Summary of Product Characteristics

1. NAAM VAN HET GENEESMIDDEL

Ofloxacine Devatis 3 mg/ml, oogdruppels, oplossing, Verpakking voor éénmalig gebruik

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 3 mg ofloxacin in a preservative free formulation.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FROM

Eye drop solution in single-dose container for administration by instillation in the conjunctival sac.
Clear, pale light yellow solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ofloxacine Devatis is indicated for the topical treatment of external ocular infections (such as conjunctivitis and keratitis) in adults and children caused by ofloxacin - sensitive organisms.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Ocular use

Posology
Instillation of one drop of Ofloxacine Devatis in the conjunctival sac of the affected eye(s) every two to four hours for the first two days, followed by four times daily.

The length of treatment should not exceed 14 days.

Paediatric population
No dose adjustment is necessary.

Elderly population
No dose adjustment is necessary (see section 4.4).

Method of administration
Patients should be instructed to avoid contact between the tip of the **single-dose** container and the eyes or areas around the eyes.

The solution from one individual single-dose container of Ofloxacine Devatis is to be used immediately after opening since sterility cannot be maintained after the individual single-dose container is opened.

If another topical agent is being used, Ofloxacine Devatis and the other agent should be administered at least 15 minutes apart. Eye ointments should always be applied at last.

4.3 Contraindications

- Hypersensitivity to the active substance, any other quinolones or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

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

If an allergic reaction occurs, treatment should be discontinued. Use ofloxacin containing eye drops with caution in patients who have exhibited sensitivities to other quinolones antibacterial agents.

Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including ofloxacin, particularly in older patients and those treated concurrently with corticosteroids. Therefore, caution should be exercised and treatment with Ofloxacin Devatis should be discontinued at the first sign of tendon inflammation (see section 4.8).

When using ofloxacin containing eye drops the risk of rhinopharyngeal passage which can contribute to the occurrence and the diffusion of bacterial resistance should be considered. As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms.

If worsening infection occurs, or if clinical improvement is not noted within a reasonable period, discontinue use and institute alternative therapy.

Data are very limited to establish efficacy and safety of ofloxacin eye drops 0.3% in the treatment of conjunctivitis in neonates.
The use of ofloxacin 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.

Clinical and non-clinical publications have reported the occurrence of corneal perforation in patients with pre-existing corneal epithelial defect or corneal ulcer, when treated with topical fluoroquinolone antibiotics. However, significant confounding factors were involved in many of these reports, including advanced age, presence of large ulcers, concomitant ocular conditions (e.g. severe dry eye), systemic inflammatory diseases (e.g. rheumatoid arthritis), and concomitant use of ocular steroids or non-steroidal anti-inflammatory drugs. Nevertheless, it is necessary to advise caution regarding the risk of corneal perforation when using product to treat patients with corneal epithelial defects or corneal ulcers.

Corneal precipitates have been reported during treatment with topical ophthalmic ofloxacin. However, a causal relationship has not been established.

Sun or UV-exposition should be avoided during use of ofloxacin due to the potential for photosensitivity.

Use of contact lenses is not recommended in patients receiving treatment for an eye infection.

4.5 Interactions with other medicinal products and other forms of interaction

It has been shown that the systemic administration of some quinolones inhibits the metabolic clearance of caffeine and theophylline. Drug interactions 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 CNS toxicity with systemic dosing of fluoroquinolones when used concomitantly with systemic nonsteroidal anti-inflammatory drugs (NSAIDs), this has not been reported with the concomitant systemic use of NSAIDs and ofloxacin.

4.6 Fertility, pregnancy and lactation

Pregnancy:
There have been no adequate and well-controlled studies performed in pregnant women. Since systemic quinolones have been shown to cause arthropathy in immature animals, it is recommended that ofloxacin not be used in pregnant women.

Breast-feeding:
Because ofloxacin and other quinolones taken systemically are excreted in breast milk, and there is potential for harm to nursing infants, a decision should be made whether to temporarily discontinue nursing or not to administer the drug, taking into account the importance of the drug to the mother.

Fertility:
Ofloxacin had no influence on fertility in rats (see section 5.3).

4.7 Effects on the ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Transient blurring of vision may occur on instillation of eye drops. Do not drive or operate hazardous machinery unless vision is clear.

4.8 Undesirable effects

General
Serious reactions after use of systemic ofloxacin are rare and most symptoms are reversible. Since a small amount of ofloxacin is systemically absorbed after topical administration, side-effects reported with systemic use could possibly occur.

The following categories have been used for classification of the frequency of undesirable effects:

Very common	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1,000 to <1/100)
Rare	(≥1/10,000 to <1/1,000)
Very rare	(<1/10,000)
Not known	(cannot be estimated from the available data)

Immune System Disorders
Very rare: Hypersensitivity (including angioedema, dyspnoea, anaphylactic reaction/shock, oropharyngeal swelling and tongue swollen)

Nervous System Disorders
Not known: Dizziness

Eye Disorders

Common: Eye irritation; Ocular discomfort
Not known: Keratitis; Conjunctivitis; Vision blurred; Photophobia; Eye oedema; Periorbital oedema (including eyelid oedema), Foreign body sensation in eyes; Lacrimation increased; Dry eye; Eye pain; Ocular hyperaemia; Hypersensitivity (including Eye pruritus and Eyelids pruritus)

Gastrointestinal Disorders
Not known: Nausea

Skin and Subcutaneous Tissue Disorders
Not known: Facial oedema, Stevens-Johnson-syndrome, Toxic epidermal necrolysis

Additional adverse reactions that have been seen with the systemic use of fluoroquinolones, and may potentially occur also with Ofloxacin Devatis:
Ruptures of the shoulder, hand, Achilles, or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving systemic fluoroquinolones. Studies and post marketing experience with systemic quinolones indicate that a risk of these ruptures may be increased in patients receiving corticosteroids, especially geriatric patients and in tendons under high stress, including Achilles tendon (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Nederlands Bijwerkingen Centrum Lareb, Website: www.lareb.nl.

4.9 Overdose

No case of overdose has been reported so far.
In the event of a topical overdosage, flush the eye with water.
If systemic side-effects occur following incorrect use or an accidental overdose these are to be treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, antiinfectives, fluoroquinolones, ofloxacin
ATC code: S01AE01

Mode of action
Ofloxacin is a derivative of chinolonic acid and inhibits bacterial DNA gyrase with bactericidal effect.

Mechanisms of resistance
Development of resistance to fluoroquinolones by the sensitive bacteria generally happens by mutation of the gyrA gene that codes for the A subunit of DNA gyrase. In addition, active efflux is responsible for low-level resistance that might act as a first step in resistance selection. Resistance can occur through a multistep process with subsequent mutations producing a progressively higher level of resistance in a stepwise fashion. Species of borderline susceptibility can become resistant in a single mutational step.
Plasmid-mediated resistance has been found in *E. coli* and *Klebsiella* organisms.
Bacteria resistant to one fluoroquinolone show cross-resistance to other members of the quinolone-group.

Breakpoints

In the resistance study mentioned below bacterial isolates were classified as susceptible or resistant in accordance with the recommendations of the European Committee of Antimicrobial Susceptibility Testing (EUCAST). Where established by EUCAST epidemiological cut-off values (ECOFF) were used, otherwise EUCAST clinical breakpoints for systemically administered antibacterial agents were applied:

	susceptible	**resistent**	**ECOFF**
Staphylococcus spp.	≤ 1 mg/l	> 1 mg/l	≤ 1 mg/l
Streptococcus pneumoniae	≤ 0,125 mg/l	> 4 mg/l	≤ 4 mg/l
Haemophilus influenzae	≤ 0,5 mg/l	> 0,5 mg/l	≤ 0,064 mg/l
Moraxella catarrhalis	≤ 0,5 mg/l	> 0,5 mg/l	≤ 0,25 mg/l
Enterobacteriaceae	≤ 0,5 mg/l	> 1 mg/l	≤ 0,25 mg/l
Acintetobacter spp.	ND	ND	≤ 1 mg/l
Pseudomonas aeruginosa	ND	ND	≤ 2 mg/l
Enterococcus faecalis	ND	ND	≤ 4 mg/l
Escherichia coli	≤ 0.5 mg/l	> 1 mg/l	≤ 0.25 mg/l
Klebsiella pneumoniae	≤ 0.5 mg/l	> 1 mg/l	≤ 0.25 mg/l
Klebsiella spp.	≤ 0.5 mg/l	> 1 mg/l	≤ 0.25 mg/l
Serratia spp.	≤ 0.5 mg/l	>1 mg/l	≤ 1 mg/l

Antibacterial spectrum

The antibaterial spectrum of ofloxacin includes obligate anaerobic germs, facultative anaerobic germs, aerobic and other germs like e.g. chlamydia. It has to be assumed that ofloxacin is absorbed after local application but without causing clinical or pathological changes.

Prevalence of acquired resistance can vary locally or in the course of time. Therefore, local information is desirable concerning the resistance situation, above all for the adequate treatment of serious infections. In case of doubts concerning the local prevalence of ofloxacin-resistance, an expert should be consulted.
Especially in severe infections or lack of efficacy a microbiological diagnosis with detection of the pathological germ and its sensitivity to ofloxacin should be done.

Data on the sensitivity in the table show the data of a study on bacterial resistance with 1391 isolates of ocular origin (mainly external swabs) from 31 German centres. The mentioned aerobic germs give a representative impression of the bacteria causing eye infections in Germany. It has to be considered that the distribution of frequencies of ophthalmologically relevant germs is not identical but similar in other countries. Therefore the germs mentioned below will be the most frequent causes of bacterial infections in other countries as well.

Usually sensitive species (rate of resistance ≤ 10 %)
Aerobic gram-positive microorganisms
Staphylococcus aureus (MSSA)
Aerobic gram-negative microorganism
Haemophilus influenzae
Haemophilus parainfluenzae

Enterobacteriaceae (Escherichia coli, Proteus mirabilis, Klebsiella oxytoca, Serratia marcescens, Enterobacter cloacae and Klebsiella pneumoniae
Acinetobacter baumannii
Acinetobacter lwoffii
Moraxella catarrhalis
Species in which acquired resistance can cause problems for the treatment (rate of resistance >10 %)
Aerobic gram-positive microorganisms
Staphylococcus aureus (MRSA)
Streptococcus pneumoniae
Coagulase-negative staphylococci
Enterococcus
Aerobic gram-negative microorganisms
Pseudomonas aeruginosa

5.2 Pharmacokinetic properties

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 2µg/ml minimum concentration of ofloxacin necessary to inhibit 90% of most ocular bacterial strains (MIC90) in-vitro.
Maximum serum ofloxacin concentrations after ten days of topical dosing were about 1000 times lower than those reported after standard oral doses of ofloxacin, and no systemic side-effects attributable to topical ofloxacin were observed.

5.3 Preclinical safety data

There are no toxicological safety issues with this product in man from topical ocular administration at clinically relevant doses.

Several in-vitro- as well as in-vivo-test on the induction of gene - and chromosomal mutations were negative. There are no long-term investigations in animals on carcinogenicity. There are no signs for a cataractogenic or co-cataractogenic effect.

Ofloxacin has no influence on fertility, on the peri- and postnatal development and is not teratogenic. In systemic application of ofloxacin to animals degenerative changes of the articular cartilage were observed. The damage of the articular cartilage was dependent on age and dosage (the younger the animal the bigger was the effect). When used systemically, ofloxacin possesses neurotoxic potential and induces reversible abnormalities in testes at high doses. Like some other quinolones, ofloxacin is phototoxic in animals at exposures in the human therapeutic range when used systemically.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide (E524) (for pH adjustment)
Hydrochloric acid (E507) (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years in the outer packaging.

After opening of the sachet: use the single-dose containers within 28 days.

After opening of the single-dose container: use immediately and discard the single-dose container after use.

6.4 Special precautions for storage

Store in the original package (sachet) in order to protect from light.

For storage conditions of the opened medicinal product, see section 6.3.

6.5 Nature and contents of container

0.5 ml transparent LDPE single-dose containers in PET/aluminium/PE sachets containing 5 single-dose containers each.

Pack-sizes: 10 x 0.5 ml, 20 x 0.5 ml, 30 x 0.5 ml, 50 x 0.5 ml and 60 x 0.5 ml single-dose containers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Devatis GmbH
Spitalstrasse 22
79539 Lörrach
Duitsland

8. NUMMER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 113360

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 5 augustus 2014
Datum van laatste verlenging: 03 juli 2019

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft rubrieken 4.4 en 4.8: 20 november 2019.