**Title:** TOPICAL COMPOSITION FOR THE TREATMENT OF APHTHOUS ULCERS CONTAINING AN ANTIMICROBIAL AGENT AND A CORTICOSTEROID

**Abstract**

For the treatment of recurrent aphthous ulcers, the use which comprises topical application of an antimicrobial agent corticosteroid mixture to the area of the ulcerous lesion and the covering of the mixture with a protective coating that results in retardation of the propagation of bacteria in the lesion and lessens the localized inflammation to allow a clean base for the reepithelialization of the lesion, covering the damaged area. Healing of the lesion occurs in as little as 24 to 72 hours after application of the treatment.
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Recurrent aphthous ulcers (RAU), also known as "canker sores" or "aphthous stomatitis", are characterized by recurrent ulcerations of the oral mucous membranes. These lesions, occurring singly or multiply throughout the mucous membranes of the mouth, are recognized by shallow necrotic centers, raised margins, erythematous halos, and by the sharp pain they cause. They occur more frequently in women than in men and the majority of patients report the onset of the disease between the ages of ten and thirty years. It has been reported that nearly 20% of the general population is affected by this disease at one time or another. E.A. Graykowski and J.J. Hooks, "Summary of Workshop on Recurrent Aphthous Stomatitis and Behcet Syndrome," 97 J.Amer.Dent.Assoc. 599-602 (1978). The frequency of outbreaks varies greatly between patients; occasional patients have continual outbreaks and are never free of lesions for extended intervals.

The onset of the disease may occur with a variety of manifestations, including the occurrences of one or more small nodules, generalized edema of the oral mucosa, paresthesia, malaise, low-grade fever, and/or localized lymphadenopathy. The aphthous ulcer begins as a single or multiple superficial erosion covered by a gray membrane which generally has a well circumscribed margin surrounded by an erythematous halo. The ulcer may vary in size from 2 to 3 mm to over 10 mm. In over 90% of patients, six or less ulcers exist during a single outbreak and the ulcers themselves generally persist for 7 to 14 days and then heal gradually with little or no evidence of scarring. E.A. Graykowski, et al., "Recurrent Aphthous Stomatitis," 196 J.Amer.Med.Assoc. 637-644 (1966).

A pleomorphic, transitional L-form of an alpha-hemolytic streptococcus, S. sanguis, has been strongly implicated as
the causative agent of the disease. Id. This organism has been consistently isolated from lesions of patients with typical aphthous ulcers, and microorganisms morphologically consistent with the L-form streptococcus have been found histologically in the vast majority of aphthous lesions.

As an alternative etiologic factor, it has been proposed that RAU is the result of an autoimmune response to the oral epithelium. T. Lehner, "Pathology of Recurrent Oral Ulceration and Oral Ulceration in Behcet's Syndrome: Light, Electron and Fluorescent Microscopy," J. Pathol. 481-494 (1969). It has been shown that both IgG and IgM immunoglobulins are bound by the epithelial cells of the spinous layer of the oral mucosa, while the same cells in healthy control patients or patients with nonspecific ulcers shown no such binding. As a result, it has been theorized that RAU is not an autoimmune disease arising from a central immunologic defect but rather represents a local immune response to an antigenically altered mucosa. L. Cohen, "Etiology, Pathogenesis and Classification of Aphthous Stomatitis and Behcet's Syndrome," 7 J. Oral Pathol. 347-352 (1978); M.Addy and A.E. Dolby, "Aphthous Ulceration: The Anti-nuclear Factor," 51 J.Dent.Research 1594-1595 (1972).


Barile and Graykowski ("L-Form of Bacteria Isolated from Recurrent Aphthous Stomatitis Lesions," 16 Oral Surg. 1395 (1963)) suggested that an antihistamine mouthwash provided symptomatic relief from RAU, but Dolby ("Recurrent Milulicz's Oral Aphthae," 124 Brit.Dent.J. 359-360 (1968)) failed to influence either the ulceration or the pattern of the discomfort experienced
in a double blind study with chlorpheniramine maleate. T.J. Ryan ("Periadenitis Mucosae Necrotica Recurrens," 59 Proc.R.Soc.Med. 256 (1966)) completely controlled the ulceration of a patient suffering from so-called major aphthous ulcers by administering oxyphenbutazone 200 mg daily for 3-4 days with 10 to 20 mg of prednisolone. However, because of changes involving the deeper capillaries and the effects of this drug on the endothelium, this treatment has not been evaluated further.

Corticosteroids have been found helpful in RAU by virtue of their anti-inflammatory and immunosuppressive actions. For instance, the steroid in KENALOG® in ORABASE® (E.R. Squibb & Sons. Inc., Princeton, N.J.), triamcinolone, demonstrates some relief, the dental paste providing both a vehicle for incorporating the steroid and a protective film over the ulcer which reportedly lasted from 15 to 20 minutes. A.H. Kutscher, et al., "Lack of Toxicity of Side Reactions Accompanying Topical Kenalog Therapy of Oral Lesions," 21 Oral Surg. Oral Med., Oral Pathol. 27-31 (1966). Also, Corlan tablets containing 2.5 mg of hydrocortisone sodium succinate were shown to reduce by about 50% the number of ulcer days and the number of new ulcers per patient over an eight week period. B.E.D. Cooke and P. Armitage, "Recurrent Mikulicz's Aphthae Treated with Topical Hydrocortisone Hemisuccinate Sodium," 1 Brit.Med.J. 764 (1960).

However effective steroids may be at reducing local inflammation, the literature does not provide any data indicating that steroids alone are effective in promoting healing of the ulcer. For instance, there is no evidence of alteration of incidence or duration of aphthous ulceration following the use of triamcinolone acetamide (Adcortyl-A in ORABASE®), ORABASE®, hydroxyquinoline, or curphate (Beta-Corlan) for a period of four weeks. I.T. MacPhee, et al., "Use of Steroids in Treatment of Aphthous Ulceration," 2 Brit.Med.J. 147 (1968). The literature even teaches that such topical steroids are not indicated in certain instances:
"We do not recommend the commercially available mixture of triamcinolone acetonide (KENALOG) 0.1% in ORABASE because this weaker steroid does not appear to be very effective in the treatment of the severe cases of RAU seen in association with HIV disease."


With the suspected bacterial involvement in the disease, it would be expected that antibiotics would be successful for treatment, but results are mixed and characterized by certain drawbacks. For instance, the need for topical application in the oral cavity is problematical. Prolonged contact between antibiotic and lesion is indicated, but use of, for instance, penicillin in a topical oral medication may result in hypersensitization and subsequent anaphylactic shock. An example is provided by a trial which utilized tetracycline mouthwash (chlorotetracycline 2% mouthwash, 250 mg per 5 ml) four times daily for 5 to 7 days, which produced good results in nearly 20% of patients tested by relieving pain, reducing the size of the lesions and reducing healing time. However, the low concentration of antibiotic at the location of the ulcer prevent more effective relief and the antibiotic, when administered in this fashion, does not stay in contact with the ulcer for a period of time long enough to effectively promote healing.

Another drawback resulting from the need for topical application is that tetracycline may cause discolorization of developing teeth.

A further problem with the use of tetracycline for such treatment arises with any antibiotic commonly used for treatment of systemic or local infection which is taken internally. Specifically, because of their utility in such treatment, it is desirable to avoid their use in any other application so as to avoid developing hypersensitivity and/or resistance. Consequently, even though such antibiotics as tetracycline and penicillin may be effective in
topical applications, it is desirable to avoid their use in that manner.

Another problem with the use of the antibiotic also relates to the problem of delivery of an efficacious dose to the site of the ulcerous lesion. Although \textit{S. sanguis} may be the causative agent of the disease, there may be other fungal, viral, or bacterial agents and/or "contributors" having different roles in causation. Further, the sensitivity of bacteria, fungi, and/or viruses to various antibiotics, anti-fungals, and anti-virals varies widely, sometimes even from strain to strain of the same causative agent (e.g., an antibiotic which is ineffective on one strain of a bacterial specie at a concentration of 1% may be effective at a concentration of 1.05% but ineffective in a second strain of that same bacterium at concentrations below 5%). With the different sensitivities of different causative agents, and without the ability to deliver a known and relatively precise dosage to the site of the lesion, consistent results are difficult to attain.

The present invention overcomes the limitations and disadvantages of prior treatments of RAU by providing a treatment for recurrent aphthous ulcers comprising applying an antimicrobial agent and a corticosteroid to an ulcerous lesion and applying a protective coating to the mixture of antimicrobial agent and corticosteroid once applied to the lesion to form a protective coating over the lesion to (1) maintain contact between the antimicrobial agent in the mixture and the lesion, thereby retarding bacterial growth in and around the dead cells comprising the lesion and promoting re-epithelialization of the lesion, (2) maintain contact between the corticosteroid in the mixture and the lesion, thereby decreasing the hyperimmune response in the area to allow more rapid re-epithelialization, and (3) protect the epithelial cells as they migrate over and re-epithelialize the lesion.

The antimicrobial agents which are preferred for use in this mixture are those with anti-\textit{S. sanguis} activity (or activity against other causative bacteria or organism not yet identified) and
which are relatively free from detrimental side effects when administered topically to the oral mucosa. Appropriate antimicrobial agents which meet these criteria may be selected by those skilled in the art who have the benefit of this disclosure from a large number of appropriate bactericides, fungicides, and virucides. By reference to the term bactericides, both topically effective antibiotics and topical anti-infective agents are contemplated. Examples of the latter include, but are not limited to, chlorhexidine, chloramines, silver compounds such as silver nitrate, and acids such as benzoic acid and such commercially available products as the mixture of copper sulfate, iodine, potassium iodide, and ethyl alcohol sold as ORA5® topical bactericidal agent for the oral mucosa (McHenry Laboratories, Inc., Edna, Texas). Appropriate antibiotics include, but are not limited to, aminoglycosides such as neomycin sulfate, penicillins, erythromycins, tetracyclines, cephalosporins such as KEFLEX®, sulfonamides such as sulfacetamide sodium, silver sulfadiazine, and mafenide acetate, antifungal antibiotics such as griseofulvin, ketoconazole, miconazole, and nystatin, β lactam antibiotics, and miscellaneous antibiotics such as bacitracin, lincomycin, polymixin B sulfate, novomycin, novobiocin, and gramicidin, and various combinations or mixtures of these antibiotics such as bacitracin with polymixin or neomycin or bacitracin, polymixin, and neomycin. A particularly preferred antibiotic for use in connection with the method of the present invention is neomycin.

Other antimicrobial agents which may be used to advantage in connection with the present invention include antifungal agents that are applied topically such as nystatin, imidazoles such as miconazole and clotrimazole, and undecylenic acid, and topically applied antivirals such as acyclovir, idoxuridine, and vidarabine. The latter two types of antimicrobial agents, however, generally are utilized in combination with other antimicrobials when indicated with a particular patient, e.g., in immunosuppressed patients prone to opportunistic infection. For
instance, this mixture may be effective in HIV positive patients in combination, i.e., antimicrobial and steroid therapy.

Selection of the specific antibiotic(s), fungicide(s), and/or virucide(s) utilized, and the dosages utilized, is a matter within the skill of those of ordinary skill in the art using reference materials well known in the art. There are, for instance, a number of common oral organisms and pathogens, some of which may be cultured and/or propagated from the aphthous lesion in addition to S. sanguis, against which some degree of bacteriocidal, bacteriostatic, viricidal, fungicidal or fungistatic activity may be desirable. By way of example, such organisms and/or pathogens may include aerobic and/or anaerobic organisms such as Group A, C and G streptococcus, staphylococcus, enterococcus, H. influenza, E. corrodens Moraxella, M. cataralas, Bacteroides sp., and Peto streptococcus; viruses such as Types 1 and 2 herpes simplex, infectious mononucleosis/Epstein-Barr virus, and enteroviruses such as coxsackieviruses and echoviruses; and fungi such as Candida albicans, mycoplasma, and chlordzaia. The specific antimicrobial agent(s) selected for treatment of each organism/pathogen, and the dosage of same, is selected from reference materials such as, for instance, the Merck Index and/or A.G. Gilman, et al., The Pharmacologic Basis of Therapeutics, New York: MacMillan & Co. (1985), but generally range in concentration from as little as about 0.001% up to about 27% final concentration (weight:weight) depending on the particular antimicrobial agent being utilized and the organism and/or pathogen (see below) against which activity is desired.

Preferred corticosteroids are those which are relatively free from detrimental side effects when administered topically to the oral mucosa, do not compromise the efficacy of the antimicrobial agent, and which are available for use in the oral cavity. Such preferred corticosteroids include, but are not limited to, triamcinolone, hydrocortisone, hydrocortisone acetate, betamethasone benzoate, valerate and dipropionate,
dexamethasone, dexamethasone sodium phosphate, methylprednisolone acetate, amcinonide, clocortolone pivalate, desonide, desoximetasone, diflorasone diacetate, flumethasone pivalate, flucinolone acetonide, flucinonide, flurandrenolide and haloconide, and mixtures of these corticosteroids, the first steroid listed being particularly preferred. As is the case with the antimicrobial agent utilized in the present invention, the particular steroid utilized and the concentration (dose) is within the skill of those skilled in the art who have the benefit of this disclosure.

The antimicrobial agent and corticosteroid are preferably mixed in a gel, cream, or emollient containing, for instance, between about 0.0025 and about 5% of the active antimicrobial agent and 0.1% of the corticosteroid triamcinolone, on a weight per weight of final product basis. The amount of other corticosteroid(s) utilized is in a final concentration which produces anti-inflammatory effect approximately equal to that of this 0.1% (weight:weight) final concentration of triamcinolone. Such final concentrations (on a weight per unit weight of final mixture basis) are determined by standardized comparisons using relative anti-inflammatory potency as set out in the scientific literature, e.g., in the Gilman, et al. text referenced above. For the most part, however, the concentrations utilized range from about 0.002% up to about 10% (weight:weight).

The mixture of antimicrobial agent and corticosteroid is either mixed with a carrier which forms a protective coating when the resulting three-component mixture is applied to the ulcerous lesion or applied to the ulcerous lesion and covered with a protective coating. Alternatively, the antimicrobial-corticosteroid mixture is impregnated into a substrate or monolithic substance such as a medically inert polymer and/or fabric, a wafer of the impregnated material is applied to the lesion, and the protective coating is utilized to adhere the wafer to the lesion. Because of the dual role of this third component of the composition utilized in
connection with the method of the present invention, this third component is referred to herein as a carrier/protective coating.

The carrier/protective coating is any bioadhesive material which is medically inert, does not react with or in any other way significantly reduce the efficacy of the antimicrobial agent or corticosteroid, and is either insoluble in water or resistant enough to solution in the aqueous environment of the oral cavity to adhere the mixture of antimicrobial agent and corticosteroid to the lesion for sufficient time to (1) maintain contact between the antimicrobial agent and the lesion to retard bacterial propagation in and around the dead cells comprising the lesion and promote re-epithelialization of the lesion, (2) maintain contact between corticosteroid and ulcer so as to decrease the hyperimmune response, thereby allowing more rapid re-epithelialization, and (3) protect the epithelial cells which re-epithelialize the lesion from physical damage, e.g., from trauma resulting from self-induced bites, contact with the tongue or particles of food, tooth brushing, irritation from orthodontic appliances or dentures, or other local disturbance which can damage this thin, fragile layer of cells.

Appropriate bioadhesives which are used as the carrier/protective coating include, but are not limited to, pectin, gelatin, cellulose derivatives, elasticized hydrocarbon gels, calcium polycarbophil, acrylic acid polymers and polymers of the various derivatives of acrylic acid such as methacrylic acid, karaya, tragacanth, locust bean, synthetic and naturally-occurring gums, algin, chitosan, starches, naturally-occurring resins, and mixtures of any one or more of these materials. A particularly preferred bioadhesive for use as the carrier/protective coating of the present invention is a commercially available dental paste sold under the trademark ORABASE® (Hoyt Laboratories Division of Colgate-Palmolive Co., Norwood, MA), which includes gelatin, pectin, and sodium carboxymethylcellulose in a plasticized hydrocarbon gel (a polyethylene and mineral oil base).
When mixed with the carrier/protective coating before application to the lesion, the antimicrobial-corticosteroid mixture is mixed with a quantity of carrier sufficient to insure the above-identified desirable functions while maintaining the final concentration of the antimicrobial agent and corticosteroid active ingredients as discussed above. Again, selection of an appropriate carrier is a matter within the skill of those skilled in the art using reference materials such as those listed above.

Appropriate materials for use as a substrate for impregnation with the antimicrobial-corticosteroid mixture and subsequent adherence to the ulcerous lesion include the various medical grade fabrics available under the GORE-TEX® trademark (W.L. Gore & Co.), inert waxes, cellulose and cellulose derivatives, hydrogels of polyvinyl alcohols and acrylic acids and their derivatives, protein gels such as those of poly-L-lysine, synthetic azo-polymers, and hydrocolloids of animal and plant origin such as elastic, keratin, fibrin, algin, karaya, pectin, carrageenan, chitin, heparin and locust bean gum. The term "impregnated" is used herein to describe the association between the antimicrobial-corticosteroid mixture and substrate and contemplates that the mixture is bonded to, dispersed in, absorbed or coated onto, or physically soaked up into (such as in the case of those hydrogels and cellulose matrices which effectively act as a sponge) the substrate. The impregnated substrate is then cut and/or otherwise fashioned into a wafer of the size and shape of the lesion and adhered thereto by the bioadhesive protective coating.

Application of the antimicrobial-corticosteroid mixture to the lesion, whether mixed with the carrier for subsequent formation of the protective coating or applied directly to the lesion and covered by the protective coating, is preferably accomplished on at least a daily (i.e., at 24 hour intervals) basis, but may also be accomplished twice daily, i.e., at approximately twelve hour intervals. To further increase the likelihood of prolonged contact with the lesions, application is preferably made immediately prior
to the patient's extended sleep period (and, if application more than once a day is indicated, before any other sleep period if the patient, for instance, takes an afternoon nap). Treatment is for one to seven days or until the lesions disappear, usually in two to four days.

The method of the present invention is better understood by reference to the following examples.

Example 1
A cream including 1 mg triaminolone acetonide (0.1%), 2.5 mg neomycin, 100,000 units of nystatin, and 0.25 mg gramicidin per gram of cream (purchased as MYCOLOG® (E.R. Squibb & Sons, Inc.) cream) was applied in a thin film to the lesion of an otherwise healthy 29-30 year old male. The lesion was dried with a cotton swab before application of the film and a layer of ORABASE applied to the film after application to the lesion. The lesion was greatly reduced in swelling within hours and healed within 1-2 days.

Example 2
In a second trial of the method of the present invention, five formulations of the above-described composition were prepared by mixing the following ingredients in the proportions indicated:

1. 20 g triamcinolone cream (0.1%), 0.5 mg gramicidin
2. 19.8 g triamcinolone cream (0.1%), 0.5 mg gramicidin, 5 mg neomycin
3. 16.8 g triamcinolone cream (0.1%), 5 mg neomycin
4. 10 g triamcinolone cream (0.1%), 5 mg neomycin
5. 9.8 g triamcinolone cream (0.1%), 1.0 mg gramicidin
6. triamcinolone cream (0.1% as a control).

The antibiotics were used as pure, powdered antibiotic (Professional Compounding Centers of America, Inc. (PCCA)), the triamcinolone cream was a commercially-available 0.1% cream.

Each of the formulations 1-6 was tested at intervals as eruptions of minor aphthous ulcers occurred in the same two
individuals, both of whom were males in their mid-40's and otherwise in good health, by application of a thin film to the ulcer followed by application of a protective coating in the form of a thin film of ORABASE (Hoyt Laboratories Division of Colgate-Palmolive Co.) and subsequent monitoring of the lesions for subjective improvement in pain/discomfort and reduction in size and/or magnitude of the lesion. Formulations 2 and 4 demonstrated consistently efficacious results, formulation 2 in particular reducing the swelling and red halo around the lesion within a matter of hours and promoting re-epithelialization within as little as 24 hours depending upon the size of the lesion and time which elapsed between the first appearance of the lesion and first application of the formulation.

During these several trials, it was discovered that best results were achieved by swabbing the lesion with, for instance, a cotton swab or gauze, to dry the surface before application of the formulation. Application before commencement of sleep periods was especially efficacious; indeed, after a first application before commencement of eight hour sleep periods, often only one additional application was needed to cause the lesion to completely disappear.

**Example 3**

On the basis of the trials described in Example 2, a formulation was made comprised of 80 g triamcinolone cream (0.1%) and 20 mg neomycin (PCCA). That formulation was applied in a thin film to the lesions of the same two individuals as described in Example 1 as they appeared after drying the lesion with a cotton swab and the film then covered with a protective layer of ORABASE®. Results were the same as reported in Example 2 for formulation 2.

**Example 4**

Additional testing was conducted using the formulation described in Example 2, above. Application of a film of each
formulation was preceded by drying the lesion with a cotton swab and followed by application of a protective layer of ORABASE.

Patient No. 1 was a 40 year old male in good health who has experienced RAU since he was about 12 years old and had tried the many medications and remedies available with mixed results. The patient generally suffered from one to three lesions at a time ranging from 0.1 to 1 cm in size. Upon treatment with formulation 2 described in Example 2 before the patient commenced his nightly sleep period, the patient reported that RAU pain was lessened within minutes and the red halo around the lesion was dispersed with 12-14 hours. First nightly treatment effects included no sharp or stinging pain, no red halo, and an initial glazing over the RAU area. A second nightly treatment was needed only for one of the three lesions with regrowth of the epithelium completed in day 4.

Patient No. 2 was a 48 year old female in good health who has experienced RAU, generally 0.1 to 0.5 cm in size, for the majority of her adult years. The patient had tried many remedies and medications, including some that were prescribed by her dentist, without satisfactory relief. Upon the first indication of formation of a lesion, the patient applied a film formulated in accordance with Example 3, above, to the oral mucosa in the evening prior to her sleep period. In the morning, the red area was somewhat smaller in size and after a second treatment on the evening of that same day, the RAU area was completely healed the next morning.

Patient No. 3 was a 22 year old male in good health who developed RAU as an apparent result of trauma. At the time of initial treatment with the formulation of Example 3, above, the RAU was in its third day and was approximately 0.4 cm by 0.5 cm in size. The perimeter of the ulcer was highly raised and a red halo extended outwardly
for up to 0.5 to 1.0 cm. An evening treatment resulted in immediate relief of pain and within 8-12 hours, the red halo was reduced in size by about half. Due to the severity of the ulcer, the film was re-applied in the morning and again that evening. By the evening application, the ulcer was starting to grow over with epithelium and there was a slight return of normal sensation to the area. Third and fourth evening applications followed with loss of all pain and full re-epithelialization after about 72 hours.

Patient No. 4 was a 43 year old male in good health who has experienced RAU the majority of his life. Numerous applications of the formulation of Example 3 have been performed of recurring ulcers over extended periods. In every instance in which the initial application was accomplished on the day on which the symptoms first appeared, healing has resulted in 24 to 72 hours.

Example 5

A formulation including 0.1% triamcinolone cream and 0.5% neomycin was used by a 9 year old male in excellent health who experienced RAU as a result of a local trauma. The ulcer was treated with the formulation of Example 3 in the evening just prior to his sleep period. Following the sleep period, the ulcer showed initial healing and substantial reduction in the size of the red halo around the ulcer. A subsequent evening treatment resulted in complete healing in the next 48 hours.

That same formulation was utilized on multiple occasions by a 46 year old male in good health with recurrent eruptions. This patient had utilized a number of prescriptions and over-the-counter treatments for prior eruptions without relief. Use of the formulation of the present invention consistently resulted in healing in 24-72 hours.
WHAT IS CLAIMED IS:

1. Use, for the preparation of a medicament for the treatment of aphthous ulcers, of a mixture of an antimicrobial agent and a corticosteroid, in combination with a carrier for providing a protective coating to the mixture once applied to an ulcerous lesion adapted to (1) maintain contact between the antimicrobial agent in the mixture and the lesion, thereby retarding the propagation of bacteria and other ulcer-causative agents in and around the dead cells comprising the lesion and promoting re-epithelialization of the lesion, (2) maintain contact between the corticosteroid and the lesion, thereby decreasing the hyper-immune response to allow more rapid re-epithelialiation of the lesion, and (3) protect the epithelial cells which migrate over and re-epithelialize the lesion.

2. Use according to Claim 1, wherein the antimicrobial agent, the corticosteroid and the carrier for providing a protective coating are presented as a three-component mixture for application to an ulcerous lesion.

3. Use according to claim 1, wherein the mixture of the antimicrobial agent with the corticosteroid, and the carrier for providing a protective coating, are presented for separate application to an ulcerous lesion.

4. Use according to claim 1, wherein the carrier for providing a protective coating is a bioadhesive comprising pectin, gelatin, cellulose derivatives, plasticized hydrocarbon gels, calcium polycarbophil, acrylic acid polymers, polymers or derivatives of acrylic acid, karaya, tragacanth, locust bean, synthetic and naturally-occurring gums, algin, chitosan, starches or naturally-occurring resins.
5. Use according to any of claims 1-4, wherein the corticosteroid is triamcinolone.

6. Use according to any of claims 1-5, wherein the antimicrobial agent is an antibiotic comprising neomycin sulfate, gramicidin, polymixin B sulfate, bacitracin, or a sulfonamide, and mixtures thereof.

7. A composition for the topical treatment of aphthous ulcers comprising an antimicrobial agent and the corticosteroid triamcinolone, in combination with and mixed in a carrier, suitable for providing a protective coating in the oral cavity, such as a gel, cream or emollient, containing between about 0.0025 and about 5.0% (w.w.) of the active antimicrobial agent and a weight percent of a corticosteroid which produces an anti-inflammatory effect approximately equal to that of 0.1% (w.w.) of the corticosteroid triamcinolone.

8. A composition for the topical treatment of aphthous ulcers comprising a mixture of antimicrobial agent and a corticosteroid in combination with a carrier characterized in that the mixture is impregnated into a substrate or monolithic substance such as a medically inert polymer and/or fabric in the form of a wafer of said substance and in that the carrier comprises a bioadhesive protective coating suitable for application to the oral cavity and for maintaining contact between the impregnated substrate or wafer and an ulcerous lesion in the oral cavity.

9. A composition according to claim 8 wherein the substrate comprises an inert wax, cellulose and cellulose derivatives, a hydrogel of polyvinyl alcohol or acrylic acid and their derivatives, a protein gel such as that of poly-L-lysine, a synthetic azo-polymer, or a hydrocolloid of animal or plant origin.
such as elastin, keratin, fibrin, algin, karaya, pectin, carrageenin, chitin, heparin or locust bean gum.

10. A composition according to claim 8 wherein the monolithic substance comprises a medically inert fabric such as GORE-TEX (Trademark of W.L. Gore & Co.).

11. A method of treating recurrent aphthous ulcers comprising the steps of:
   applying a mixture of an antimicrobial agent and a corticosteroid to an ulcerous lesion and
   applying a protective coating to the mixture of antimicrobial agent and corticosteroid once applied to the lesion to form a protective coating to (1) maintain contact between the antimicrobial agent in the mixture and the lesion, thereby retarding the propagation of bacteria and other caustive agent in and around the dead cells comprising the lesion and promoting re-epithelialization of the lesion, (2) maintain contact between the corticosteroid and the lesion, thereby decreasing the hyper-immune response to allow more rapid re-epithelization of the lesion, and (3) protect the epithelial cells which migrate over and re-epithelialize lesion.

12. The method of claim 11 wherein the mixture of antimicrobial agent and corticosteroid is mixed with a carrier before application to the lesion, the carrier forming the protective coating after application thereto.

13. The method of claim 11 wherein the mixture of antimicrobial agent and corticosteroid is applied to the lesion and the protective coating applied thereto at a time immediately prior to the patient's extended sleep period.
14. The method of claim 13 wherein applications are repeated at approximately 24 hour intervals.

15. The method of claim 11 additionally comprising swabbing the lesion before application of the mixture of antimicrobial agent and corticosteroid thereto.

16. In a method of treating recurrent aphthous ulcers in which an antimicrobial agent is applied to an ulcerous lesion, the improvement comprising mixing the antimicrobial agent with a corticosteroid and either (1) applying the mixture to the lesion and covering the applied mixture with a protective coating or (2) mixing the mixture of antimicrobial agent and corticosteroid with a carrier and applying the resulting antimicrobial agent, corticosteroid, and carrier mixture to the lesion, the carrier forming a protective coating once applied to the lesion.

17. The method of claim 16 wherein the mixture of antimicrobial agent and corticosteroid is impregnated into a wafer for application to the lesion, the protective coating adhering the wafer thereto.

18. The method of claim 16 wherein the protective coating is comprised of a bioadhesive selected from the group consisting of pectin, gelatin, cellulose derivative, plasticized hydrocarbon gels, calcium polycarbophil, acrylic acid polymers, polymers or derivatives of acrylic acid, karaya, tragacanth, locust bean, synthetic and naturally-occurring gums, algin, chitosan, starches, and naturally-occurring resins.

19. The method of claim 16 wherein the mixture is applied to the lesion immediately before the patient's extended sleep period.
20. The method of claim 16 wherein the corticosteroid is triamcinolone.

21. The method of claim 16 wherein the antimicrobial agent is an antibiotic selected from the group consisting of neomycin sulfate, gramicidin, polymixin B sulfate, bacitracin, or a sulfonamide, and mixtures thereof.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

| IPC   | A61K38/08 | A61K38/04 | A61K31/71 | A61K31/57 | A61K31/18 |

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   | 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

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<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>J INDIAN DENT ASSOC, APR 1979, 51 (4) P121-2, INDIA, RAO P 'Therapeutic evaluation of Kenalog-S in oral lesions.' see page 121, column 2, paragraph 1-3</td>
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<td>A</td>
<td>US-A-4 013 792 (EICHMAN MARTIN L ET AL) 22 March 1977 see abstract</td>
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<td>A</td>
<td>DE-A-33 25 506 (REICHLE MANFRED) 24 January 1985 see abstract</td>
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

Date of the actual completion of the international search

28 June 1995

Date of mailing of the international search report

06.07.95

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

Leherte, C
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<td>A</td>
<td>TIJDSCHR. GENEESKD., 1992, 48/8 (623-630), BELGIUM, VEYS R. ET AL 'Recurrent aphthous ulcerations. Differential diagnosis and treatment' see page 626, column 2, paragraph 4 – page 628, column 1, paragraph 4</td>
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<td>CALIF MED, 116 (6), 1972 50-51, ROTH R J 'APHTHOUS STOMATITIS' see page 51, column 1, paragraph 3</td>
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INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   Remark: Although claims 11-21 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. □ Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. □ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. □ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

□ The additional search fees were accompanied by the applicant’s protest.

□ No protest accompanied the payment of additional search fees.
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Form PCT/ISA/219 (patent family annex) (July 1992)