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<b>(21) International Application Number:</b> PCT/US98/06483 <b>(22) International Filing Date:</b> 2 April 1998 (02.04.98) <b>(30) Priority Data:</b> 60/044,306                      30 April 1997 (30.04.97)                      US <b>(71) Applicant (for all designated States except US):</b> WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> SEGAL, Catherine, A. [US/US]; 60 Shawnee Avenue, Rockaway, NJ 07866 (US). <b>(74) Agents:</b> RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.	<b>(81) Designated States:</b> AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, 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, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>	
<b>(54) Title:</b> TOPICAL NASAL ANTIINFLAMMATORY COMPOSITIONS		
<b>(57) Abstract</b>  <p>The present invention provides topically applicable nasal compositions comprising a therapeutically effective amount of an antiinflammatory agent and a therapeutically effective amount of at least one agent selected from the group consisting of a vasoconstrictor, a neuramidinase inhibitor, a leukotriene inhibitor, an antihistamine, an antiallergic agent, an anticholinergic agent, an anesthetic and a mucolytic agent. The present compositions are useful as nasal sprays and nose drops for the treatment of nasal and sinus conditions.</p>		

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## **TOPICAL NASAL ANTIINFLAMMATORY COMPOSITIONS**

### SPECIFICATION

#### *BACKGROUND OF THE INVENTION*

5 Topical nasal antiinflammatory preparations are known in the art for  
the treatment of inflammatory conditions of the nasal mucous membranes, and in  
particular for relief of the symptoms of nasal and sinus conditions such as rhinitis.  
However, nasal and sinus conditions may be characterized by diverse symptoms  
requiring treatment with multiple therapeutic agents. For example, allergic rhinitis  
may be characterized by rhinorrhea, nasal itching, sneezing, congestion and postnasal  
10 drip and treatment may require antihistamines, decongestants, antiallergics and  
anesthetics in addition to antiinflammatories.

The use of multiple topical nasal preparations to administer multiple  
therapeutic agents suffers from significant disadvantages. The volume of liquid that  
can effectively be applied nasally is limited by the surface area of the nostril and the  
15 bioadhesiveness of the liquid. In addition, a sufficient contact time between topical  
preparations and the surface area of the nostril is required to assure adequate dosing  
of a therapeutic agent. Further, spray formulations require a threshold surface  
tension to form droplets. Accordingly, the delivery volume per actuation is limited to  
the volume that will be retained in the nostril without premature drainage. Thus  
20 multiple topical nasal preparations cannot be effectively administered simultaneously.

Another disadvantage of the administration of multiple topical nasal preparations is patient inconvenience. Patient compliance may be compromised by the inconvenience of applying multiple spray products or nose drops. Patients complain when excess spray drains into their throats where it can be tasted, resulting in a need for flavor masking of bitter medicaments.

Accordingly, a need exists for a convenient means of nasal administration of multiple therapeutic agents.

### *SUMMARY OF THE INVENTION*

The present invention provides topically applicable nasal compositions comprising a therapeutically effective amount of a topical antiinflammatory agent and a therapeutically effective amount of at least one agent suitable for topical nasal administration and selected from the group consisting of a vasoconstrictor, a neuramidinase inhibitor, an anticholinergic agent, a leukotriene inhibitor, an antihistamine, an antiallergic agent, an anesthetic, and a mucolytic agent.

### *DETAILED DESCRIPTION OF THE INVENTION*

The present invention provides topically applicable nasal compositions comprising a topical antiinflammatory agent and at least one additional therapeutic agent. The present compositions are useful for the treatment of nasal and sinus conditions, for example allergic rhinitis or the common cold.

The topical antiinflammatory agents in the compositions of the present invention are corticosteroids known in the art to suppress inflammation. In a preferred embodiment the topical antiinflammatory agent is beclomethasone dipropionate, budesonide, dexamethasone, mometasone furoate, fluticasone propionate or triamcinolone acetonide. The compositions contain a therapeutically effective amount of the selected antiinflammatory agent. Those of ordinary skill in the art can determine an amount that is therapeutically effective for the suppression of inflammation. The precise amount will depend upon the method of administration and the age, weight and condition of the subject to be treated. Generally the

antiinflammatory agents are utilized in dosages known in the art to be therapeutically effective upon nasal administration.

The compositions of the invention further comprise at least one additional therapeutic agent, and thus allow the convenient administration of an antiinflammatory agent and at least one additional therapeutic agent in a single topical nasal composition. The additional therapeutical agent is suitable for topical nasal administration and is selected from the group consisting of a vasoconstrictor, a neuramidinase inhibitor, a leukotriene inhibitor, an anticholinergic agent, an antihistamine, an antiallergic agent, a local anesthetic and a mucolytic agent. The use of an additional therapeutic agent in combination with an antiinflammatory agent provides additive and synergistic effects in the treatment of nasal and sinus conditions.

Vasoconstrictors suitable for topical nasal administration in the compositions of the present invention are oxymetazoline naphazoline, xylometazoline, and phenylephrine. Leukotriene inhibitors include zafirlukast, a selective, competitive receptor antagonist of the three leukotrienes C4, D4, and E4; pranlukast, a selective, competitive receptor antagonist of D4; and zileuton, a leukotriene inhibitor. A neuramidinase inhibitor includes zanamivir (GG-167). Suitable antihistamines are diphenhydramine, chlorpheniramine, cetirizine terfenadine, fenofexadine, astemizole norastemizole, azelastine, and azatidine. Antiallergic agents include cromolyn sodium and nedocromil levocabastine. An anticholinergic agent useful in the compositions of the present invention is ipratropium bromide. Local topical anesthetics include dyclonine, pramoxine, and benzocaine. Mucolytic agents suitable for topical nasal administration are acetylcysteine, guaifenisin and mucocysteine. The therapeutically effect amount of foregoing agents can be determined by the ordinarily skilled artisan with regard to the known use of these agents in the art and taking into account the method of administration and the age, weight and condition of the subject to be treated.

The compositions of the present invention are formulated as aqueous solutions comprising an antiinflammatory agent and at least one additional therapeutic agent and further comprising a pharmaceutically acceptable nasal carrier.

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