SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ottoflox 3 mg/ml ear drops, solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ofloxacin 3 mg/ml.

Excipient(s) with known effect:
Each ml of the solution contains 0.2 mg of benzalkonium chloride (50% solution).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ear drops, solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ottoflox ear drops is indicated for the treatment of ear infections caused by sensitive microorganisms in the specific situations listed below:
Otitis externa in adults and children, over 6 months of age, caused by Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus.
Chronic suppurative otitis media due to Proteus mirabilis, Pseudomonas aeruginosa or Staphylococcus aureus in individuals over 12 years of age with tympanic membrane perforation.
Acute otitis media due to Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa, Staphylococcus aureus or Streptococcus pneumoniae in individuals over 1 year of age with tympanostomy tube.

4.2 Posology and method of administration

Posology

Ottoflox ear drops posology as well as the treatment duration should be established by the physician on a case-by-case.
However, the usual recommended dosage for the treatment of ear infections with Ottoflox ear drops is the following:

Ear disorder	Age	Dosage	Treatment period
Otitis externa	6 months to 13 years	5 drops (0.25 ml) in the affected ear, once a day	7 days
	≥ 13 years	10 drops (0.5 ml) in the affected ear, once a day	

Chronic suppurative otitis media	≥ 12 years	10 drops (0.5 ml) in the affected ear, twice daily	14 days
Acute otitis media	1 to 12 years	5 drops (0.25 ml) in the affected ear, twice daily	10 days

Method of administration

The hands should be washed with water and soap before Ottoflox ear drops is administrated.
If necessary, any discharge that can be removed from the outer ear should be cleaned carefully.
NO OBJECTS OR COTTON BUDS SHOULD BE INSERTED IN THE EAR CANAL.
Prior to administration of Ottoflox ear drops, the solution should be warmed by holding the bottle between the hands for a minute or two to avoid dizziness which may result from the instillation of a cold drop in the ear.
In order to perform the instillation, the individual should tilt the head to one side or, preferably, lie on the side opposite to the affected ear. Afterwards, the drops prescribed in the recommended dosage should be instilled in the affected ear.
The tip of the dropper bottle shouldn't touch the fingers, the ear or other surfaces in order to avoid contamination of the ear drops, solution.

The instructions below should be followed according to the patient's specific ear infection:

Otitis media: After the instillation, gently press the tragus of the ear 4 times to help the drops penetrate the middle ear.
This procedure allows the drops to flow along the ear canal into the middle ear.

Otitis externa: After the instillation of the drops in the ear, gently pull the outer ear upward and backward to help the drops to flow down into the ear canal.

After the administration the head should be maintained tilted or the patient should remain on his/her side for 5 minutes to help the drops penetrate the ear canal.

If both ears are infected, the procedures described above should be repeated in the opposite ear.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Ottoflox is not for injection.

Ofloxacin, like other quinolones, can cause serious, potentially fatal, hypersensitivity reactions, after systemic administration. The individuals receiving Ottoflox ear drops should be advised of the possibility of the occurrence of similar reactions with the topically administered drug and should be instructed to discontinue the treatment and contact their physician at the first sign of rash or any other sign of hypersensitivity.

Treatment should be reevaluated in case of persistence or worsening of symptoms or pathology.

As with other anti-infective preparations, prolonged use may result in over-growth of nonsusceptible microorganisms, including fungi. If the infection is not improved after 10 days it

is necessary to reassess the patient and the treatment.Cultures should be obtained in order to establish the most appropriate therapy. Additionally, if otorrhea persists after a full course of therapy, or if two or more episodes of otorrhea occur within 6 months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumor.

Paediatric population
Safety and efficacy of Ofloxacin ear drops was demonstrated in pediatric patients of the following ages for the indications listed below:
- 6 months and older: otitis externa with intact tympanic membrane.
- 1 year and older: acute otitis media with tympanostomy tubes.
- 12 years and older: chronic suppurative otitis media with tympanic membrane perforation.

Safety and efficacy in pediatric patients below these ages have not been established.
Although no data are available on patients with less than 6 months, there are no know safety concerns or differences in the disease process in this population that will preclude use of this product.
No changes in hearing function were observed on audiometric evaluation in a limited number of children treated with ofloxacin ear drops.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. However, due to the negligible plasma levels observed after auricular use, it is unlikely that ofloxacin may have a clinically significant systemic drug interaction with other drugs.

The combination with other medicinal products for auricular use is not recommended. If it is necessary to administer more than one medicinal product in the ear, it is recommended to administer it separately.

4.6 Fertility, pregnancy and lactation

Pregnancy: There are no adequate and controlled studies using ofloxacin ear drops in pregnant women, and the medicine should be used during pregnancy only when the potential benefits justify the possible risks to the fetus. While quinolones should not be used systemically in pregnant or nursing women because of serious bone toxicity observed in animals, there currently is no evidence of similar toxicity occurring when these drugs are administered topically to the ear.

Lactation: It is not known whether ofloxacin is distributed into milk following topical application to the ear; however, ofloxacin is distributed into milk following systemic administration. Because of the potential for serious adverse effects of ofloxacin in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Ottoflox ear drop is generally well tolerated following topical application.

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.

Adverse reactions listed below are classified according to frequency and system organ class. Frequency categories: 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) and not known (cannot be estimated from the available data).

Infections and infestations
Uncommon
- Otitis externa
- Otitis media
- Fungal infection
- Rhinitis
- Sinusitis

Immune system disorders
Rare
- Hypersensitivy

Psychiatric disorders
Uncommon
- Insomnia

Nervous system disorders
Common
- Taste changes in individuals with non-intact war drums
- Dizziness
- Paraesthesia

Uncommon
- Hypoesthesia
- Headache
- Dysesthesia
- Hyperkinesis
- Tremor

Ear and labyrinth disorders
Common
- Vertigo

Uncommon
- Otalgia
- Tinnitus
- Transient loss of hearing
- Otorragia

Cardiac disorders
Uncommon
- Tachycardia

Vascular disorders
Uncommon

- Hypertension
- Flushing

General disorders and administration site conditions
Very common
- Local reactions on the administration site

Uncommon
- Fever
- Inflammation
- Pain

Respiratory, thoracic and mediastinal disorders
Uncommon
- Cough

Gastrointestinal disorders
Uncommon
- Dyspepsia
- Diarrhea
- Nausea
- Vomiting
- Xerostomia
- Abdominal pain
- Halitosis

Skin and subcutaneous tissue disorders
Common
- Itching
- Rash

Uncommon
- Dermatitis
- Eczema
- Urticaria

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.

4.9 Overdose

There is no information available regarding cases of overdose after topical administration of ofloxacin. Overdose after oral ingestion of a bottle of Ottoflox 3 mg/ml ear drops, solution (10 ml) unlikely due to the small amount of ofloxacin present in the solution.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Otologicals, anti-infectives, quinolones.
ATC code: S 02 AA16 Antiinfectives (OFLOXACIN)

Mechanism of action
Ofloxacin exerts its antibacterial activity by inhibiting DNA gyrase (a bacterial topoisomerase). DNA gyrase is an essential enzyme which controls DNA topology and assists in DNA replication, repair, deactivation and transcription.

Spectrum of action
Ofloxacin has *in vitro* activity against a wide range of gram-positive and gram-negative bacteria, namely against the majority of the bacterial pathogens responsible for ear infections, such as Escherichia coli, Haemophilus influenza, Moraxella catarrhalis, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus and Streptococcus pneumonia.
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Resistance
Cross-resistance has been observed between ofloxacin and other fluoroquinolones. There is generally no cross-resistance between ofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

5.2 Pharmacokinetic properties

Absorption
The extent of otic and systemic absorption of ofloxacin following topical application to the ear has not been fully elucidated; however, serum concentrations achieved following such application are minimal relative to those produced by usual oral or parenteral doses of the drug. While topical application of ofloxacin to the ear canal is associated with minimal penetration into the middle ear when the tympanic membrane is intact, penetration is enhanced in the presence of a perforated tympanic membrane. Following topical application of ofloxacin 0.3 mg/ml ear drops, solution in adults with perforated tympanic membranes, drug concentrations in middle ear mucosa showed considerable interindividual variation and ranged from undetectable to 602 mcg/g. Following topical application of ofloxacin 3 mg/ml ear drops, solution in patients with perforated tympanic membranes, drug concentrations in otorrhea ranged from 389–2850 µg/g 30 minutes after the dose. However, concentration of ofloxacin in otorrhea may not reflect exposure of the middle ear to the drug.
Some systemic absorption of ofloxacin occurs following topical application to the ear. Following otic administration of a single dose of ofloxacin 0.3 mg/ml ear drops, solution (10 drops, 0.5 mL, 1.5 mg of ofloxacin) in adults with tympanostomy tubes with or without otorrhea, serum ofloxacin concentrations averaged 4.1 or 5.4 ng/mL, respectively. Following administration of ofloxacin 3 mg/ml ear drops, solution in adults with perforated tympanic membranes, a peak serum concentration of 10 ng/mL was reported.

Distribution
Ofloxacin crosses the placenta and is distributed into amniotic fluid and into breast milk.

5.3 Preclinical safety data

Reproductive toxicity:
Reproductive studies in rats using oral ofloxacin dosages of 810 and 160 mg/kg daily have not revealed evidence of teratogenicity. However, fetotoxicity (decreased fetal body weight and/or increased fetal mortality) did occur in rats and rabbits receiving similar dosages. In rats receiving 810 mg/kg daily, retardation in the degree of ossification and minor skeletal variations, such as cervical ribs and shortened or absent 13th ribs, occurred.
Perinatal and postnatal studies in rats given oral ofloxacin dosages up to 360 mg/kg daily revealed a decrease in food intake during gestation and an increase in food and water intake during lactation, but did not reveal evidence of adverse effects on late fetal development, labor, delivery, lactation, neonatal viability, or growth of the offspring.

Studies in male and female rats using ofloxacin dosages up to 360 mg/kg daily indicate that the drug does not have an appreciable effect on fertility or reproductive performance.

Mutagenicity and Carcinogenicity:
Ofloxacin was not mutagenic in the *in* vitro bacterial mutagenicity test (Ames test) and *in vitro* and *in vivo* cytogenic assays, including the sister chromatid exchange (Chinese hamster and human cell lines) assay, DNA repair assay using human fibroblasts, dominant lethal assay, or mouse micronucleus assay.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monobasic sodium phosphate monohydrate, dibasic sodium phosphate dodecahydrate, sodium chloride, 50% benzalkonium chloride solution and water for injections. It may contain hydrochloric acid or sodium hydroxide for pH adjustment.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Closed bottle: 2 years.
After first opening of the primary packaging: 28 days.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Ottoflox ear drops, solution is supplied in an opaque white LDPE 10 ml bottle with transparent LDPE dropper insert and opaque white HDPE cap with tamper-proof closure (safety seal).

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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Avenida 25 de Abril, 6-6A
2795-225 Linda–a–Velha
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8. MARKETING AUTHORISATION NUMBER(S)

05306/07430/REN/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Sep 1, 2020

10. DATE OF REVISION OF THE TEXT

05/2020