SCHEDULING STATUS
Schedule 4

PROPRIETARY NAME AND DOSAGE FORM
EXOCIN® Ophthalmic Solution (Eye Drops)

COMPOSITION
EXOCIN® Ophthalmic Solution contains:
Ofloxacin 3,0 mg/ml
Preservative: Benzalkonium chloride 0,005 % m/v
Other ingredients are sodium chloride and purified water.

PHARMACOLOGICAL CLASSIFICATION
A. 15.1 Ophthalmic preparations with antibiotics.

PHARMACOLOGICAL ACTION
Pharmacodynamic properties
Ofloxacin is a synthetic fluorinated 4-quinolone antibacterial agent with activity against a broad spectrum of Gram-negative, and to a lesser degree, Gram-positive organisms.

Ofloxacin is bacteriocidal at concentrations equal to or slightly greater than inhibitory concentrations.

The primary mechanism of action is through inhibition of bacterial DNA gyrase, the enzyme responsible for maintaining the structure of DNA.

Ofloxacin possesses an additional bacteriocidal mechanism, which is not dependent on protein or RNA synthesis. It is bacteriocidal in both replicating and non-replicating stages of bacterial growth.

Cross-resistance has been observed between ofloxacin and other fluoroquinolones.

The safety and effectiveness of ofloxacin in treating ophthalmologic infections due to the following microorganisms have not been established in adequate and well-controlled clinical trials:
Aerobes, Gram-Positive
Enterococcus faecalis       Streptococcus mitis
Listeria monocytogenes      Staphylococcus simulans
Staphylococcus capitis      Staphylococcus hominus
Streptococcus pyogenes

Aerobes, Gram-Negative
Acinetobacter calcoaceticus var. anitratum    Klebsiella pneumonia
Acinetobacter calcoaceticus var. wolffii      Moraxella (branhameila) catarrhalis
Citrobacter diversus             Moraxella lacunata
Citrobacter freundii             Morganella morganii
Enterobacter aerogenes             Neisseria gonorrhoeae
Enterobacter agglomerans          Pseudomonas acidovorans
Escherichia coli                 Pseudomonas fluorescens
Haemophilus parainfluenzae        Shigella sonnei
Klebsiella oxytoca

Other
Chlamydia trachomatis

Pharmacokinetic properties
Systemic absorption of ofloxacin was detected following ocular administration. In man, the systemic absorption of ofloxacin was in the low ng/ml range.

After ophthalmic instillation, ofloxacin is well maintained in the tear film.

In a healthy volunteer study, mean tear film concentrations of ofloxacin measured four hours after topical dosing (9.2 μg/g) were higher than the 2 μg/g minimum concentration of ofloxacin necessary to inhibit 90 % of most ocular bacterial strains (MIC<sub>90</sub>) in vitro.

INDICATIONS
EXOCIN® is indicated for the topical treatment of external ocular infections caused by ofloxacin susceptible bacteria.

CONTRAINDICATIONS
EXOCIN® is contraindicated in patients hypersensitive to ofloxacin or any of its components. Since systemic quinolones have been shown to cause arthropathy in immature animals, it is recommended that EXOCIN® not be used by pregnant or lactating women (see ‘PREGNANCY AND LACTATION’). Safety and effectiveness in infants
below the age of one year have not been established (see ‘WARNINGS AND SPECIAL PRECAUTIONS’).

**WARNINGS AND SPECIAL PRECAUTIONS**

EXOCIN® is not for injection.

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

If an allergic reaction to EXOCIN® occurs, discontinue the product and contact your physician. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated. Use EXOCIN® with caution in patients who have exhibited sensitivities to other quinolone antibacterial agents.

When using EXOCIN® eye drops the risk of rhinopharyngeal passage, which can contribute the occurrence and the diffusion of bacterial resistance, should be considered. Prolonged use may result in overgrowth of non-susceptible organisms. If superinfection occurs, or if clinical improvement is not noted within a reasonable period, discontinue use and institute appropriate therapy.

Stevens-Johnson syndrome, toxic epidermal necrolysis and anaphylactic reaction/shock have been reported in patients receiving EXOCIN®.

Corneal precipitates, and corneal perforation in patients with pre-existing corneal epithelial defect or corneal ulcer, have been reported during treatment with EXOCIN®.

Long-term, high-dose use of fluoroquinolones in experimental animals has caused lenticular opacities. However, this effect has not been reported in human patients.

EXOCIN® contains the preservative benzalkonium chloride, which may cause eye irritation.

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 ophthalmic 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 disease.

The use of EXOCIN® while wearing soft contact lenses is not recommended. Benzalkonium chloride may be absorbed by soft contact lenses and discolour them. Contact lenses should be removed prior to installation and may be reinserted 15 minutes following administration.

**Geriatric use**
No comparative data are available with topical dosing in the elderly versus other age groups.

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

The use of EXOCIN® eye drops in neonates with ophthalmia neonatorum caused by *Neisseria gonorrhoeae* or *Chlamydia trachomatis* is not recommended as it has not been evaluated in such patients. Neonates with ophthalmia neonatorum should receive appropriate treatment for their condition, e.g. systemic treatment in cases caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

Ofloxacin have been shown to cause arthropathy in immature animals after oral administration; however, topical ocular administration of EXOCIN® to immature animals has not shown any arthropathy (see ‘CONTRAINDICATIONS’).

**Effects on the ability to drive and use machines**
Transient blurring of vision may occur on instillation of eye drops. Do not drive or operate hazardous machinery unless vision is clear.

**INTERACTIONS**
It has been shown that the systemic administration of some quinolones inhibits the metabolic clearance of caffeine and theophylline. Interaction studies conducted with systemic ofloxacin have demonstrated that metabolic clearance of caffeine and theophylline are not significantly affected by ofloxacin.

Although there have been reports of an increased prevalence of central nervous system toxicity with systemic dosing of fluoroquinolones when used concomitantly with systemic non-steroidal anti-inflammatory drugs (NSAIDs), this has not been reported with the concomitant systemic use of NSAIDs and ofloxacin.

No interaction studies with EXOCIN® have been performed.
PREGNANCY AND LACTATION

Pregnancy
Since systemic quinolones have been shown to cause arthropathy in immature animals, it is recommended that EXOCIN® not be used in pregnant women (see ‘CONTRAINDICATIONS’).

Lactation
Ofloxacin and other quinolones are excreted in breast milk, therefore there is a potential for harm to nursing infants. EXOCIN® is not recommended for breastfeeding women and temporary discontinuation of breastfeeding should be considered (see ‘CONTRAINDICATIONS’).

DOSAGE AND DIRECTIONS FOR USE

The recommended dosage for the treatment of bacterial conjunctivitis is:
One drop every two to four hours for the first two days, then four times daily in the affected eye(s).
Treatment should not exceed ten days.

The recommended dosage regimen for the treatment of bacterial corneal ulcer is:
Days 1 and 2: Instil one to two drops into the affected eye every 30 minutes, while awake. Awaken at approximately four and six hours after retiring and instil one to two drops.
Days 3 through 7 to 9: Instil one or two drops hourly, while awake.
Days 7 to 9 through treatment completion: Instil one to two drops, four times daily.

SIDE EFFECTS

General
Since a small amount of EXOCIN® is systemically absorbed after topical administration, adverse events reported with systemic use could possibly occur.

Nervous system disorders
Frequency unknown: Dizziness

Eye disorders
Frequent: Eye irritation, ocular discomfort
Frequency unknown: Keratitis, conjunctivitis, vision blurred, photophobia, eye oedema, foreign body sensation in eyes, lacrimation increased, dry eye, eye pain, eye pruritus, eyelids pruritus, ocular hyperaemia, periorbital oedema (including eyelid oedema)
Gastrointestinal disorders
Nausea

Skin and subcutaneous tissue disorders
Frequency unknown: Stevens-Johnson syndrome

Immune system disorders
Frequency unknown: Hypersensitivity reactions, anaphylactic reactions (such as angioedema, dyspnea, anaphylactic shock, oropharyngeal swelling and tongue swollen) and allergic dermatitis

General disorders and administrative site conditions
Frequency unknown: Facial oedema

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
In the event of accidental ingestion of 10 ml of EXOCIN®, 30 mg of ofloxacin would be ingested. This amount does not appear to be clinically significant in terms of overdosage. However, there would be an increased potential for systemic reactions (see ‘WARNINGS AND SPECIAL PRECAUTIONS’).

In the event of a topical overdosage, flush the eye with a topical ocular irrigant.

Treatment is symptomatic and supportive.

IDENTIFICATION
EXOCIN® is a clear, pale to light yellow-green solution practically free from particulate matter.

PRESENTATION
EXOCIN® is supplied in sterile dropper bottles containing 5 ml solution.

STORAGE INSTRUCTIONS
Store at or below 25 °C. Do not use more than 30 days after opening.
KEEP OUT OF REACH OF CHILDREN.

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DATE OF PUBLICATION OF THE PACKAGE INSERT
Date of registration: 9 August 1994
Date of most recent package insert as approved by Council: 11 October 2013