IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0290/069/002
Case No: 2069252

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Alcon Laboratories (UK) Ltd

Pentagon Park, **Boundary Way**, **Hemel Hempstead**, **Hertfordshire HP2 7UD**, **England**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Ciloxan 3 mg/g Eye Ointment

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **24/02/2010**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ciloxan 3 mg/g Eye Ointment

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ciprofloxacin hydrochloride equivalent to 3 mg/g ciprofloxacin
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye ointment
White to off-white eye ointment.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

CILOXAN Eye Ointment will be indicated for adults and children a follows:
Adults and Children 1 year and above

Ciloxan 3mg/g Eye Ointment is indicated for treatment of bacterial conjunctivitis in patients, who are resistant to other antibiotics.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Adults and Children 1 year and above

The recommended dosage regimens for adults is:
- Bacterial conjunctivitis: 1.25 cm ribbon applied into the conjunctival sac three times daily for two days, then twice daily for a further five days.
- Do not touch tube tip to any surface, as this may contaminate the contents.

Use in hepatic and renal impairment
No studies have been performed using CILOXAN 3 mg/g Eye Ointment in patients with kidney or liver problems.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Hypersensitivity to quinolones.

4.4 Special warnings and precautions for use

There is no experience in children less than 1 year old.

CILOXAN 3 mg/g Eye Ointment should be administered under the supervision of a specialist ophthalmology service, having the facilities for regular monitoring of clinical and microbiological effects during and after administration.

When using CILOXAN eye ointment one should take into account the risk of a rhinopharyngeal passage which can contribute to the occurrence and the diffusion of bacterial resistance.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, were observed in patients receiving treatment based on systematically administered quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions.

As with all antibacterial preparations prolonged use may lead to overgrowth of non-susceptible bacterial strains or fungi. If superinfection occurs, appropriate therapy should be initiated.

Likewise CILOXAN 3mg/g Eye Ointment should be suspended immediately at the first appearance of a skin rash or any other sign of hypersensitivity reaction and medical advice should be sought.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

Pregnancy
For CILOXAN 3 mg/g Eye Ointment no clinical data from well-controlled studies in pregnant women are available.

Animal studies do not indicate direct or indirect harmful effects with respect to fertility and embryonic / foetal development. Studies in rabbits have shown an increased risk of abortion due to maternal weight loss. The relevance of these data for humans is unknown *(see section 5.3).*

In animal studies, systemic doses of ciprofloxacin cause joint or tendon connective tissue disorders in immature animal, as do other drugs of this series.

CILOXAN 3 mg/g Eye Ointment should not be used during pregnancy unless clearly necessary and only if the potential benefit justifies the potential risk to the foetus.

Women of child-bearing potential
No special recommendations for women of childbearing potential.

Lactation
It is not known whether topically applied ciprofloxacin is excreted in human milk. It crosses the placenta and is excreted in breast milk and amniotic fluid in animal studies.
Caution should be exercised when CILOXAN 3 mg/g Eye Ointment is administered to a nursing mother.

Fertility
No special recommendations *(see section 5.3).*

4.7 Effects on ability to drive and use machines

As with any ocular medication, if transient, blurred vision occurs at application, the patient should wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

In clinical trials with CILOXAN 3 mg/g Eye Ointment, the following treatment related signs and symptoms were reported:

Common

Ocular: White precipitate (3.0%) and ocular discomfort (transient stinging and burning upon application) (1.4%). In patients with corneal ulcer or frequent administration of the drug, white precipitates have been observed which resolved after continuous application of CILOXAN 3 mg/g Eye Ointment. The precipitate does not preclude continued use of CILOXAN 3 mg/g Eye Ointment nor does it adversely affect the clinical course of the recovery process.

Uncommon

Ocular effects: Blurred vision (0.8%), hyperaemia (0.7%), pruritus (0.6%), decreased visual acuity (0.6%), pain (0.6%), tearing (0.4%), and photophobia (0.3%).

Special senses effects: Taste perversion (metallic taste) (0.5%).

Skin Effects: Dermatitis (0.2%).

With locally applied fluoroquinolones (generalized) rash, toxic epidermolysis, dermatitis exfoliative, Stevens-Johnson syndrome and urticaria occur very rarely

Safety and effectiveness of CILOXAN 3mg/g eye ointment were determined in 103 children between the ages of one and 12 years of age. No serious adverse drug reaction was reported in these patients.

4.9 Overdose

A topical ocular overdose of CILOXAN 3 mg/g Eye Ointment may be rinsed from the eye(s) with lukewarm tap water.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-infectives; Other anti-infectives.
ATC code: S01AX13

Ciprofloxacin has *in vitro* activity against a range of Gram-positive and Gram-negative organisms. The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase that is needed for the synthesis of bacterial DNA.

Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least
some types of infections is questionable.

Category 1-Commonly susceptible species

Ciprofloxacin has been shown to be active against most strains of the following organisms; an asterisk denotes species against which it is considered that ciprofloxacin activity has been satisfactorily demonstrated in clinical studies; no asterisk indicates that the clinical significance of these data in ophthalmic infections is unknown:

Aerobic Gram-Positive Microorganisms:	Ciprofloxacin Breakpoint [a,b]
***Staphylococcus aureus**	≤1 / >1
***Staphylococcus epidermidis**	≤1 / >1
***Staphylococcus spp.,** other coagulase-negative spp**.**	≤1 / >1
***Corynebacterium** spp.	≤1
***Streptococcus pneumoniae**	≤0.125/ >2
***Streptococcus,** *Viridans group*	≤1
Bacillus species	≤1
Staphylococcus haemolyticus	≤1 / >1
Staphylococcus hominis	≤1 / >1
Aerobic Gram-Negative Microorganisms:	
***Acinetobacter spp.**	≤1/>1
***Haemophilus influenzae**	≤0.5/ >0.5
***Pseudomonas aeruginosa**	≤0.5/ >1
***Moraxella spp.** (including *M.* [*Branhamella*] *catarrhalis*)	≤0.5/ >0.5
Acinetobacter calcoaceticus	≤1
Enterobacter aerogenes	≤1
Escherichia coli	≤1
Haemophilus parainfluenzae	≤1
Klebsiella pneumoniae	≤1
Neisseria gonorrhoeae	≤1
Proteus mirabilis	≤1
Proteus vulgaris	≤1
Serratia marcescens	≤1
Anaerobic Microorganisms:	
Peptococcus spp.	≤1
Peptostreptococcus spp.	≤1
Propionibacterium acnes	≤1
Clostridium pefringens	≤1

[a] S≤R> denotes EUCAST Clinical MIC Breakpoints

[b] Breakpoints apply to systemic use and may not be applicable due to the local concentrations and physicochemical conditions that apply to activity of ciprofloxacin applied topically in the eye.

Category 2-Species for which acquired resistance may be a problem

Aerobic Gram-Positive Microorganisms:
Staphylococcus haemolyticus

Category 3-Inherently Resistant Organisms

Aerobic Gram-Negative Microogramisms:
Burkholderia (*Pseudomonas*) *cepacia*
Stenotrophomonas (*Pseudomonas*) *maltophilia*
Bacteroides fragilis

Other Information:
Ciprofloxacin does not cross-react with other antimicrobial agents such as beta-lactams or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin.
Bacterial susceptibility studies demonstrate that most microorganisms resistant to ciprofloxacin are resistant to the other ophthalmic quinolones as well.

5.2 Pharmacokinetic properties

Absorption studies in humans with the ointment have not been conducted. Two systemic absorption studies were performed with CILOXAN 3 mg/ml Eye Drops using the conjunctivitis or corneal ulcer dosing regimen. In the study involving the more intensive dosing regimen (i.e., corneal ulcer/abscess indication), two drops were administered in one eye every 15 minutes for six hours, every 30 minutes for 18 hours, then two drops hourly for one day, followed by two drops every four hours for five additional days. In each study, the maximum reported plasma concentration of ciprofloxacin was less than 5 ng/ml. The mean concentrations in each of the studies were less than 2.5 ng/ml.

There are no pharmacokinetic data available in respect of use in children.

5.3 Preclinical safety data

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested following oral administration. The degree of cartilage involvement was found to be dependent on age, specieis and dosage. With 30mg/kg ciprofloxacin the effect on the joint was minimal.

A one month topical ocular study with ciprofloxacin 3mg/ml eye drops, solution in immature beagle dogs did not demonstrate any articular lesions. Likewise there is no evidence that the ophthalmic dosage form has any effect on the weight bearing joints.

In 634 children treated orally with ciprofloxacin, clinical and radiological monitoring did not reveal any skeletal toxicity.

Reproduction studies have been performed in rats and mice at doses up to six times the usual daily human oral does and have revealed no evidence of impaired fertility or harm to the foetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg oral) produced gastrointestinal disturbances resulting in material weight loss and an increased incidence or abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced and no embryotoxicity or teratogenicity was observed.

It is known that orally administered ciprofloxacin is excreted in the milk of lactating rats, and oral ciprofloxacin has been reported in human breast milk after a single 500 mg dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid Paraffin
White Soft Paraffin

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years

4 weeks after first opening.

6.4 Special precautions for storage

Do not store above 30º C.

6.5 Nature and contents of container

Epoxy-phenolic lined aluminium tube with polyethylene nozzle and HDPE screw cap.
The tube contains 3.5g of eye ointment.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Alcon Laboratories (UK) Limited,
Pentagon Park,
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8 MARKETING AUTHORISATION NUMBER

PA 0290/069/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of fist authorisation: 05 November 2004
Date of next renewal: 05 November 2009

10 DATE OF REVISION OF THE TEXT

February 2010