1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

VYZULTA™ Latanoprostene bunod 0,024 % eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains:

Latanoprostene bunod 0,24 mg (0,024 % *m/v*)

Preservative: Benzalkonium chloride 0,2 mg (0,02 % *m/v*)

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution

VYZULTA is a clear and colourless to slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VYZULTA is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

4.2 Posology and method of administration

One drop in the conjunctival sac of the affected eye(s) once daily in the evening.

Do not administer VYZULTA more than once daily since it has been shown that more frequent administration of prostaglandin analogues may lessen the intraocular pressure lowering effect.

If VYZULTA is to be used concomitantly with other topical ophthalmic medicinal products to lower intraocular pressure, administer each medicine at least five (5) minutes apart.

Paediatric population

Use in paediatric patients aged 16 years and younger is not recommended because of potential safety concerns relating to the increased pigmentation following long-term chronic use.

Geriatric population

No overall clinical differences in safety and effectiveness have been observed between elderly and other adult patients.

4.3 Contraindications

Hypersensitivity to latanoprostene bunod or any other ingredients (see 6.1).

4.4 Special warnings and precautions for use

When to seek medical advice

Patients should seek medical advice concerning the use of VYZULTA if they develop a new ocular condition (e.g. trauma or infection), experience a sudden decrease in visual acuity, have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions.

Pigmentation

VYZULTA may cause changes to pigmented tissues, especially increased pigmentation of the iris and periorbital tissue (eyelids). (See section 4.8 c)

After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue is likely to be reversible in most patients. The long-term effects of increased pigmentation are not known.

While treatment with VYZULTA can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes

There is a possibility of eyelash and vellus hair changes in the treated eye during treatment with VYZULTA. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or misdirection of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment. (See section 4.8 c)

Intraocular Inflammation

VYZULTA should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation as it may exacerbate this condition.

Macular Oedema

Macular oedema, including cystoid macular oedema, has been reported during treatment with prostaglandin analogues. These reports have mainly occurred in aphakic patients, in psuedophakic patients with torn posterior lens capsule. VYZULTA should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or anterior chamber lenses or in patients with known risk factors for cystoid macular oedema (such as diabetic retinopathy and retinal vein occlusion).

Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Handling the container

Avoid allowing the tip of the dispensing container to touch the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Benzalkonium chloride

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 ophthalmological 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.

Use with Contact Lenses

Contact lenses may absorb benzalkonium chloride which may change the colour of the contact lenses. They should be removed prior to the administration of VYZULTA.

Lenses may be reinserted 15 minutes after administration.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed with VYZULTA.

If more than one topical ophthalmic medicine is being used, the medicines should be administered with at least five (5) minutes between applications.

There have been reports of paradoxical elevations in IOP following the concomitant ophthalmic administration of two prostaglandin analogues. Therefore, the use of two or more prostaglandins, prostaglandin analogues or prostaglandin derivatives is not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no available human data for the use of VYZULTA during pregnancy to inform any medicine associated risks.

Latanoprostene bunod has caused miscarriages, abortion, and foetal harm in rabbits. Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (IV) to pregnant rabbits at exposures ≥ 0,28 times the clinical dose. Dos ≥ 20 mcg/kg/day (23 times the clinical dose) produced 100 % embryofoetal lethality. Structural abnormalities observed in rabbit foetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension and oedema. Latanoprostene bunod was not teratogenic in the rat when administered IV at 150 mcg/kg/day (87 times the clinical dose) (see 5.3).

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4 %, and of miscarriage is 15 to 20 %, of clinically recognized pregnancies.

Breastfeeding

There are no data on the presence of VYZULTA in human milk, the effects on the breastfed infant, or the effects on milk production.

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

Fertility

Fertility studies have not been conducted with latanoprostene bunod. The potential to impact fertility can be partially characterized by exposure to latanoprost acid, a common metabolite of both latanoprostene bunod and latanoprost. Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

VYZULTA was evaluated in 811 patients in 2 controlled clinical trials of up to 12 months duration. The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperaemia (6 %), eye irritation (4 %), eye pain (3 %), and instillation site pain (2 %).

Approximately 0,6 % of patients discontinued therapy due to ocular adverse reactions including ocular hyperaemia, conjunctival irritation, eye irritation, eye pain, conjunctival oedema, blurred vision, punctate keratitis and foreign body sensation.

b. Tabulated list of adverse reactions

Common (≥1/100 to <1/10); Uncommon (≥1/1000 to <1/100)

Eye disorders	
Common: conjunctival hyperaemia, ocular hyperaemia, eye irritation, eye pain, eye pruritis, foreign body sensation in the eye	*Uncommon:* abnormal sensation in the eye, asthenopia, blepharitis, blurred vision, chemical eye injury, conjunctival disorder, conjunctival haemorrhage, conjunctival irritation, conjunctival oedema, cornea presents vital dye staining, dry eye, eye colour change*, eye discharge, eyelid erythema, eyelid hypopigmentation, eyelid margin crusting, eyelid oedema, eyelid pain, eyelid pigmentation*, eyelids pruritis, growth of eyelashes*, increased lacrimation, iris hyperpigmentation*, increased intraocular pressure, keratitis*, meibomianitis, ocular discomfort, photophobia, punctate keratitis, reduced visual acuity, transiently reduced visual acuity, trichiasis, uveitis
General disorders and administrative site conditions	
Common: **Ocular:** instillation site pain	*Uncommon:* **Ocular:** instillation site discomfort, instillation site erythema, instillation site hypersensitivity, instillation site irritation, instillation site reaction, pain

	Non-ocular: chest discomfort, fatigue
Skin and subcutaneous tissue disorders *Uncommon:* **Ocular:** abnormal hair growth*, hair colour changes*, madarosis, rash, skin hyperpigmentation* **Non-ocular:** hyperhidrosis, urticaria	
Infections and infestations *Uncommon:* ear infection, tooth infection, urinary tract infection, vaginal infection	
Psychiatric disorders *Uncommon:* insomnia	
Nervous system disorders *Uncommon:* dysgeusia, headache	
Respiratory, thoracic and mediastinal disorders *Uncommon:* cough, dyspnoea, sinus congestion	
Gastrointestinal disorders *Uncommon:* dry mouth, nausea	
Reproductive system and breast disorders *Uncommon:* breast mass	

**See section c*

c. Description of selected adverse reactions

Pigmentation

VYZULTA may cause changes to pigmented tissues. The most frequently reported changes with prostaglandin analogues have been increased pigmentation of the iris and periorbital tissue (eyelid).

Pigmentation is expected to increase as long as VYZULTA is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes are likely to be reversible in most patients. Patients who receive prostaglandin analogues, including VYZULTA, should be informed of the possibility of increased pigmentation, including permanent changes. The long-term effects of increased pigmentation are not known.

Iris colour change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. (See section 4.4)

Eyelash changes

VYZULTA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and the number of lashes or hairs. Eyelash changes are usually reversible upon discontinuation of treatment. (See section 4.4)

Bacterial keratitis

See section 4.4

d. Paediatric population

There were no notable differences in incidence of specific adverse reactions across treatment groups and age groups.

The use of VYZULTA in paediatric patients aged 16 years and younger is not recommended because of potential safety concerns relating to the increased pigmentation following long-term chronic use.

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 SAHRA 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 at the following e-mail address: PV-SouthAfrica@bausch.com

4.9 Overdose

No overdose evaluation was conducted with VYZULTA.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

15.4 Ophthalmic preparations - others

Mechanism of action

Latanoprostene bunod is a selective FP receptor agonist. It is thought to lower intraocular pressure by increasing the outflow of aqueous humour through both the trabecular meshwork and uveoscleral routes. Intraocular pressure is a major modifiable risk factor for glaucoma progression. Reduction of intraocular pressure reduces risk of glaucomatous visual field loss.

Pharmacodynamic effects

Reduction of the intraocular pressure starts approximately 1 to 3 hours after the first administration with the maximum effect reached after 11 to 13 hours in eyes with elevated intraocular pressure.

Clinical efficacy

In clinical studies up to 12 months duration, patients with open-angle glaucoma or ocular hypertension with average baseline intraocular pressures (IOPs) of 26,7 mmHg, the IOP-lowering effect of VYZULTA once daily (in the evening) was up to 7 to 9 mmHg.

5.2 Pharmacokinetic properties

Absorption

The systemic exposure of latanoprostene bunod and its metabolites latanoprost acid and butanediol mononitrate were evaluated in one study with 22 healthy subjects after topical ocular administration of VYZULTA once daily (one drop bilaterally in the morning) for 28 days. There were no quantifiable plasma concentrations of latanoprostene bunod (lower limit of quantitation, LLOQ, of 10,0 pg/mL) or butanediol mononitrate (LLOQ of 200 pg/mL) post-dose on Day 1 and Day 28. The mean maximal plasma concentrations (C_{max}) of latanoprost acid (LLOQ of 30 pg/mL) were 59,1 pg/mL and 51.1 pg/mL on Day 1 and Day 28, respectively. The mean time to

maximal plasma concentration (T_{max}) for latanoprost acid was approximately 5 minutes post-administration on both Day 1 and Day 28.

Distribution

There were no ocular distribution studies performed in humans.

Metabolism

After topical ocular administration, latanoprostene bunod is rapidly metabolized in the eye to latanoprost acid (active moiety), an F2α prostaglandin analogue, and butanediol mononitrate. After latanoprost acid reaches the systemic circulation, it is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β-oxidation.
Butanediol mononitrate is metabolized to 1,4-butanediol and nitric oxide. The metabolite 1,4-butanediol is further oxidized to succinic acid and enters the tricarboxylic acid (TCA) cycle.

Elimination

The elimination of latanoprost acid from human plasma is rapid as latanoprost acid plasma concentration dropped below the LLOQ (30 pg/mL) in the majority of subjects by 15 minutes following ocular administration of VYZULTA in humans. Latanoprost T½ is 17 min after both intravenous and topical administration. Systemic clearance is approximately 7 mL/min/kg. Following hepatic ß-oxidation, the metabolites are mainly eliminated via the kidneys.

5.3 Preclinical safety data

Genotoxicity

Latanoprostene bunod was not mutagenic in bacteria and did not induce micronuclei formation in the *in vivo* rat bone marrow micronucleus assay. Chromosomal aberrations were observed *in vitro* with human lymphocytes in the absence of metabolic activation.

Carcinogenicity

Latanoprostene bunod has not been tested for carcinogenic activity in long-term animal studies. Latanoprost acid is a main metabolite of latanoprostene bunod. Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime rodent bioassays, was not carcinogenic.

Pregnancy

Embryofoetal studies were conducted in pregnant rabbits administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 19, to target the period of organogenesis. The doses administered ranged from 0,24 to 80 mcg/kg/day. Abortion occurred at doses ≥ 0,24 mcg/kg/day latanoprostene bunod (0,28 times the clinical dose, on a body surface area basis, assuming 100 % absorption). Embryofoetal lethality (resorption) was increased in latanoprostene bunod treatment groups, as evidenced by increases in early resorptions at doses ≥ 0,24 mcg/kg/day and late resorptions at doses ≥ 6 mcg/kg/day (approximately 7 times the clinical dose). No foetuses survived in any rabbit pregnancy at doses of 20 mcg/kg/day (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0,24 mcg/kg/day (0,28 times the clinical dose). Malformations included anomalies of sternum, coarctation of the aorta with pulmonary trunk dilation, retroesophageal subclavian artery with absent brachiocephalic artery, domed head, forepaw hyperextension and hindlimb malrotation, abdominal distention/oedema, and missing/fused caudal vertebrae.

An embryofoetal study was conducted in pregnant rats administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 17, to target the period of organogenesis. The doses administered ranged from 150 to 1 500 mcg/kg/day. Maternal toxicity was produced at 1 500 mcg/kg/day (870 times the clinical dose, on a body surface area basis, assuming 100 %

absorption), as evidenced by reduced maternal weight gain. Embryofetal lethality (resorption and fetal death) and structural anomalies were produced at doses ≥ 300 mcg/kg/day (174 times the clinical dose).

Malformations included anomalies of the sternum, domed head, forepaw hyperextension and hindlimb malrotation, vertebral anomalies and delayed ossification of distal limb bones. A no observed adverse effect level (NOAEL) was established at 150 mcg/kg/day (87 times the clinical dose) in this study.

Fertility

Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

Toxicology

A 9-month toxicology study administered topical ocular doses of latanoprostene bunod to one eye of cynomolgus monkeys: control (vehicle only), one drop of 0,024 % bid, one drop of 0,04 % bid and two drops of 0,04 % per dose, bid. The systemic exposures are equivalent to 4,2-fold, 7,9-fold, and 13,5-fold the clinical dose, respectively, on a body surface area basis (assuming 100 % absorption). Microscopic evaluation of the lungs after 9 months observed pleural/subpleural chronic fibrosis/inflammation in the 0,04 % dose male groups, with increasing incidence and severity compared to controls. Lung toxicity was not observed at the 0,024 % dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Polysorbate 80

Edetate disodium dihydrate

Sodium citrate dihydrate

Citric acid anhydrous

Glycerine

Water for injection

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

Once a bottle is opined it may be stored for 8 weeks.

6.4 Special precautions for storage

The unopened bottle should be stored between 2 – 8 °C.

Once a bottle is opened, it may be stored at 2 – 25 °C.

Protect from light. Do not freeze.

6.5 Nature and contents of container

VYZULTA is supplied as a 5 mL solution in a 7,5 mL clear, low density polyethylene (LDPE) bottle with a controlled dropper tip and turquoise polypropylene cap.

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

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8 REGISTRATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT