SUMMARY OF PRODUCT CHARACTERISTICS

ONABRIMO TL Eye Drops, Solution (Brimonidine Tartrate 0.2% w/v / Timolol 0.5% w/v)

1. NAME OF THE MEDICINAL PRODUCT

ONABRIMO TL (Brimonidine Tartrate 0.2% w/v and Timolol 0.5% w/v Eye Drops, Solution)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml sterile eye drop solution contains brimonidine tartrate 0.2% w/v and timolol 0.5% w/v.

Excipients with known effect:

Contains benzalkonium chloride 0.05 mg/mL. For warnings, see section 4.4.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

Clear, greenish-yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP) in patients with chronic open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers.

4.2 Posology and method of administration

Adults (including the elderly)

One drop in the affected eye(s) twice daily, approximately 12 hours apart. If more than one topical ophthalmic product is to be used, the different products should be instilled at least 5 minutes apart.

Nasolacrimal occlusion / eyelid closure

To reduce possible systemic absorption, it is recommended that the lacrimal sac be compressed at the medial canthus (punctal occlusion) or eyelids are closed for 2 minutes immediately following instillation of each drop. This may decrease systemic side effects and increase local activity.

Renal and hepatic impairment

ONABRIMO TL has not been studied in patients with hepatic or renal impairment. Caution should be used in treating such patients.

Paediatric population

ONABRIMO TL is contraindicated in neonates and infants (less than 2 years of age). Safety and effectiveness in children and adolescents (2 to 17 years of age) have not been established; use is not recommended in this age group.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Reactive airway disease including bronchial asthma or a history of bronchial asthma; severe chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block not controlled with a pacemaker, overt cardiac failure, cardiogenic shock.
- Use in neonates and infants (less than 2 years of age).
- Patients receiving MAO inhibitor therapy.
- Patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin).

4.4 Special warnings and precautions for use

Paediatric population

Children of 2 years of age and above, especially those aged 2–7 years and/or weighing ≤20 kg, should be treated with caution and closely monitored due to the high incidence and severity of somnolence. Safety and effectiveness in children and adolescents (2–17 years) have not been established.

Ocular allergic reactions

Some patients have experienced ocular allergic reactions (allergic conjunctivitis — 5.2% of patients; onset typically 3–9 months; overall discontinuation rate 3.1%; allergic blepharitis — uncommon <1%). If allergic reactions are observed, treatment should be discontinued. Delayed ocular hypersensitivity reactions have been reported with brimonidine tartrate, sometimes associated with an increase in IOP.

Systemic absorption

Like other topically applied ophthalmic agents, ONABRIMO TL may be absorbed systemically. Due to the beta-adrenergic component (timolol), the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur, although incidence is lower than with systemic administration.

Cardiac disorders

Cardiac reactions, including rarely death associated with cardiac failure, have been reported following topical timolol. In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina, cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed. Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first-degree heart block. If discontinuation is needed in patients with coronary heart disease, therapy should be withdrawn gradually to avoid rhythm disorders, MI or sudden death.

Vascular disorders

Patients with severe peripheral circulatory disturbances (severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Respiratory disorders

Respiratory reactions, including death due to bronchospasm in patients with asthma, have been reported following administration of ophthalmic beta-blockers. Use with caution in patients with mild/moderate COPD and only if the potential benefit outweighs the potential risk.

Hypoglycaemia / diabetes

Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or with labile diabetes, as beta-blockers may mask signs and symptoms of acute hypoglycaemia.

Hyperthyroidism

Beta-blockers may mask signs of hyperthyroidism.

Other precautions

Use with caution in patients with metabolic acidosis and untreated phaeochromocytoma. Ophthalmic beta-blockers may induce dryness of eyes; caution in patients with corneal diseases. The use of two topical beta-adrenergic blocking agents is not recommended.

Anaphylactic reactions

Patients with a history of atopy or severe anaphylactic reactions may be more reactive to repeated allergen challenge and unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

Choroidal detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy after filtration procedures.

Surgical anaesthesia

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects. The anaesthetist must be informed if the patient is receiving timolol.

Benzalkonium chloride content

The preservative benzalkonium chloride may cause eye irritation. Contact lenses must be removed before application and may be reinserted 15 minutes after use. Benzalkonium chloride is known to discolour soft contact lenses.

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been conducted with ONABRIMO TL. The potential for additive or potentiating effects with CNS depressants (alcohol, barbiturates, opiates, sedatives, anaesthetics) should be considered.

Additive hypotension and/or bradycardia may result from concomitant use with: oral calcium channel blockers; beta-adrenergic blocking agents; antiarrhythmics (including amiodarone); digitalis glycosides; parasympathomimetics; guanethidine.

After application of brimonidine, very rare cases of hypotension have been reported; caution is advised with systemic antihypertensives.

Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents. Beta-blockers can mask signs and symptoms of hypoglycaemia.

CYP2D6 inhibitors (quinidine, fluoxetine, paroxetine):

Potentiated systemic beta-blockade (decreased heart rate, depression) has been reported with combined use of CYP2D6 inhibitors and timolol.

MAOIs (contraindicated):

Brimonidine is contraindicated in patients receiving MAOI therapy; a 14-day washout period after MAOI discontinuation is required before commencing ONABRIMO TL.

Antidepressants affecting noradrenergic transmission (contraindicated):

Tricyclic antidepressants and mianserin are contraindicated with brimonidine.

Clonidine:

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.

Iodine contrast products; IV lidocaine; cimetidine, hydralazine, alcohol:

Caution should be exercised; cimetidine, hydralazine and alcohol may increase timolol plasma concentrations.

Alpha-adrenergic agents (isoprenaline, prazosin):

Caution when initiating or changing the dose of any systemic agent which may interact with alpha-adrenergic agonists.

4.6 Fertility, pregnancy and lactation

Pregnancy

ONABRIMO TL should not be used during pregnancy unless clearly necessary. Brimonidine: Animal studies have shown reproductive toxicity at high maternotoxic doses; potential risk for humans is unknown. Timolol: Epidemiological studies have not revealed malformative effects but have shown a risk of intrauterine growth retardation when beta-blockers are administered orally. Beta-blockade signs and symptoms (bradycardia, hypotension, respiratory distress, hypoglycaemia) have been observed in neonates born of mothers who received beta-blockers until delivery. If administered in pregnancy up to delivery, the neonate should be carefully monitored during the first days of life.

Breast-feeding

ONABRIMO TL should not be used by women breast-feeding infants. Brimonidine: Not known if excreted in human milk; excreted in rat milk. Timolol: Beta-blockers are excreted in breast milk; at therapeutic ophthalmic doses, amounts present in breast milk are unlikely to produce clinical beta-blockade symptoms in the infant. To reduce systemic absorption, punctal occlusion is recommended (see section 4.2).

Fertility

No specific data available on the effect of this combination on fertility.

4.7 Effects on ability to drive and use machines

ONABRIMO TL has minor influence on the ability to drive and use machines. Transient blurring of vision, visual disturbance, fatigue and/or drowsiness may occur which may impair the ability to drive or operate machines. The patient should wait until these symptoms have cleared.

4.8 Undesirable effects

Summary of the safety profile

Based on 12-month clinical data, the most commonly reported ADRs were conjunctival hyperaemia (approximately 15% of patients) and burning sensation in the eye (approximately 11% of patients). These reactions were mostly mild, with discontinuation rates of 3.4% and 0.5%, respectively.

System Organ Class	Very common	Common	Uncommon	Not known
Eye disorders	Conjunctival hyperaemia, burning sensation	Stinging, allergic conjunctivitis, corneal erosion, punctate keratitis, eye pruritus, conjunctival folliculosis, visual	Visual acuity worsened, conjunctival oedema, follicular conjunctivitis, allergic blepharitis, photophobia, corneal	Vision blurred

System Organ Class	Very common	Common	Uncommon	Not known
		disturbance, blepharitis, epiphora, eye dryness, eye discharge, eye pain, eye irritation, foreign body sensation	oedema, vitreous detachment	
Psychiatric		Depression		Insomnia
Nervous system		Somnolence, headache	Dizziness, syncope	
Cardiac			Congestive heart failure, palpitations	Arrhythmia, bradycardia, tachycardia, cardiac arrest
Vascular		Hypertension		Hypotension
Respiratory			Rhinitis, nasal dryness	
Gastrointestinal		Oral dryness	Taste perversion, nausea, diarrhoea	
Skin		Eyelid oedema, eyelid pruritus, eyelid erythema	Allergic contact dermatitis	Facial erythema
General		Asthenic conditions		

Additional adverse reactions from brimonidine monotherapy: iritis, iridocyclitis (anterior uveitis), miosis, upper respiratory symptoms, systemic allergic reactions, skin reactions including erythema and vasodilatation. In neonates and infants treated for congenital glaucoma, symptoms of brimonidine overdose including loss of consciousness, lethargy, somnolence, hypotension, bradycardia, hypothermia, cyanosis and apnoea have been reported. A high incidence and severity of somnolence has been reported in children aged 2 years and above, especially aged 2–7 years and/or weighing ≤20 kg.

Additional adverse reactions from timolol monotherapy: systemic allergic reactions (angioedema, urticaria, anaphylaxis), hypoglycaemia, insomnia, nightmares, memory loss, hallucinations, cerebrovascular accident, keratitis, choroidal detachment, chest pain, AV block, cardiac arrest, cardiac failure, Raynaud's phenomenon, bronchospasm, alopecia, psoriasiform rash, myalgia, sexual dysfunction, fatigue.

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 National Regulatory Authority.

4.9 Overdose

Rare reports of ophthalmic overdosage with ONABRIMO TL have resulted in no adverse outcome. Treatment of an overdose includes supportive and symptomatic therapy; a patient's airway should be maintained.

Brimonidine systemic overdose/accidental ingestion (adults): hypotension (followed by rebound hypertension), asthenia, vomiting, lethargy, sedation, bradycardia, arrhythmias, miosis, apnoea, hypotonia, hypothermia, respiratory depression, seizures. Paediatric ingestion: CNS depression, temporary coma, lethargy, somnolence, hypotonia, bradycardia, hypothermia, pallor, respiratory depression and apnoea — all patients reported to have made full recovery (usually within 6–24 hours).

Timolol systemic overdose: bradycardia, hypotension, bronchospasm, headache, dizziness, cardiac arrest. Timolol did not dialyse readily.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmological — antiglaucoma preparations and miotics, beta-blocking agents — timolol, combinations. ATC code: S01ED51.

ONABRIMO TL decreases elevated IOP by complementary mechanisms. The combined effect results in additional IOP reduction compared to either compound alone.

Brimonidine tartrate:

An alpha-2 adrenergic receptor agonist with 1,000-fold selectivity for the alpha-2 adrenoceptor over alpha-1; this selectivity results in no mydriasis and absence of vasoconstriction in retinal microvessels. Brimonidine lowers IOP by enhancing uveoscleral outflow and reducing aqueous humour formation.

Timolol maleate:

A beta1 and beta2 non-selective adrenergic receptor blocking agent without significant intrinsic sympathomimetic, direct myocardial depressant or local anaesthetic (membrane-stabilising) activity. Timolol lowers IOP by reducing aqueous humour formation, probably through inhibition of beta-adrenergic-stimulated cyclic AMP synthesis.

Clinical efficacy: In three controlled clinical studies, ONABRIMO TL (twice daily) produced a clinically meaningful additive decrease in mean diurnal IOP compared with timolol monotherapy and brimonidine monotherapy. The IOP-lowering effect was maintained in double-masked studies of up to 12 months.

5.2 Pharmacokinetic properties

Brimonidine

After ocular administration of 0.2% eye drops in humans, plasma brimonidine concentrations are low. Human plasma protein binding is approximately 29%. Mean apparent half-life in the systemic circulation approximately 3 hours after topical dosing. Following oral administration, brimonidine is well absorbed and rapidly eliminated; approximately 74% of the dose was excreted as metabolites in urine within 5 days; no unchanged drug was detected in urine. Hepatic metabolism via aldehyde oxidase and cytochrome P450. Brimonidine binds extensively and reversibly to melanin in ocular tissues without untoward effects; accumulation does not occur in the absence of melanin.

Timolol

After ocular administration of 0.5% eye drops, peak aqueous humour concentration was 898 ng/ml at 1 hour post-dose. Part of the dose is absorbed systemically and extensively metabolised in the liver. Plasma half-life approximately 7 hours. Timolol and its metabolites are excreted by the kidney. Timolol is not extensively bound to plasma proteins.

5.3 Preclinical safety data

The ocular and systemic safety profile of the individual components is well established. Non-clinical data for each component reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity. Additional ocular repeated dose toxicity studies on the combination showed no special hazard. Brimonidine caused abortion in rabbits and postnatal growth reduction in rats at exposures approximately 37-fold and 134-fold above human therapeutic exposure, respectively; no teratogenic effects. Timolol caused embryotoxicity (resorption) in rabbits and foetotoxicity (delayed ossification) in rats at high maternal doses; no teratogenicity in mice, rats or rabbits at oral doses up to 4,200 times the human daily dose in ONABRIMO TL.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride solution (excipient with known effect — 0.05 mg/mL), sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dodecahydrate, water for injections.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years. After first opening: use within 28 days.

6.4 Special precautions for storage

Do not store above 30°C. Keep the bottle in the outer carton to protect from light. Keep out of the reach and sight of children.

6.5 Nature and contents of container

White LDPE bottle with natural LDPE nozzle and white HDPE cap. Pack size: 1 × 5 ml.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

DAWA LIMITED

Plot No. 7879/8, Baba Dogo Road, Ruaraka,

P.O. Box 16633-00620, Nairobi, Kenya.

8. MARKETING AUTHORISATION NUMBER (PPB REGISTRATION NUMBER)

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