PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

BESIVANCE™ Besifloxacin 0,6 % eye drops, suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains:

Besifloxacin (as hydrochloride) 6 mg (0,6 % *m/v*)

Preservative: Benzalkonium chloride 0,1 mg (0,01 % *m/v*)

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, suspension

BESIVANCE is a sterile ophthalmic suspension of besifloxacin formulated with DuraSite®. The suspension is isotonic with an osmolality of approximately 290 mOsm/kg. It is an off-white to slightly yellow, opaque liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BESIVANCE is indicated for treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria in patients of at least one year of age:

*Aerococcus viridans**

CDC coryneform group G

*Corynebacterium pseudodiphtheriticum**

*Corynebacterium striatum**

Haemophilus influenzae

*Moraxella catarrhalis**

*Moraxella lacunata**

*Pseudomonas aeruginosa**

Staphylococcus aureus

Staphylococcus epidermidis

*Staphylococcus hominis**

*Staphylococcus lugdunensis**

*Staphylococcus warneri**

Streptococcus mitis group

Streptococcus oralis

Streptococcus pneumoniae

*Streptococcus salivarius**

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

4.2 Posology and method of administration

Invert closed bottle and shake once before use.

Adults and children aged one year and older: Instill one drop in the affected eye(s) 3 times a day, 4 to 12 hours apart for 7 days.

Handling the container: To avoid contamination, do not let the applicator tip touch the surface of the eye, fingers, or any other surface.

Paediatric population

The safety and efficacy of BESIVANCE in infants below one year of age have not been established. No data are available.

The efficacy of BESIVANCE in treating bacterial conjunctivitis in paediatric patients one year or older, at the same dose as for adults, has been demonstrated in controlled clinical trials.

Elderly population

No overall differences in effectiveness have been observed between elderly and younger patients.

4.3 Contraindications

Hypersensitivity to besifloxacin or any other ingredients (see **6.1 List of excipients**).

4.4 Special warnings and precautions for use

Not for injection into the eye or other tissue

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

Avoidance of contact lenses: Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with BESIVANCE.

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. BESIVANCE should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.

4.5 Interaction with other medicines and other forms of interaction

BESIVANCE is administered locally to the eye at low dose levels, and the resulting systemic exposure to besifloxacin is minimal. Therefore, no specific medicine interaction studies were performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no available human data for the use of BESIVANCE during pregnancy to inform any medicine-associated risks; however, systemic exposure to besifloxacin from ocular administration is low (see section **5.2**).

Breastfeeding

There are no data on the presence of BESIVANCE in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to besifloxacin following topical ocular administration is low (see section **5.2**) and it is not known whether measurable levels of besifloxacin would be present in maternal milk following topical ocular administration.

Developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for BESIVANCE, and any potential adverse effects on the breastfed infant from BESIVANCE.

Caution should be exercised when BESIVANCE is administered to a nursing mother.

Fertility

In a fertility and early embryonic development study in rats, besifloxacin did not impair the fertility of male or female rats at oral doses of up to 500 mg/kg/day. This dose is approximately 26 500 times higher than the mean plasma concentration measured in humans at the recommended ophthalmic use.

4.7 Effects on ability to drive and use machines

Patients may experience temporary blurred vision or irritation, pain or itching of the treated eye(s). If blurred vision occurs at instillation, patients should wait until their vision clears before driving or using machinery.

4.8 Undesirable effects

a. Summary of the safety profile

The data described below reflect exposure to BESIVANCE in approximately 1 000 patients between 1 and 98 years old with clinical signs and symptoms of bacterial conjunctivitis.

The most frequently reported ocular adverse reaction was conjunctival redness, reported in approximately 2 % of patients. Other adverse reactions reported in patients receiving BESIVANCE occurring in approximately 1-2 % of patients included: blurred vision, eye pain, eye irritation, eye pruritus and headache.

b. Tabulated list of adverse reactions

Common (≥1/100 to <1/10):	Uncommon (≥1/1000 to <1/100):
Conjunctivitis Blurred vision Eye irritation Eye pain Eye pruritus Headache	Conjunctival haemorrhage Eye discharge Eyelid oedema Conjunctival hyperaemia Punctate keratitis Ocular hyperaemia Viral conjunctivitis Dry eye Limbal hyperaemia Increased lacrimation

d. Paediatric population

The safety of BESIVANCE in infants below one year of age have not been established.

e. Other special populations

Elderly use: No overall differences in safety have been observed between elderly and younger patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit-risk balance of the medicine. Health care providers are asked

to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

Suspected adverse reactions may also be reported directly to the Holder of the Certificate of registration using the following e-mail address: PV-SouthAfrica@bauschhealth.com

4.9 Overdose

Overdosage of this medicine is unlikely to occur via the ophthalmic route.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

15.1 Ophthalmic preparations with antibiotics and/or sulphonamides

Mechanism of action

Besifloxacin is a broad spectrum fluoroquinolone antibiotic that is active against Gram-positive and Gram-negative bacteria mainly due to the inhibition of both bacterial DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme required for replication, transcription and repair of bacterial DNA. Topoisomerase IV is an essential enzyme required for partitioning of the chromosomal DNA during bacterial cell division.

Besifloxacin has been shown to be active against most isolates of the following bacteria both in vitro and in conjunctival infections treated in clinical trials:

*Aerococcus viridans**

CDC coryneform group G

*Corynebacterium pseudodiphtheriticum**

*Corynebacterium striatum**

Haemophilus influenzae

*Moraxella catarrhalis**

*Moraxella lacunata**

*Pseudomonas aeruginosa**

Staphylococcus aureus

Staphylococcus epidermidis

*Staphylococcus hominis**

*Staphylococcus lugdunensis**

*Staphylococcus warneri**

Streptococcus mitis group

Streptococcus oralis

Streptococcus pneumoniae

*Streptococcus salivarius**

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

Clinical efficacy and safety

In a randomised, double-masked, vehicle-controlled, multi-centre clinical trial, in which patients 1-98 years of age were dosed 3 times a day for 5 days, BESIVANCE was superior to its vehicle in patients with bacterial conjunctivitis.

Clinical resolution was achieved in 45 % (90/199) for the BESIVANCE-treated group versus 33 % (63/191) for the vehicle-treated group (difference 12 %, 95 % CI 3 % - 22 %).

Microbiological outcomes demonstrated a statistically significant eradication rate for causative pathogens of 91 % (182/199) for the BESIVANCE-treated group versus 60 % (114/191) for the vehicle-treated group (difference 31 %, 95 % CI 23 % - 40 %).

Microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.

5.2 Pharmacokinetic properties

Plasma concentrations of besifloxacin were measured in adult patients with suspected bacterial conjunctivitis who received BESIVANCE bilaterally three times a day (16 doses total). Following the first and last dose, the maximum plasma besifloxacin concentration in each patient was less than 1,3 ng/mL. The mean besifloxacin C_{max} was 0,37 ng/mL on day 1 and 0,43 ng/mL on day 6. The average elimination half-life of besifloxacin in plasma following multiple dosing was estimated to be 7 hours.

5.3 Preclinical safety data

Toxicology studies reveal no risk to humans either locally or at the systemic level, considering the intended dosing regimen and route of administration.

Development toxicity

In an embryofoetal development study in rats, the administration of besifloxacin at oral doses up to 1 000 mg/kg/day during organogenesis was not associated with visceral or skeletal malformations in rat foetuses, although this dose was associated with maternal toxicity (reduced body weight gain and food consumption) and maternal mortality. Increased post-implantation loss, decreased foetal body weights, and decreased foetal ossification were also observed. At this dose, the mean C_{max} in the rat dams was approximately 20 mcg/mL, approximately 46 500 times

the mean plasma concentrations measured in humans at the recommended human ophthalmic dose (RHOD). The No Observed Adverse Effect Level (NOAEL) for this embryofoetal development study was 100 mg/kg/day (C_{max}, 5 mcg/mL, approximately 11 600 times the mean plasma concentrations measured in humans at the RHOD).

In a prenatal and postnatal development study in rats, the NOAELs for both foetal/neonate and maternal toxicity were 100 mg/kg/day. At 1 000 mg/kg/day, pups weighed significantly less than controls and had a reduced neonatal survival rate. Attainment of developmental landmarks and sexual maturation was delayed, although surviving pups from this dose group that were reared to maturity did not demonstrate deficits in behaviour, including activity, learning and memory, and their reproductive capacity appeared normal.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Polycarbophil*

Mannitol

Poloxamer 407

Sodium chloride*

Edetate disodium*

Sodium hydroxide* (for pH-adjustment)

Water for injection

*These ingredients comprise the DuraSite® delivery system.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf life is 24 months for the 5 mL fill size and 18 months for the 2 mL fill size.

Do not use more than 28 days after opening.

6.4 Special precautions for storage

Store at or below 30 °C. Protect from light.

6.5 Nature and contents of container

BESIVANCE is supplied in a round, white low density polyethylene (LDPE) bottle with a white LLDPE controlled dropper tip and beige polypropylene cap.

The 5 mL fill size is supplied in a 7,5 mL bottle, and the 2 mL fill size in a 4 mL bottle. Not all pack sizes may be marketed.

Tamper evidence is provided with a shrink band around the cap and neck area of the package.

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Soflens (Pty) Ltd

254 Hall Street

Centurion

0157

South Africa

Tel: +27 10 025 2100

Manufactured by:

Bausch & Lomb Incorporated

8500 Hidden River Parkway

Tampa, Florida 33637

USA

8 REGISTRATION NUMBER(S)

47/15.1/1186

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 September 2020

10 DATE OF REVISION OF THE TEXT

22 September 2020

NAMIBIA

Scheduling status: NS2

Registration number: 20/15.1/0062

Date of first authorisation: 02 July 2020