Title: USE OF RIMEXOLOMIE IN THE TREATMENT OF DRY EYE

Abstract: Topical ophthalmic compositions and methods for treating dry eye are described. The compositions and methods of the invention are based on the finding that the ocular surface selective properties of the glucocorticoid rimexolone make this anti-inflammatory agent particularly well-suited for treating dry eye. As a result of the limited ability of rimexolone to penetrate the cornea, a high portion of the drug remains on the surface of the eye, which is the primary focus of the inflammatory conditions associated with dry eye. This enables a very low concentration of drug to be utilized, which in turn reduces the potential for elevations of intraocular pressure and cataract formation.
USE OF RIMEXOLONE IN THE TREATMENT OF DRY EYE

Background of the Invention

The present invention is directed to compositions and methods for treating dry eye conditions. More specifically, the invention is directed to the use of an oculosurface selective glucocorticoid having limited ocular bioavailability for the treatment of dry eye.

Dry eye conditions can be caused by a variety of factors. For example, inflammation of the lacrimal gland and denervation of the cornea can curb tear production, and meibomian gland dysfunction and incomplete lid closure are frequently to blame for rapid tear evaporation. The conditions may also be attributable to systemic health factors (e.g., Sjögren's syndrome, other collagen vascular diseases or allergies), medications (e.g., antihistamines) or environmental factors (e.g., dust or smoke). The following publication may be referred to for further background regarding the diagnosis of dry eye conditions and various prior approaches to treating those conditions: "The Once and Future Treatment of Dry Eye", Review of Optometry Online, (February 15, 2000); "Attacking the Root Causes of Ocular Surface Disease", Review of Optometry Online, (June, 1998); and "Dry Eye Syndrome", The EyeSite, (August, 1999).

Dry eye, or keratoconjunctivitis sicca, is a common ophthalmological disorder that affects a significant proportion of the worldwide population. Some of these
individuals suffer from Sjogren's disease. Women of post-menopausal age comprise another segment of the dry eye population. Dry eye may afflict individuals with differing severity. In mild cases, a patient may experience burning, a feeling of dryness, and other symptoms of ocular discomfort. In severe cases, vision may be substantially impaired.

Although dry eye may have a variety of unrelated pathogenic causes, all these share as a common effect the breakdown of the ocular tear film, with dehydration of and subsequent damage to the exposed outer ocular surfaces. There is increasing evidence that inflammation may be an important factor in the pathogenesis of keratoconjunctivitis sicca, such as identification of elevated levels of pro-inflammatory mediators including IL-1 in the conjunctival epithelium in Sjögren's patients.

Individuals afflicted with the systemic autoimmune disease known as Sjögrens syndrome typically suffer with severe dry eye. In this disease, inflammation of the lacrimal gland impairs normal secretory processes, resulting in abnormalities in the tear film. Changes to the ocular surface include the production and accumulation of a variety of mediators of inflammation. These pro-inflammatory products may be derived from injured corneal and conjunctival epithelial cells as well as the inflamed lacrimal gland.

The prior therapies for dry eye have included both palliative agents, such as artificial tear formulations, and drugs, such as topical steroids, topical retinoids (e.g., Vitamin A), oral pilocarpine, and topical cyclosporin. In general, the palliative
therapies are capable of providing short-term relief from some of the symptoms of dry eye, but frequent application of the palliative products to the eye is required to maintain this relief, since these products generally do not eliminate the physiological sources of the dry eye conditions. The drug therapies that have been proposed in the prior art have had limited success in treating dry eye conditions. The limited efficacy of prior drug therapies has generally been attributable to the inability of the drug to eliminate or reduce the root causes of the dry eye conditions, side effects from the drugs that threaten the overall ocular health of the patient or result in poor patient compliance, or a combination of these factors.

The use of sex hormones and glucocorticoids in the treatment of dry eye has been discussed extensively in prior scientific papers and patent publications. The following publications may be referred to for further background in this regard: Marsh and Pflugfelder, "Topical Nonpreserved Methyprednisolone Therapy for Keratoconjunctivitis Sicca in Sjögren Syndrome", *Ophthalmology*, Volume 106, number 4, pages 881-816 (April, 1999); U.S. Patent No. Re. 34,578 (Lubkin); U.S. Patent No. 5,620,921 (Sullivan); and U.S. Patent No. 6,153,607 (Pflugfelder, et al.).

It is known that certain glucocorticoids have a greater potential for elevating intraocular pressure ("IOP") than other compounds in this class. For example, it is known that prednisolone, which is a very potent ocular anti-inflammatory agent, has a greater tendency to elevate IOP than fluorometholone, which has moderate ocular anti-inflammatory activity.
It is also known that the risk of IOP elevations associated with the topical ophthalmic use of glucocorticoids increases over time. In other words, the chronic (i.e., long-term) use of these agents increases the risk of significant IOP elevations.

Unlike bacterial infections or acute ocular inflammation associated with physical trauma, which require short-term therapy on the order of a few weeks, dry eye conditions require treatment for extended periods of time, generally several months or more. This chronic use of corticosteroids significantly increases the risk of IOP elevations. Prolonged use of corticosteroids is also known to increase the risk of cataract formation.

It has been suggested that the above-cited problems associated with chronic corticosteroid therapy can be addressed by means of a "pulse" treatment regimen, wherein the patient is only treated with potent corticosteroids (e.g., prednisolone) for relatively short, intermittent periods. (See the 1999 article by Marsh and Pflugfelder, cited above.) However, in view of the practical limits of achieving patient compliance with such a regimen, particularly in elderly patients, a more viable solution to the above-discussed problems is needed. The present invention is directed to satisfying this need via the use of very low concentrations of the oculosurface selective glucocorticoid rimexolone.

The use of rimexolone to treat ophthalmic inflammation is described in U.S. Patent No. 4,686,214 (Boltralik). A commercial product containing 1% rimexolone has been marketed by Alcon Laboratories, Inc. for several years under the name "VEXOL® 1% (Rimexolone) Ophthalmic Suspension".
Summary of the Invention

The present invention is based on a finding that the glucocorticoid rimexolone is particularly well suited for use in the treatment of dry eye conditions, particularly for chronic therapy (i.e., daily administration for extended periods of time, such as several months or more).

Most glucocorticoids, including rimexolone, are relatively insoluble in water. However, there is no direct correlation between aqueous solubility and the ability of these drugs to penetrate the cornea and become dispersed in intraocular fluids and tissues. Two glucocorticoids that are generally considered to be potent ophthalmic anti-inflammatory agents, prednisolone and dexamethasone, are able to penetrate the cornea to a greater extent than rimexolone, and therefore exhibit a much higher level of intraocular bioavailability, but are also relatively insoluble in water.

The present invention is based on a finding that the limited intraocular bioavailability of rimexolone is a significant advantage in the treatment of dry eye conditions, particularly with respect to chronic therapy. The advantages are twofold. First, as a result of the limited corneal penetration of rimexolone, the risks of elevating IOP, precipitating cataract formation, or causing other significant ocular side effects are reduced substantially. As indicated above, this reduction of risks is particularly important in chronic therapy situations. Second, the fact that rimexolone only penetrates the cornea to a limited extent means that most of the drug remains
on the surface of the cornea and sclera. This feature of rimexolone is referred to herein as "oculosurface selective".

The selectivity of rimexolone for remaining on the ocular surface, rather than being dispersed throughout the eye, is a distinct advantage in dry eye patients because the target tissues in such patients (i.e., the tissues that are primarily affected) are present on the ocular surface. As a result of this selectivity for the ocular surface, it has been found that rimexolone is effective in treating dry eye conditions, even at very low concentrations. The effectiveness of rimexolone at such low concentrations further reduces the risks of IOP increases, cataract formation and other potential ocular side effects.

The present invention is also based on the finding that ophthalmic suspensions containing very low concentrations of rimexolone can be formulated as preserved, multi-dose products, rather than as preservative-free unit dose products. The use of preserved, multi-dose products for treating dry eye conditions has been discouraged in the prior art (see, e.g., the 1999 article by Marsh and Pflugfelder, cited above).

The prior art teaching to avoid the use of antimicrobial preservatives in ophthalmic products generally, and particularly ophthalmic glucocorticoid products for treating dry eye, is based on the fact that the antimicrobial agent conventionally used to preserve such products, benzalkonium chloride, has been shown to cause ocular irritation and exacerbate ocular inflammatory conditions, such as dry eye.
The prior art therefore teaches that such antimicrobial preservatives should be completely removed. Since the sterility of the ophthalmic products must be maintained, the removal of the antimicrobial preservatives requires that the products be packaged in a unit dose format, i.e., each dose of sterile solution is packaged in a small, sealed plastic vial. This approach has the advantage of eliminating the antimicrobial preservatives entirely, but also has several drawbacks, such as, a risk of microbial contamination of products, inconvenience, wasteful use of packaging materials and costliness.

The present invention has overcome the above-discussed problems by replacing the conventional preservative benzalkonium chloride ("BAC") with a preservative system that is very mild, relative to BAC, but yet effective in preventing microbial contamination of multi-dose ophthalmic compositions containing rimexolone. The preservative system comprises a buffer system having antimicrobial activity, and preferably also a very low concentration of an antimicrobial agent that does not cause irritation or other discomfort when applied to the eyes of dry eye patients. The preferred antimicrobial agent is polyquaternium-1, at a concentration of five parts per million (i.e., 0.0005 w/v %). It has also been determined that the use of a non-hydrophilic suspending agent, preferably polyvinyl pyrrolidone, is advantageous in order to effectively suspend rimexolone and facilitate the use of such low concentrations of polyquaternium-1.

Brief Description of the Drawings

Figure 1 is a graphic summary of the TBUT data discussed in Example 2;
Figure 2 is a graphic summary of the corneal protection data discussed in Example 2;

Figure 3 is a graphic summary of the TBUT data discussed in Example 3; and

Figure 4 is a graphic summary of the corneal protection data discussed in Example 3.

**Detailed Description of the Invention**

The present invention is based on the finding that rimexolone is effective in treating dry eye conditions at concentrations that are significantly less than the concentration currently utilized for treatment of ophthalmic inflammation. The concentrations of rimexolone utilized in the present invention are 0.1 weight/volume percent ("w/v%") or less, while the concentration currently utilized in VEXOL® is 1%. Thus, there is a difference in concentrations of at least tenfold.

The rimexolone concentration range for the compositions of the present invention is 0.001 to 0.1 w/v%, preferably 0.05 to 0.075 w/v%. The most preferred concentration is 0.075%.

The compositions of the present invention contain a buffer system that functions to maintain the pH of the compositions at or near physiologically compatible levels, and to provide a low level of antimicrobial activity. The low-level
antimicrobial activity helps to prevent contamination of the compositions by bacteria, fungi or other microorganisms. This function is referred to herein as "antimicrobial preservation".

The level of antimicrobial activity required in order to achieve antimicrobial preservation of multi-dose ophthalmic pharmaceutical products is described in the United States Pharmacopoeia ("USP"), European Pharmacopoeia ("EP") and corresponding preservative efficacy standards in other countries. The buffer systems utilized in the present invention provide sufficient antimicrobial activity to either enable such standards to be satisfied without inclusion of any conventional antimicrobial agents, or to enable the concentration of conventional antimicrobial agent to be reduced significantly. The amount of buffer system required to achieve the above-cited objectives is referred to herein as "an antimicrobial enhancing amount".

The compositions of the present invention have a pH of 6 to 8, most preferably about 7.4. The pH of the compositions can be adjusted at the time of manufacture by adding small amounts of sodium hydroxide and/or hydrochloric acid. However, in order to maintain the pH of the compositions within the above-specified range over extended periods of one to two years or longer, a buffering system is required.

The preferred buffer system is a combination of one or more borate components and one or more polyol components that interact to form borate/polyol complexes. The use of borate/polyol complexes to enhance the antimicrobial activity
of ophthalmic compositions is described in United States Patent No. 6,143,799 (Chowhan, et al.), the entire contents of which are hereby incorporated in the present specification by reference.

As used herein, the term "borate" refers to boric acid, salts of boric acid and other pharmaceutically acceptable borates, or combinations thereof, and the term "polyol" refers to any compound having at least one hydroxyl group on each of two adjacent carbons that are not in trans configuration relative to each other. The most suitable borates are: boric acid, sodium borate, potassium borate, calcium borate, magnesium borate, manganese borate, and other such borate salts. The polyols can be linear or circular, substituted or unsubstituted, or mixtures thereof, so long as the resultant borate/polyol complex is water-soluble and pharmaceutically acceptable. Such compounds include sugars, sugar alcohols, sugar acids and uronic acids. Preferred polyols are sugars, sugar alcohols and sugar acids, including, but not limited to: mannitol, glycerin, propylene glycol and sorbitol. Especially preferred polyols are mannitol and glycerin; most preferred is mannitol. The molar ratio of borate to polyol is generally between about 1:0.1 and about 1:10, and is preferably between about 1:0.25 and about 1:2.5.

The borate polyol complexes are utilized in the compositions of the present invention in an amount between about 0.5 to about 6.0 percent by weight (wt %), preferably between about 1.0 to about 2.5 wt %. The optimum amount, however, will depend upon the complexity of the product, since potential interactions may occur with the other components of a composition. Such optimum amount can be readily determined by one skilled in the formulatory arts.
In another preferred embodiment of the invention, the buffer system comprises a combination of tromethamine and boric acid. The concentration of boric acid will generally range from 0.1 to 1.5 w/v%, preferably 0.6 w/v%. The concentration of tromethamine will generally range from 0.05 to 0.6 w/v%, preferably 0.25 w/v%.

The preservative system utilized in the compositions of the present invention preferably also includes a small amount of an antimicrobial agent that is not irritating to the eyes of dry eye patients when repeatedly applied to the eyes over extended periods of time. This agent is referred to herein as a "non-irritating, ophthalmically acceptable antimicrobial agent." It is utilized in an amount sufficient to further enhance the antimicrobial preservative efficacy of the compositions, relative to the level of antimicrobial activity achieved with the buffer system alone. The preferred antimicrobial agent is polyquaternium-1. The concentration of polyquaternium-1 will generally be from about 0.0001 to 0.001 w/v%, preferably about 0.0005 w/v%. The compositions of the present invention do not contain benzalkonium chloride and therefore may be referred to as "BAC-free".

As indicated above, rimexolone is relatively insoluble in water. The aqueous compositions of the present invention are therefore preferably formulated as suspensions.

Rimexolone is an extremely hydrophobic molecule, and consequently it is difficult to maintain it in a suspended state. If the rimexolone does not remain in
suspension, it will form a cake that cannot be resuspended upon shaking of the container. This caking problem frequently occurs when cellulosic agents, such as HPMC or HEC, are utilized to suspend rimexolone. However, it has been found that caking can be avoided by using polyvinyl pyrrolidone ("PVP") as the suspending agent. It is believed that PVP interacts with the surfaces of the rimexolone particles to form a protective layer. This interaction results in a steric stabilization of the particles in the suspension.

It has also been determined that PVP does not adversely affect the antimicrobial activity of polyquaternium-1, which is a polymeric quaternary ammonium compound. This compatibility between PVP and polyquaternium-1 allows a very low concentration of polyquaternium-1 to be utilized in the multi-dose, preserved compositions of the present invention (e.g., preferably 0.0005 w/v %).

Based on the above-described advantages, the use of PVP as a suspending agent is preferred.

The amount of suspending agent required can be readily determined by persons skilled in the art, but will generally be in the range of about 0.1 to 2.0 w/v %.

The compositions of the present invention preferably also contain a nonionic surfactant in an amount 0.01 to 0.2 w/v%. Many nonionic surfactants are known that are acceptable for topical ophthalmic formulations. Such surfactants include: tyloxapol; polyoxyethylene sorbitan esters, such as polysorbate 80, polysorbate 60, and polysorbate 20; polyethoxylated castor oils, such as Cremophore EL;
polyethoxylated hydrogenated castor oils, such as HCO-40; and poloxamers. The preferred surfactant is tyloxapol at a concentration in the range of 0.01 to 0.1%, preferably 0.008%.

The compositions of the present invention are formulated to be isotonic, relative to the natural tear fluids. The compositions are therefore formulated to have an osmolality of about 280 to 320 milliosmoles per kilogram water ("mOsm/kg"). If necessary, the compositions may contain ophthalmically acceptable toxicity-adjusting agents, such as sodium chloride, potassium chloride, glycerin, sorbitol or mannitol. The preferred toxicity adjusting agent is sodium chloride, at a concentration in the range of 0.4 to 0.6%, preferably 0.6%.

The present invention is also directed to the provision of methods for treating dry eye conditions. The methods comprise the topical application of an ophthalmic composition of the type described above to the affected eye. The frequency of the application may vary somewhat depending on the severity of the dry eye conditions being treated, but will generally be from two to four times per day (i.e., 24 hours).

The duration of the therapy may also vary somewhat from patient to patient, but the therapy will generally continue for a period of from several weeks (e.g., six or more weeks) to several months (e.g., six or more months). Due to the limited corneal penetration of rimexolone, and the extremely low concentrations of rimexolone employed in the compositions of the present invention, it is possible to utilize the compositions of the present invention for chronic treatment of dry eye conditions with very little risk of elevating intraocular pressure, suppressing the
ocular immune response, or other side effects frequently associated with prior uses of corticosteroids in the eye.

The compositions and methods of the present invention are further illustrated by the following examples.
Example 1

The following formulation is representative of the preferred topical ophthalmic compositions of the present invention:

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>COMPENDIAL DESIGNATION</th>
<th>CONCENTRATION (w/v%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rimexolone</td>
<td>Non-Compendial</td>
<td>0.005-0.1</td>
</tr>
<tr>
<td>Polyquaternium-1</td>
<td>Non-Compendial</td>
<td>0.0005</td>
</tr>
<tr>
<td>Boric Acid</td>
<td>NF</td>
<td>0.6</td>
</tr>
<tr>
<td>Povidone K90</td>
<td>USP</td>
<td>1.5</td>
</tr>
<tr>
<td>Tyloxapol</td>
<td>USP</td>
<td>0.008</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>USP</td>
<td>0.5</td>
</tr>
<tr>
<td>Mannitol</td>
<td>USP</td>
<td>0.2</td>
</tr>
<tr>
<td>Tromethamine</td>
<td>USP</td>
<td>0.25</td>
</tr>
<tr>
<td>Sodium Hydroxide</td>
<td>NF</td>
<td>Adjust pH to 7.4 ± 0.2</td>
</tr>
<tr>
<td>And/or Hydrochloric Acid</td>
<td>NF</td>
<td></td>
</tr>
<tr>
<td>Purified Water</td>
<td>USP</td>
<td>Q.S. 100</td>
</tr>
</tbody>
</table>

The above-described formulations may be prepared as described below:

A measured amount of rimexolone is micronized using a portion of the specified amount of tyloxapol as a wetting agent and purified water as vehicle in appropriate ball milling or micronization equipment.

In a separate vessel containing purified water (60 to 80°C), the polyvinyl pyrrolidone is added and dissolved. Boric acid, mannitol, sodium chloride, tromethamine and the remainder of the tyloxapol solution are added and dissolved
into this solution. The resulting solution is allowed to cool to room temperature and the pH is adjusted to 7.4 using HCl and/or NaOH. The micronized rimexolone slurry containing drug, tyloxapol and purified water is then added to this solution. The resulting suspension is adjusted to final weight, and is then subjected to steam sterilization using an appropriate sterilizing cycle. The suspension is allowed to cool to room temperature, followed by aseptic addition of the calculated quantity of pre-sterilized polyquartemium-1 solution. The suspension is finally adjusted to specified weight by the addition of purified water.

The preserved, multi-dose formulation described above has been evaluated relative to the ability of the formulation to satisfy the preservative efficacy standards of the United States Pharmacopoeia ("USP") and European Pharmacopoeia ("EP") and similar standards. It has been determined that the formulation satisfies the preservative efficacy requirements of the USP and EP.

**Example 2**

The ability of low doses of rimexolone to alleviate dry eye conditions was evaluated. The compositions tested were the same as the formulation described in Example 1 above, with rimexolone concentrations of 0.005%, 0.01%, 0.05 and 0.1%, respectively. The experimental procedures are described below.

Dry eye was induced in New Zealand white rabbits (approximately 2kg) by eliciting bilateral inflammation of the lacrimal glands. Tear function was assessed by measuring tear breakup time ("TBUT") daily for three days, following the induction of
dry eye. TBUT was determined by instilling 5µl sodium fluorescein into the cul de sac and manually blinking the lids to distribute the fluorescein within the tear film. Under slit lamp observation, the eye was held open and the time to tear film breakup recorded. Efficacy was determined by comparing TBUT relative to pre-inflammation baseline values in drug and vehicle treated animals.

In a separate group of animals, susceptibility to desiccation-induced corneal injury was assessed following the induction of lacrimal gland inflammation. Desiccation was initiated by placing the rabbits in a low humidity environment continuously for up to three days. Corneal injury was assessed by determining the uptake of the vital dye, methylene blue. Under general anesthesia, the ocular surface was bathed in a 1% solution of methylene blue for five minutes and then washed. The animals were euthanized, eyes were excised and an 8mm-diameter section of cornea was isolated and extracted overnight. The concentration of extracted dye was determined spectrophotometrically (A_{660}). Protection of the cornea is indicated by a lesser uptake of dye in drug treated animals relative to that in vehicle treated rabbits. For both TBUT and corneal injury determinations, dosing (QID) was initiated 24-hours prior to inducing inflammation and was continued for the duration of the study.

The results of the above-described tests are summarized in Figure 1 and 2, respectively. The low-dose rimexolone formulations of the present invention were significantly effective at each concentration tested. The maximally effective concentration for restoration of TBUT, as well as for prevention of desiccation-induced corneal staining, was 0.1%. Figure 2 illustrates the effect of rimexolone on
susceptibility to desiccation-induced corneal injury following lacrimal gland inflammation. A bell-shaped dose-response curve with peak efficacy of 74% inhibition at 0.1% was observed. When TBUT data is expressed as percent of baseline on day three (Figure 1), rimexolone demonstrated a bell-shaped dose-response which was maximal (66% of baseline) at the 0.1% concentration. These results establish that the 0.1% concentration is the maximally effective concentration.

Example 3

A second dose-response study was conducted using the procedures described in Example 2 above. The results of the study are summarized in Figures 3 and 4.

The rimexolone compositions of Example 1 were significantly effective at each concentration tested. The maximally effective concentration for restoration of TBUT, as well as for prevention of desiccation-induced corneal staining, was 0.1%. At the 0.1% concentration, rimexolone inhibited corneal staining by 77% (Figure 4) and restored TBUT to 71% of baseline on day three (Figure 3).

Example 4

A clinical study in human patients has been conducted to evaluate the efficacy and safety of rimexolone in relieving the ocular signs and symptoms of dry eye in patients with autoimmune connective tissue disease. The formulation described in Example 1 above was utilized in the study. Three different suspensions, containing rimexolone at concentrations of 0.005%, 0.05% and 0.1%, respectively, were utilized in the study. A fourth formulation, which was identical to the three rimexolone
suspensions except for the elimination of rimexolone, was utilized as a control (i.e., placebo). The number of patients treated with each of the formulations was as follows:

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.005% Rimexolone</td>
<td>30</td>
</tr>
<tr>
<td>0.05% Rimexolone</td>
<td>26</td>
</tr>
<tr>
<td>0.1% Rimexolone</td>
<td>27</td>
</tr>
<tr>
<td>Vehicle/Placebo</td>
<td>23</td>
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</table>

The patients in each group administered one drop of the respective formulations to each eye four times per day for six weeks. Following the end of the six week drug administration period, the patients’ symptoms were evaluated.

The results of the study demonstrate that the patients who were treated with the suspensions containing rimexolone had less dry eye symptoms (i.e., discomfort) than the patients treated with the vehicle/placebo. In addition, the patients treated with the rimexolone suspensions did not exhibit any clinically relevant increases in intraocular pressure.
We Claim:

1. A method of treating chronic dry eye conditions, which comprises applying a therapeutically effective amount of a topical ophthalmic composition to the cornea of the affected eye on a daily basis for a period of from several weeks to several months or more, said composition comprising an effective amount of an oculosurface selective glucocorticoid.

2. A method according to Claim 1, wherein the oculosurface selective glucocorticoid comprises rimexolone.

3. A method according to Claim 2, wherein the composition contains rimexolone at a concentration of 0.001 to 0.1 w/v%.

4. A method according to Claim 3, wherein the composition contains rimexolone at a concentration of less than 0.1 w/v%.

5. A method according to Claim 4, wherein the composition contains rimexolone at a concentration of 0.05 to 0.075 w/v%.

6. A method according to Claim 2, wherein the composition is a preserved, multidose composition.

7. A method according to Claim 6, wherein the composition is an aqueous suspension, and further comprises an amount of polyvinyl pyrrolidone sufficient to suspend the rimexolone in the composition.
8. A method according to Claim 7, wherein the composition further comprises a preservative effective amount of polyquaternium-1.

9. A method according to Claim 8, wherein the composition contains polyquaternium-1 at a concentration of from 0.0001 to 0.001 w/v%.

10. A method according to Claim 9, wherein the composition contains polyquaternium-1 at a concentration of 0.0005 w/v%.

11. A method according to Claim 10, wherein the composition further comprises an antimicrobial enhancing amount of a buffer system having antimicrobial activity.

12. A method according to Claim 11, wherein the buffer system comprises a borate/polyol complex.

13. A topical ophthalmic composition for treating dry eye, comprising 0.005 to 0.1 w/v% rimexolone and an ophthalmically acceptable vehicle therefor.

14. A topical ophthalmic composition according to Claim 13, wherein the composition is a multi-dose suspension, and further comprises an effective amount of an antimicrobial preservative and an amount of polyvinyl pyrrolidone sufficient to suspend the rimexolone in the composition.

15. A topical ophthalmic composition according to Claim 13, wherein the composition contains rimexolone at a concentration of 0.05 to 0.075 w/v%.
16. A topical ophthalmic composition according to Claim 15, wherein the composition contains rimexolone at a concentration of 0.075 w/v%.

17. A topical ophthalmic composition according to Claim 13, wherein the composition contains rimexolone at a concentration of 0.1 w/v%.

18. A topical ophthalmic composition according to Claim 14, wherein the antimicrobial preservative comprises polyquaternium-1.

19. A topical ophthalmic composition according to Claim 18, wherein the concentration of polyquaternium-1 in the composition is less than 0.001 w/v%.

20. A topical ophthalmic composition according to Claim 19, wherein the concentration of polyquaternium-1 is 0.0005 w/v%.

21. A topical ophthalmic composition according to Claim 20, wherein the composition further comprises an antimicrobial enhancing amount of a buffer system having antimicrobial activity.
Tear Breakup Time (TBUT) on Day 3

Effect of AL-02178 (Rimexolone)

Figure 1
Rabbit Lacrimal Gland Inflammation: Corneal Staining

Effect of AL-02178 (Rimexolone)

![Graph showing % Inhibition vs. AL-02178 concentration.]

* p<0.01 compared to group-specific vehicle, t-test

**Figure 2**
Tear Breakup Time (TBUT) on Day 3: Effect of Rimexolone (AL-02178)

![Graph showing the effect of different concentrations of Rimexolone on Tear Breakup Time (TBUT). The x-axis represents different concentrations (0.005%, 0.01%, 0.05%, 0.1%) and the y-axis represents % Baseline. Bars with error bars are shown for each concentration. Asterisks indicate statistically significant differences (p<0.05, compared to group-specific vehicle, t-test).]

* p<0.05, compared to group-specific vehicle, t-test

Figure 3
Corneal Staining: Effect of Rimexolone (AL-02178)

* p<0.05, compared to group specific vehicle, t-test

Figure 4
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 A61K31/57 A61K31/573 A61K31/575 A61P27/02

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 7 A61K A61P

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)

EPO—Internal, WPI Data, PAJ, FSTA, EMBASE, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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**X** Further documents are listed in the continuation of box C.

**X** Patent family members are listed in annex.

* Special categories of cited documents:

- **A** document defining the general state of the art which is not considered to be of particular relevance
- **E** earlier document but published on or after the international filing date
- **L** later 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)
- **C** 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

**+** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

**X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone or in combination with one or more other such documents, such combination being obvious to a person skilled in the art

**Y** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is taken alone or in combination with one or more other such documents, each combination being obvious to a person skilled in the art

**&** document of the same patent family

**Date of the actual completion of the international search**

28 April 2004

**Date of mailing of the International search report**

07/05/2004

**Name and mailing address of the ISA**

European Patent Office, P.B. 5813 Patentlaan 2 NL—2280 HV Rijswijk
Tel. (+31—70) 540-2040, Tx. 31 661 epo nl, Fax: (+31—70) 340-3016

**Authorized officer**

Houyvet, C

Pct/US03/40374 (second sheet) (January 2004)
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<th>Relevant to claims No.</th>
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<td>WO 93/17664 A (ALCON LAB INC) 16 September 1993 (1993-09-16) page 3, line 1,2 page 4, line 10,14-29</td>
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<td>A</td>
<td>EP 0 280 797 A (ALCON LAB INC) 7 September 1988 (1988-09-07) cited in the application page 2, line 3,4,20-49 page 3, line 1-32; example 1</td>
<td>1-21</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:
   Although claims 1-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1 (in part)
   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:
   see FURTHER INFORMATION sheet PCT/ISA/210

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.
Continuation of Box I.2

Claims Nos.: 1 (in part)

Present claim 1 relate to the use of a compound defined by reference to a desirable property, namely: an oculosurface selective glucocorticoid. The claim cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only one such compound. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. It may indeed well be the case that compounds for the treatment of dry eyes are well known but not yet defined as oculosurface selective glucocorticoid. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the use of the compound rimexolone in the treatment of dry eyes.

The applicant’s attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.
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