethyl cellulose
- g) 0.2 - 0.5 % by weight of parahydroxy bensoic acid methyl ester
- h) 0.05 - 2.0 % by weight of sodium fluoride

The preparation also includes 1.0 - 5.0 % by weight of silica as a polishing agent.

The inventive preparation is used for the production of a medicament for the treatment of aphtae.

Other embodiments of the invention are defined in the dependent Claims.

Detailed description of the invention

The present invention relates to a preparation for the treatment of aphtae in its different forms. The inventive preparation includes orange terpenes, which are included in orange oil among other substances. The orange terpenes have been found particularly effective in capture proteins and polysaccharides and moving these away from the site of the attack. In the most preferred embodiment of the present invention, the preparation includes orange oil. Orange oil is fat dissolving and is able to dissolve and absorb lipids in plaque.

Cocoamphodiacetate is an ampholytic surfactant which loosens up the plaque layer, therewith providing for the effectiveness of the orange terpenes. The inventive preparation therefore also includes cocoamphodiacetate. The toothpaste form does not include sodium lauryl sulphate, which is a surfactant. In a Norwegian scientific research investigation, G. Embery and G. Rølla, Clinical and Biological Aspects of Dentifrices, pages 173-180, have shown that sodium lauryl sulphate is a contributory cause of aphtae. It was observed in this investigation that aphtae failed to appear in about 70% of the cases in which sodium lauryl sulphate was excluded from toothpaste. Most of the toothpastes (dentifrices) commercially available at present contain sodium lauryl sulphate.

Another substance which renders the present preparation favourable in respect of the treatment of aphtae is glycyrrhizin, which is included in liquorice root extract among other things. Glycyrrhizin has a bacteria-inhibiting effect and will inhibit preferably the growth of streptococcus mutans. Glycyrrhizin is also pH-reducing in vivo.

The inventive preparation also includes xylitol. Xylitol acts synergetically with the aforesaid substances, therewith enhancing the effectiveness of the preparation. Bacteria take up xylitol, especially when other sugars are present in small quantities. Xylitol prevents the normal metabolism of the

bacteria, by forming xylitol phosphate which is poisonous to the bacteria and thus prevents their growth. The bacteria transport xylitol phosphate out through the bacteria membrane. The process is highly energy consuming and the xylitol phosphate will thus be accumulated in the bacteria. Xylitol also has the advantage of not decomposing to organic acids, as is the case of other sugars. The use of xylitol as a sweetener enables the pH to be maintained at a more favourable level and also enables the demineralisation of dental enamel to be avoided.

With the intention of investigating the effect of the inventive composition, a dentifrice (toothpaste) that included the composition was prepared. The form of the preparation described in the following example shall not be taken as limiting the scope of the invention, and it will be understood that the intention is to show the form in which the preparation was administered to those persons taking part in the study.

Preparation

A toothpaste was produced by dry-mixing 10.0 g/kg glycyrrhizin and 22.0 g/kg of carboxymethyl cellulose, and thereafter adding 100.0 g/kg 85% glycerine whilst stirring uniformly to obtain a smooth mixture with no lumps. 50.0 g/kg orange terpene, 50.0 g/kg polyethylene (20) sorbitan monostearate and 3.0 g/kg parahydroxybenzoic acid methyl ester were heated to a temperature of 40°C whilst stirring until all parahydroxybenzoic acid methyl ester had dissolved, thereafter the solution was left to cool to ambient temperature. The ambient temperature solution was added to said mixture whilst stirring uniformly. 10.0 g/kg xylitol and 2.4 g/kg sodium fluoride were dissolved in 545.0 g/l H₂O and the solution added to the mixture. Finally, 50.0 g/kg cocoamphodiacetate were dissolved in 127.6 g/l water and stirred down into said mixture together with 30.9 g/kg silica. The mixture was then stirred to provide a smooth paste.

Pilot study

With the intention of testing the effect of the inventive preparation, there were selected thirty persons suffering from aphthos stomatitis in the mucous membrane of the mouth. These persons were treated with dentifrice (toothpaste) with no additional water on each treatment occasion and on a daily basis for six months. The study was carried out in the form of a double-blind study. The pilot study showed that several people treated with the inventive preparation experienced a marked improvement when using the toothpaste in question. This result was also strengthened by the fact that several patients treated with the toothpaste outside the study also reported a positive result.

CLAIMS

1. An aphtae treatment preparation including:
 - a) 5.0 - 10.0 % by weight of orange terpenes
 - 5 b) 0.1 - 3.0 % by weight of glycyrrhizin
 - c) 0.1 - 1.5 % by weight of xylitol
 - d) 1.0 - 10.0 % by weight of cocoamphodiacetate
- 10 2. The preparation according to Claim 1, **characterised** in that the preparation also includes an emulsifier, a thickener, a preserving agent, and sodium fluoride.
3. The preparation according to Claim 2, **characterised** in
15 that the preparation also includes a polishing agent.
4. The preparation according to Claim 1, **characterised** in that the preparation also includes water, preserving agent and sodium fluoride.
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5. An aphtae treatment preparation including:
 - a) 5.0 - 10.0 % BY weight of orange terpenes
 - b) 0.1 - 3.0 % by weight of glycyrrhizin
 - 25 c) 0.1 - 1.5 % by weight of xylitol
 - d) 1.0 - 10.0 % by weight of cocoamphodiacetate
 - e) 1.0 - 10.0 % by weight of polyethylene (20) sorbitan monostearate
 - f) 1.5 - 3.2 % by weight of carboxymethyl cellulose
 - 30 g) 0.2 - 0.5 % by weight of parahydroxybensoic acid methyl ester
 - h) 0.05 - 2.0 % by weight of sodium fluoride
6. The preparation according to Claim 5, **characterised** in
35 that the preparation also includes 1.0 - 5.0 % by weight of silica as a polishing agent.

7. The preparation according to any one of Claims 1 - 6, **characterised** in that the preparation is in the form of a paste, mouthwash, tablets, capsules or chewing gum.

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8. A use of the preparation according to any one of Claims 1 - 7, for the preparation of pharmaceuticals for the treatment of aphtae, preferable aphtae stomatitis.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/02366

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 35/78, A61K 31/015, A61K 31/70

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)

IPC6: A61K

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

SE,DK,FI,NO classes as above

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

REG, CAPLUS, WPI, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0604158 A1 (SUNSTAR KABUSHIKI KAISHA), 29 June 1994 (29.06.94), See page 3 --	1-8
A	File WPI, Derwent accession no. 96-246882, Lion Corp: "Oral compsns. for prevention of periodontal disease - contains e.g. ascorbic acid phosphate and limonene"; JP,A,8099849, 960416, DW9625 --	1-8
A	BE 891987 A (BIOREX LABORATORIES LIMITED), 27 May 1982 (27.05.82) --	1-8

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

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5229425 A (DOYLE E. CHASTAIN ET AL), 20 July 1993 (20.07.93) --	1-8
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Information on patent family members

International application No.

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