PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 31/42, 31/44, 31/495, 31/535

A1

(11) International Publication Number: **WO 00/03710**

(43) International Publication Date: 27 January 2000 (27.01.00)

(21) International Application Number: PCT/US99/12367

(22) International Filing Date: 7 July 1999 (07.07.99)

(30) Priority Data:
60/092,765 14 July 1998 (14.07.98) US

(71) Applicant *(for all designated States except US)*: PHARMACIA & UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: COCHRAN, Robert [US/US]; 1074 Tumbleweed Drive, Loveland, OH 45140 (US). FORD, Charles, W. [US/US]; 1306 Carriage, Portage, MI 49024 (US).

(74) Agent: STEIN, Bruce; Intellectual Property Legal Services, Pharmacia & Upjohn Company, 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(81) Designated States: AE, 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, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, 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
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: OXAZOLIDINONES TO TREAT EYE INFECTIONS

(57) Abstract

The present invention involves a method of treating an ophthalmic infection in a useful warm blooded mammal who is in need of such treatment which comprises topical administration of an ophthalmologicallly effective amount of an OXAZOLIDINONE.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

OXAZOLIDINONES TO TREAT EYE INFECTIONS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is a method of treating various ophthalmic infections with known pharmaceutically useful oxazolidinone antibacterials.

2. Description of the Related Art

US Patents 5,164,510, 5,231,188, 5,565,571, 5,652,238, 5,688,792, 5,698,574 and 5,627,181 all disclose various oxazolidinone antibiotics which are well known to those skilled in the art.

US Patent 5,688,792 discloses various oxazolidinone antibiotics which can be administered orally, parenterally or topically. The topical application being by gel or cream vehicle.

Many of the presentations and posters presented at the May 11-16, 1997 at the Association for Research in Vision and Ophthalmology presented a lot of evidence that resistant microorganisms is becoming a significant problem.

Review of Ophthalmology, 94 (January 1997) discloses the use of antibacterial/antibiotic agents for ophthalmic purposes. It discloses that the "big gun" of topical antibiotics is vancomycin but that it is poorly tolerated. It further disclosed that other antibacterial agents such as the two fluoroquinolones, ciprofloxacin and ofloxacin, as well as other agents such as cepharlosporins and an aminoglycoside. It appears that while the agents of choice are the fluoroquinolones that more effective agents are needed and that the fluoroquinolones have the drawback of very rapid *de novo* resistance development.

The *Investigative Ophthalmology & Visual Science*, 37(3) Abstracts 4060 - B846 and 4056 - B842 (1996) both disclose that while there was no resistance to ciprofloxacin in gram positive microorganisms in the late 1980's or early 1990's, significant resistance had developed by the mid 1990's.

The *Investigative Ophthalmology & Visual Science*, 39(4) Abstract 4951 - B70 and 4950 - B701 (1998) both disclose problems with decreased susceptibility (increased resistance) of *S. aureus* because of the use of broad spectrum antibiotics in treating ophthalmic infections. This makes it more difficult for physicians to treat eye infections.

SUMMARY OF INVENTION

Disclosed is a method of treating an ophthalmic infection in a useful warm blooded mammal who is in need of such treatment which comprises topical administration of an ophthalmologically effective amount of an OXAZOLIDINONE.

DETAILED DESCRIPTION OF THE INVENTION

The method of the present invention is a method of treating an ophthalmic infection in a useful warm blooded mammal who is in need of such treatment which comprises topical administration of an ophthalmologically effective amount of an OXAZOLIDINONE.

US Patent 5,688,792 which disclosed various oxazolidinone antibiotics disclosed they could be administered orally, parenterally or topically. There are a number of antibacterial agents which can be used topically but are much too toxic to be used ophthalmologically to treat bacterial infections of the eye.

Useful warm blooded mammals which are within the scope of the present invention include humans, pets such as dogs, cats and commercially important mammals such as horses, cattle, pigs. It is preferred that the mammal be a human, dog or cat; more preferably a human.

The OXAZOLIDINONEs of the present invention are known, see EXAMPLES 1 thru 5 (OXAZOLIDINONEs). It is preferred that the OXAZOLIDINONE be selected from the group consisting of

(*S*)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

(*S*)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

N-((5*S*)-3-(3-fluoro-4-(4-(2-fluoroethyl)-3-oxopiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl)acetamide,

(*S*)-N-[[3-[5-(3-pyridyl)thiophen-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide and

(*S*)-N-[[3-[5-(4-pyridyl)pyrid-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide hydrochloride; it is more preferred that the OXAZOLIDINONE be selected from the group consisting of:

(*S*)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and

(*S*)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. It is even more preferred that the OXAZOLIDINONE be (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

Ophthalmic infections in this invention refer to inflammation of the conjunctiva (conjunctivitis) by staphylococci, streptococci and enterococci, and inflammation of the cornea (keratitis) caused by the same organisms and corneal ulcers. Bacterial conjunctivitis is the most common form of infectious conjunctivitis and bacterial keratitis accounts for 65-90% of all bacterial corneal infections. It is preferred that the ophthalmic infection be bacterial keratitis and bacterial conjunctivitis.

The gram positive microorganisms which cause the ophthalmic infections treated by the OXAZOLIDINONEs of the present invention include *Staphylococci, Streptococci, Enterococci, Bacillus, Corynebacterium, Chlamydia and Neisseria.* It is preferred that the microorganism be a *Staphylococci, Streptococci or Enterococci.* It is more preferred that the infection be caused by *Staphylococci* and/or *Streptococci.* The important species of these genus are *Staphloccus aureus, Streptococcus viridans, Staphloccus epidermidis* and *Streptococcus pneumoniae.* The OXAZOLIDINONEs of the present invention also treat gram positive and gram negative infections caused by anaerobes such as *Bacteroides fragilis.*

The ophthalmic infections are treated by administering the desired OXAZOLIDINONE(s) directly to the eye by use of a pharmaceutical formulation consisting of a solution, cream, ointment, emulsion, suspension and slow release formulations. It is preferred that the pharmaceutical formulation be a solution, cream, ointment, emulsion and suspension; it is more preferred that the ophthalmic pharmaceutical formulation be solution. It is preferred that the ophthalmologically effective amount of the OXAZOLIDINONE for treatment of ophthalmic infections is from about 0.3% to about 20%, it is more preferred that the ophthalmologically effective amount be from about 0.5% to about 18%. It is even more preferred that the ophthalmologically effective amount be from about 6% to about 16%. The OXAZOLIDINONE should be administered in the pharmaceutical formulation two thru four times daily for 7 thru 10 days or until the infection is gone. It is preferable if about 0.03 to about 2.0 ml of the ophthalmic pharmaceutical formulation containing

the OXAZOLIDINONE is used each time it is administered. It is more preferable if about 0.05 (about 1 drop) to about 0.25 ml (about 5 drops) is administered.

International Publication WO96/06581 discloses a treatment fluid container having at least one opening of sufficient diameter and where the fluid is under sufficient pressure to discharge the solution as discrete jets and/or droplets. These known treatment fluid containers are useful in administering solutions containing the OXAZOLIDINONE(s). Inserts are also useful for administration of solutions of OXAZOLIDINONE(s) to the eye.

In the method of the present invention, the OXAZOLIDINONEs can be used either individually or in combination with each other. Further, they can be used in combination with other antibacterial agents. In addition, the OXAZOLIDINONEs can be used with non-antibacterial agents in treating the infections of this invention.

The exact dosage and frequency of administration depends on the particular OXAZOLIDINONE used, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, other medication the individual may be taking as is well known to those skilled in the art and can be more accurately determined by measuring the blood level or concentration of the OXAZOLIDINONE in the patient's blood and/or the patient's response to the particular condition being treated.

DEFINITIONS

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

All temperatures are in degrees Centigrade.

THF refers to tetrahydrofuran.

DMF refers to dimethylformamide.

Saline refers to an aqueous saturated sodium chloride solution.

Chromatography (column and flash chromatography) refers to purification/separation of compounds expressed as (support, eluent). It is understood that the appropriate fractions are pooled and concentrated to give the desired compound(s).

Ether refers to diethyl ether.

TLC refers to thin-layer chromatography.

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

OXAZOLIDINONE refers to the compounds of EXAMPLES 1 thru 5 of the present invention.

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

EXAMPLE 1 (*S*)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

(*S*)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide is known, see US Patent 5,652,238, EXAMPLE 1.

EXAMPLE 2 (*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide is known, see US Patent 5,688,792, EXAMPLE 5.

EXAMPLE 3 N-((5*S*)-3-(3-Fluoro-4-(4-(2-fluoroethyl)-3-oxopiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl)acetamide

N-((5*S*)-3-(3-Fluoro-4-(4-(2-fluoroethyl)-3-oxopiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl)acetamide is known, see International Publication WO97/27188 (Example 4).

1-*t*-Butoxycarbonyl-3-oxopiperazine (21.6 g) is dissolved in dry DMF (500 ml) and potassium *t*-butoxide (24.2 g) is added. The mixture is stirred at 20-25° for 30

minutes, then 1-(4-methylphenylsulfonyloxy)-2-fluoroethane (*J. Med. Chem.*, 23(9), 985-90 (1980), 25.9 g) is added and stirring continued at the same temperature for 24 hours. The solvent is removed and the residue partitioned between ethyl acetate and water. The organic phase is washed with water and concentrated. The residue is dissolved in isopropanol and diluted with iso-hexane forming a precipitate which is removed by filtration. The mixture is chromatographed (silica; eluting with a gradient increasing in polarity from 0 to 50% isopropanol in iso-hexane) to give 1-*t*-butoxycarbonyl-4-(2-fluoroethyl)-3-oxopiperazine.

1-*t*-Butoxycarbonyl-4-(2-fluoroethyl)-3-oxopiperazine (6.65 g) is dissolved in dichloromethane (500 ml), cooled in an ice-bath and trifluoroacetic acid (150 ml) added. The mixture is stirred at the same temperature for 2 hours. The solvent is removed to give a crude product which is dissolved in the minimum volume of ethyl acetate. Slow addition of ether causes precipitation of 1-(2-fluoroethyl)-2-oxopiperazine as the mono trifluoroacetic acid salt.

1-(2-Fluoroethyl)-2-oxopiperazine trifluoroacetate (6.1 g) is dissolved in acetonitrile (100 ml). N,N-Diisopropylethylamine (13 ml) is added to the mixture, followed by 3,4-difluoronitrobenzene (3.39 g) and the mixture heated to reflux for 18 hours. The solvent is removed and the residue chromatographed (silica; eluting with a gradient increasing in polarity from 0 to 4% methanol in dichloromethane) to give 3-fluoro-4-(4-{2-fluoroethyl}-3-oxopiperazin-1-yl)nitrobenzene.

3-Fluoro-4-(4-{2-fluoroethyl}-3-oxopiperazin-1-yl)nitrobenzene (4.35 g) is dissolved in a mixture of ethyl acetate (250 ml) and DMF (5 ml), and the solution flushed with argon. Palladium (10% on carbon, 200 mg) is added and the mixture hydrogenated under ambient pressure. After gas uptake had ceased, the mixture is filtered through celite and solvent removed. The residue is taken up in ethyl acetate, washed twice with water, dried over magnesium sulfate and the solvent is removed to give 5-amino-2-[4-(2-fluoroethyl)-3-oxopiperazin-1-yl]fluorobenzene which is used without further purification.

5-Amino-2-(4-[2-fluoroethyl]-3-oxopiperazin-1-yl)fluorobenzene (2.6 g) is dissolved in dry dichloromethane (50 ml) under argon. Pyridine (1.03 ml) is added, and the mixture cooled to -20°. Benzyl chloroformate (1.6 ml) is added and the mixture stirred for 10 minutes at -20°, before allowing the temperature to rise to 20-25° over 1.5 hours. The solvents are removed and the residue is dissolved in

dichloromethane and washed with sodium bicarbonate solution. After drying over magnesium sulfate and removal of the solvent, the residue is chromatographed (silica, eluting with a gradient increasing in polarity from 0 to 5% methanol in dichloromethane) to give 5-benzyloxycarbonylamino-2-(4-[2-fluoroethyl]-3-oxopiperazin-1-yl)fluorobenzene.

A solution of lithium *t*-butoxide is prepared by addition of *n*-butyllithium (1.6 M in hexane, 2.9 ml) to a stirred solution of *t*-butanol (0.43 g) in anhydrous THF (10 ml) at -10° under argon. After cooling to -70°, a solution of 5-benzyloxycarbonylamino-2-(4-[2-fluoroethyl]-3-oxopiperazin-1-yl)fluorobenzene (1.5 g) in dry THF (15 ml) is added. After 10 minutes, (R)-glycidylbutyrate (0.67 g) in dry THF (15 ml) is added to the resulting mixture, and stirring continued at -70° for 15 minutes, before allowing the temperature to rise to 20-25° over 16 hours. Methanol (10 ml) is added, followed by saturated sodium bicarbonate solution (20 ml) and water (10 ml). The organic phase is separated and extracted into ethyl acetate (3 x 25 ml), washed with saline and dried over magnesium sulfate. The solvent is removed and the residue purified by chromatography (silica; eluting with a gradient increasing in polarity from 0 to 3% methanol in dichloromethane) to give (5R)-3-(3-fluoro-4-[4-(2-fluoroethyl)-3-oxopiperazin-1-yl]phenyl)-5-hydroxymethyloxazolidin-2-one.

(5R)-3-(3-Fluoro-4-[4-(2-fluoroethyl)-3-oxopiperazin-1-yl]phenyl)-5-hydroxymethyloxazolidin-2-one (0.8 g) is dissolved in pyridine (15 ml) and the mixture cooled to 0°. Triethylamine (0.38 ml) and methanesulfonyl chloride (0.19 ml) are added to the mixture, and stirring continued at 20-25° for 2 hours. The solvent is removed and the residue dissolved in dichloromethane, washed with water, saline, dried over magnesium sulfate and concentrated. The resulting residue is triturated with ether to give (5R)-3-(3-fluoro-4-[4-(2-fluoroethyl)-3-oxopiperazin-1-yl]phenyl)-5-(methanesulfonyloxymethyl)oxazolidin-2-one (0.76 g) which is used without further purification.

(5R)-3-(3-Fluoro-4-[4-(2-fluoroethyl)-3-oxopiperazin-1-yl]-5-(methanesulfonyloxymethyl)oxazolidin-2-one (719 mg) is dissolved in dry DMF (15 ml) and sodium azide (647 mg) is added to the mixture. The mixture is heated at 80° for 6 hrs and then concentrated to dryness. The resulting residue is dissolved in ethyl acetate, washed twice with water, and dried over magnesium sulfate. Removal of the

solvent gives (5R)-5-azidomethyl-3-(3-fluoro-4-(4-(2-fluoroethyl)-3-oxopiperazin-1-yl)phenyl)oxazolidin-2-one (413 mg) which is used without further purification.

(5R)-5-Azidomethyl-3-(3-fluoro-4-[4-(2-fluoroethyl)-3-oxopiperazin-1-yl]phenyl)oxazolidin-2-one (360 mg) is dissolved in dry DMF (20 ml) and the mixture purged with argon. Palladium (10% on carbon, 72 mg) is added, followed by acetic anhydride (0.17 ml) and the mixture stirred at 20-25° under hydrogen confined in a balloon for 3 hr. The mixture is filtered through celite, concentrated to dryness and partitioned between ethyl acetate and water. The organic extract is washed with saline, dried over magnesium sulfate and concentrated. The residue is chromatographed (silica gel; eluting with a gradient increasing in polarity from 0 to 2.5% methanol/dichloromethane). The appropriate fractions are pooled and concentrated to give the title compound.

EXAMPLE 4 (*S*)-N-[[3-[5-(3-Pyridyl)thiophen-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide

(*S*)-N-[[3-[5-(3-Pyridyl)thiophen-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide is known, see US Patent 5,698,574 (Example 124).

EXAMPLE 5 (*S*)-N-[[3-[5-(4-Pyridyl)pyrid-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide hydrochloride

(*S*)-N-[[3-[5-(4-Pyridyl)pyrid-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide hydrochloride is prepared following the general procedure of US Patent 5,627,181 EXAMPLEs 36 and 52 and making non-critical variations but using a 4-pyridinyl adduct.

EXAMPLE 6 Bacterial Keratitis

A 32 year old male presents complaining of eye pain when blinking and b blurred vision. Upon examination the cornea appears subtly less transparent to the physician than normal cornea and may have actual ulcers in its surface. The diagnosis is infectious keratitis of bacterial etiology which is confirmed by laboratory findings. The physician prescribes a 10% solution of (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and instructs the patient to drop 3-5 drops of the solution onto the surface of the eye four times daily for 7 days.

EXAMPLE 7 Bacterial Conjunctivitis

A ten year old female presents complaining of reddened and swollen eyelids and the presence of mucoid secretions on the eye which interfere with vision. The diagnosis is conjunctivitis and the physician prescribes an oxazolidinone solution which contains 12% of (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and instructs the patient to drop 3 drops onto the surface of the eye three times daily for 10 days.

CLAIMS

1. A method of treating an ophthalmic infection in a useful warm blooded mammal who is in need of such treatment which comprises topical administration of an ophthalmologically effective amount of an OXAZOLIDINONE.

2. A method of treating an ophthalmic infection according to claim 1 where the useful warm blooded mammal is a human.

3. A method of treating an ophthalmic infection according to claim 1 where the useful warm blooded mammal is a dog or cat.

4. A method of treating an ophthalmic infection according to claim 1 where the OXAZOLIDINONE is selected from the group consisting of:

(*S*)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

(*S*)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

N-((5*S*)-3-(3-fluoro-4-(4-(2-fluoroethyl)-3-oxopiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl)acetamide,

(*S*)-N-[[3-[5-(3-pyridyl)thiophen-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide and

(*S*)-N-[[3-[5-(4-pyridyl)pyrid-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide hydrochloride.

5. A method of treating an ophthalmic infection according to claim 4 where the OXAZOLIDINONE is selected from the group consisting of:

(*S*)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and

(*S*)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

6. A method of treating an ophthalmic infection according to claim 5 where the OXAZOLIDINONE is:

(S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

7. A method of treating an ophthalmic infection according to claim 1 where the OXAZOLIDINONE is administered in a pharmaceutical formulation selected from the group consisting of a solution, cream, ointment, emulsion, suspension and slow release formulations.

8. A method of treating an ophthalmic infection according to claim 7 where the OXAZOLIDINONE is administered in a pharmaceutical formulation selected from the group consisting of a solution, cream, ointment, emulsion and suspension.

9. A method of treating an ophthalmic infection according to claim 7 where the solution is administered in an insert or treatment fluid container.

10. A method of treating an ophthalmic infection according to claim 1 where the OXAZOLIDINONE is administered from 2 thru 4 times daily.

11. A method of treating an ophthalmic infection according to claim 1 where the ophthalmologically effective amount is from about 0.3% to about 20%.

12. A method of treating an ophthalmic infection according to claim 11 where the ophthalmologically effective amount is from about 0.5% to about 18%.

13. A method of treating an ophthalmic infection according to claim 1 where the infection is caused by *Staphylococci, Streptococci, Enterococci, Bacillus, Corynebacterium, Chlamydia and Neisseria.*

14. A method of treating an ophthalmic infection according to claim 13 where the infection is caused by *Staphylococci, Streptococci and Enterococci.*

15. A method of treating an opthalmic infection according to claim 14 where the infection is caused by *Staphylococci* and *Streptococci.*

16. A method of treating an ophthalmic infection according to claim 1 where the ophthalmic infection is selected from the group consisting of bacterial keratitis, bacterial conjunctivitis and corneal ulcers.

17. A method of treating an ophthalmic infection according to claim 16 where the ophthalmic infection is bacterial keratitis and bacterial conjunctivitis.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 99/12367

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/42 A61K31/44 A61K31/495 A61K31/535

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

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

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VERNIMB G D: "A FURAZOLIDONE AEROSOL POWDER ANTI INFECT IN THE PREVENTION AND TREATMENT OF KERATO CONJUNCTIVITIS IN CATTLE AND SHEEP." VM/SAC, VET. MED. SMALL ANIM. CLIN., (1969) 64 (8), 708-710. , XP002121460 abstract ---	1-3, 7-12,16, 17
X	GEORGE L ET AL: "Topically applied furazolidone or parenterally administered oxytetracycline for the treatment of infectious bovine keratoconjunctivitis." JOURNAL OF THE AMERICAN VETERINARY MEDICAL ASSOCIATION, (1988 MAY 15) 192 (10) 1415-22. , XP002121461 abstract ---	1-3, 7-12,16, 17

-/--

[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" 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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

"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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 November 1999	22/11/1999

Name and mailing address of the ISA	Authorized officer
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	A. Jakobs

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 99/12367

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 45447 A (SCRIPPS RESEARCH INST ;BROOKS PETER (US); CHERESH DAVID A (US); FR) 4 December 1997 (1997-12-04) see compounds 15-18 abstract	1
A	US 5 164 510 A (BRICKNER STEVEN J) 17 November 1992 (1992-11-17) cited in the application the whole document	1-17
A	US 5 565 571 A (BARBACHYN MICHAEL R ET AL) 15 October 1996 (1996-10-15) cited in the application the whole document	1-17
A	US 5 652 238 A (BRICKNER STEVEN J ET AL) 29 July 1997 (1997-07-29) cited in the application the whole document	1-17
A	US 5 688 792 A (BARBACHYN MICHAEL R ET AL) 18 November 1997 (1997-11-18) cited in the application the whole document	1-17
A	US 5 698 574 A (RIEDL BERND ET AL) 16 December 1997 (1997-12-16) cited in the application the whole document	1-17
A	US 5 627 181 A (RIEDL BERND ET AL) 6 May 1997 (1997-05-06) cited in the application the whole document	1-17
A	US 5 231 188 A (BRICKNER STEVEN J) 27 July 1993 (1993-07-27) cited in the application the whole document	1-17

2

INTERNATIONAL SEARCH REPORT

In. ational application No.
PCT/US 99/ 12367

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 1-17 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. [ ] 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:

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-3,7-17 relate to an extremely large number of possible compounds in relation to their use. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. 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. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to substituted or unsubstituted but not ring-fused 2-oxazolidinones, the specifically claimed compounds, and the general idea underlying the present application.

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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/US 99/12367

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9745447 A	04-12-1997	AU 3218397 A	05-01-1998
		AU 3289397 A	05-01-1998
		CN 1226254 A	18-08-1999
		CZ 9803800 A	12-05-1999
		CZ 9803834 A	12-05-1999
		EP 0907661 A	14-04-1999
		EP 0951295 A	27-10-1999
		HU 9901628 A	30-08-1999
		HU 9902099 A	28-09-1999
		NO 985574 A	01-02-1999
		NO 985575 A	01-02-1999
		PL 330240 A	10-05-1999
		PL 330241 A	10-05-1999
		WO 9745137 A	04-12-1997
		CN 1226172 A	18-08-1999
US 5164510 A	17-11-1992	US 5182403 A	26-01-1993
		US 5225565 A	06-07-1993
		AT 112773 T	15-10-1994
		AU 617871 B	05-12-1991
		AU 4195789 A	02-04-1990
		CA 1335103 A	04-04-1995
		DE 68918792 D	17-11-1994
		DK 45591 A	13-03-1991
		EP 0359418 A	21-03-1990
		EP 0434714 A	03-07-1991
		EP 0609905 A	10-08-1994
		HK 1002234 A	07-08-1998
		JP 11080139 A	26-03-1999
		JP 2865211 B	08-03-1999
		JP 4500665 T	06-02-1992
		KR 138262 B	15-05-1998
		WO 9002744 A	22-03-1990
US 5565571 A	15-10-1996	US 5801246 A	01-09-1998
		US 5654428 A	05-08-1997
		US 5756732 A	26-05-1998
		US 5654435 A	05-08-1997
		US 5929248 A	27-07-1999
		AT 146783 T	15-01-1997
		AU 667198 B	14-03-1996
		AU 2689892 A	07-06-1993
		CA 2119556 A	13-05-1993
		DE 69216251 D	06-02-1997
		DE 69216251 T	15-05-1997
		DK 610265 T	09-06-1997
		EP 0610265 A	17-08-1994
		GR 3022340 T	30-04-1997
		JP 7500603 T	19-01-1995
		WO 9309103 A	13-05-1993
US 5652238 A	29-07-1997	AT 182142 T	15-07-1999
		AU 698699 B	05-11-1998
		AU 8010394 A	13-06-1995
		CA 2174107 A	01-06-1995
		CN 1135752 A	13-11-1996
		DE 69419523 D	19-08-1999
		EP 0730591 A	11-09-1996

INTERNATIONAL SEARCH REPORT

information on patent family members

Interr ıal Application No
PCT/US 99/12367

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5652238 A		ES 2133588 T	16-09-1999
		JP 9505582 T	03-06-1997
		NZ 274966 A	26-01-1998
		WO 9514684 A	01-06-1995
		ZA 9407885 A	09-04-1996
US 5688792 A	18-11-1997	US 5880118 A	09-03-1999
		AU 687866 B	05-03-1998
		AU 7557094 A	27-03-1995
		EP 0717738 A	26-06-1996
		JP 9502436 T	11-03-1997
		NZ 271805 A	26-02-1998
US 5698574 A	16-12-1997	DE 4425613 A	25-01-1996
		AU 695661 B	20-08-1998
		AU 2498895 A	01-02-1996
		BG 99791 A	30-04-1996
		CA 2154026 A	21-01-1996
		CN 1121919 A	08-05-1996
		CZ 9501873 A	14-02-1996
		EP 0693491 A	24-01-1996
		FI 953476 A	21-01-1996
		HR 950391 A	30-06-1997
		HU 74003 A	28-10-1996
		IL 114622 A	14-07-1999
		JP 8053443 A	27-02-1996
		NO 952866 A	22-01-1996
		NZ 272596 A	24-03-1997
		PL 309685 A	22-01-1996
		SG 33428 A	18-10-1996
		SK 91695 A	07-02-1996
		ZA 9506015 A	22-02-1996
US 5627181 A	06-05-1997	DE 4425612 A	04-04-1996
		AU 699940 B	17-12-1998
		AU 2498595 A	01-02-1996
		BG 99790 A	30-04-1996
		CA 2154025 A	21-01-1996
		CN 1119647 A	03-04-1996
		CZ 9501872 A	14-02-1996
		EP 0694543 A	31-01-1996
		FI 953477 A	21-01-1996
		HR 950408 A	30-04-1997
		HU 75035 A	28-03-1997
		JP 8041056 A	13-02-1996
		NO 952865 A	22-01-1996
		NZ 272597 A	29-01-1997
		PL 309686 A	22-01-1996
		SG 33427 A	18-10-1996
		SK 91795 A	07-02-1996
		US 5843967 A	01-12-1998
		ZA 9506018 A	13-03-1996
US 5231188 A	27-07-1993	US 5247090 A	21-09-1993
		AT 133417 T	15-02-1996
		AU 630768 B	05-11-1992
		AU 6724690 A	13-06-1991
		CA 2066191 A	18-05-1991

INTERNATIONAL SEARCH REPORT

information on patent family members

Interr nal Application No
PCT/US 99/12367

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5231188 A		DE 69025071 D	07-03-1996
		DE 69025071 T	13-06-1996
		DK 500686 T	10-06-1996
		EP 0500686 A	02-09-1992
		GR 3019605 T	31-07-1996
		HK 1002704 A	11-09-1998
		JP 5501553 T	25-03-1993
		WO 9107409 A	30-05-1991