SCHEDULING STATUS
Schedule 4

PROPRIETARY NAME AND DOSAGE FORM
ZYMAR® eye drops (ophthalmic solution)

COMPOSITION
Each ml contains 3 mg gatifloxacin (0,3 % m/v)
Preservative: benzalkonium chloride 0,005 % m/v

PHARMACOLOGICAL CLASSIFICATION
A 15.1. Ophthalmic preparations with antibiotics and/or sulphonamides

PHARMACOLOGICAL ACTION
Microbiology
Gatifloxacin is an 8-methoxyfluoroquinolone with a 3-methylpiperazinyl substituent at C7. The antibacterial action of gatifloxacin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of chromosomal DNA during bacterial cell division.

Resistance to gatifloxacin *in vitro* develops via multiple-step mutations. The most common reported species showing resistance are methicillin resistant *Staphylococcus aureus* (0-54 %), *Pseudomonas aeruginosa* (0-13 %), *Enterobacteriaceae* (0-3,4 %) and coagulase negative *Staphylococci* sp. (0-8 %).

Gatifloxacin has been shown to be active against most strains of the following organisms both *in vitro* and clinically, in conjunctival infections as described in the indications section. *In vitro* activity does not necessarily imply *in vivo* activity.

Aerobes, Gram-Positive
Corynebacterium propinquum, Staphylococcus aureus* (variable sensitivity), *Staphylococcus epidermidis, Streptococcus mitis*, Streptococcus pneumoniae.*

Aerobes, Gram-Negative
Haemophilus influenzae

* Efficacy for this organism was studied in fewer than 10 infections.

Clinical studies
In a randomised double-blind, multicentre clinical trial, where patients were dosed for 5 days, gatifloxacin solution was superior to its vehicle on day 5-7 in patients with

conjunctivitis and positive conjunctival cultures. Clinical outcomes for the trial demonstrated clinical cure of 77 % (40/52) for the gatifloxacin treated group versus 58 % (28/48) for the placebo treated group.

Microbiological outcomes for the same clinical trial demonstrated a statistically superior eradication rate for causative pathogens of 92 % (48/52) for gatifloxacin vs. 72 % (34/48) for placebo. Please note that microbiological eradication does not always correlate with clinical outcome in anti-infective trials.

Pharmacokinetics
Gatifloxacin ophthalmic solution 0,3 % or 0,5 % was administered to one eye of 6 healthy male subjects each in an escalated dosing regimen starting with a single 2 drop dose, then 2 drops 4 times daily for 7 days and finally 2 drops 8 times daily for 3 days.

At all time points, serum gatifloxacin levels were below the lower limit of quantification (5 ng/ml) in all subjects.

INDICATIONS
ZYMAR® solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

Aerobic Gram-Positive bacteria
Corynebacterium propinquum, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus mitis*, Streptococcus pneumoniae.*

Aerobic Gram-Negative bacteria
Haemophilus influenzae

* Efficacy for this organism was studied in fewer than 10 infections.

CONTRA-INDICATIONS
ZYMAR® solution is contra-indicated in patients with a history of hypersensitivity to gatifloxacin, to other quinolones, or to any of the components in this medication.

WARNINGS AND SPECIAL PRECAUTIONS
NOT SUITABLE FOR INJECTION.
ZYMAR® solution should not be injected subconjunctivally, nor should it be introduced directly in the anterior chamber of the eye.

As the possibility of adverse effects on the corneal permeability, and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations, cannot be excluded, regular ophthalmological

examination is required. Caution should be exercised in the use of benzalkonium chloride preserved topical medication over an extended period in patients with extensive ocular surface diseases.

In patients receiving systemic quinolones, including gatifloxacin, serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial oedema), airway obstruction, dyspnoea, urticaria, and itching.

There have been reports of Steven-Johnson Syndrome and anaphylactic reaction reported in associated with topical gatifloxacin use. If a rash or an allergic reaction to gatifloxacin occurs, discontinue the medicine and contact your doctor. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

Prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs discontinue use and institute alternative therapy. Whenever clinical judgement dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis. ZYMAR® contains the preservative benzalkonium chloride, which may be absorbed by and cause discolouration of soft contact lenses. Patients wearing soft (hydrophilic) contact lenses should be instructed to remove contact lenses prior to administration of ZYMAR® and wait at least 15 minutes following administration before reinserting soft contact lenses.

Patients should be instructed to avoid allowing the tip of the bottle to contact the eye or surrounding structures, fingers, or any other surface.

Paediatric use
Safety and effectiveness in infants below the age of one year have not been established.

Geriatric use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

Effects on the ability to drive and use machines
If transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

INTERACTIONS

Specific medicine interaction studies have not been conducted with ZYMAR® ophthalmic solution. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, and enhance the effects of the oral anticoagulant warfarin and its derivatives, and has been associated with transient elevations in serum creatinine in patients receiving systemic cyclosporine concomitantly.

PREGNANCY AND LACTATION

Because there are no adequate and well-controlled studies in pregnant women, ZYMAR® solution should not be used during pregnancy.

Nursing mothers: It is not known whether this medicine is excreted in human milk. ZYMAR® should not be used by nursing mothers.

DOSAGE AND DIRECTIONS FOR USE

The recommended dosage regimen for the treatment of bacterial conjunctivitis is:
Days 1 and 2: Instil one drop every two hours in the affected eye(s) while awake, up to 8 times daily.
Days 3 through 7: Instil one drop up to four times daily while awake.

SIDE EFFECTS

For each indication the frequency of adverse reactions arising from clinical experience is given as follows: Very common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1 000, <1/100); Rare (≥1/10 000, <1/1 000); Very rare (<1/10 000).

Eye disorders
Very common: Conjunctivitis NEC[1]
Common: Punctate keratitis, papillary conjunctivitis, increased lacrimation, conjunctival disorder NOS[2], eyelid oedema, reduced visual acuity, red eye, eye irritation, eye pain, eye discharge, dry eye NEC[1], conjunctival haemorrhage.
Uncommon: Chemosis

Skin and subcutaneous tissue disorders
Common: Erythema NEC[1]
Uncommon: Contact dermatitis

Gastrointestinal disorders
Common: Taste disturbance

Nervous system disorders
Common: Headache NOS[2]

[1] NEC = not elsewhere classified
[2] NOS = not otherwise specified

Post-marketing experience
The following adverse reactions have been identified during post-marketing use of ZYMAR® in clinical practice. Because post-marketing reporting of these reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions. The reactions have been chosen for inclusion due to a combination of the frequency of reporting and possible causal connection to ZYMAR®.

Eye disorders
Blepharitis, conjunctival/ocular hyperaemia, blurred vision, eye pruritus, eye swelling (including corneal and conjunctival oedema), eye irritation, eye pain

Gastrointestinal disorders
Nausea

Immune system disorders
Hypersensitivity, anaphylactic reactions and angioedema (including pharyngeal, oral or facial oedema)

Respiratory, thoracic and mediastinal disorders
Dyspnoea

Skin and subcutaneous tissue disorders
Pruritus (including generalised pruritus), rash, urticaria

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
See SIDE EFFECTS. Treatment is symptomatic and supportive.

IDENTIFICATION
ZYMAR® is a sterile, clear, pale yellow coloured solution.

PRESENTATION
ZYMAR® (gatifloxacin ophthalmic solution) is supplied sterile in a white, low density polyethylene (LDPE) bottle with a controlled dropper tip and a beige, high impact polystyrene (HIPS) cap in the following pack size: 5 ml in an 8 ml bottle.

STORAGE INSTRUCTIONS
Store below 25 ºC. Do not freeze. KEEP OUT OF REACH OF CHILDREN.

Do not use more than 30 days after opening. Discard any unused portion.

REGISTRATION NUMBER
A39/15.1/0367

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
Allergan Pharmaceuticals (Pty) Ltd
30 New Road (entrance off Bavaria Road)
Randjespark Ext. 11, Midrand, 1682
Johannesburg, Gauteng
SOUTH AFRICA

DATE OF PUBLICATION OF THE PACKAGE INSERT
Date of registration: 20 October 2006
Date of most recently revised package insert as approved by Council: 20 October 2006