

Professional Information for Medicines for Human Use: RAVTAGON FORTE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

RAVTAGON FORTE eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL eye drops, solution contains:

Travoprost 0,04 mg and timolol maleate equivalent to 5 mg timolol.

Preservative: 0,30 mL Benzalkonium Chloride Solution (50 % aq.) in

each millilitre eye drop solution which is equivalent to 0,15 mL

Benzalkonium Chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution

RAVTAGON FORTE Eye drops solution is clear, colourless solution,

practically free of visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Decrease of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma for whom treatment with either travoprost or timolol given alone provides insufficient IOP reduction.

4.2 Posology and method of administration

Posology

Use in adults, including the elderly

The dose is one drop of RAVTAGON FORTE in the conjunctival sac of the affected eye(s) once daily, in the morning or in the evening.

RAVTAGON FORTE should be used at the same time each day.

Nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of RAVTAGON FORTE administered via the ocular route and result in a decrease in systemic side-effects.

If more than one topical ophthalmic medicine is being used, the medicines must be administered at least 5 minutes apart (see section 4.5).

If a dose is missed, treatment should continue with the next dose as planned.

The dose should not exceed one drop in the affected eye(s) daily.

When substituting another ophthalmic antiglaucoma medicine with RAVTAGON FORTE, discontinue the other medicine and start the following day with RAVTAGON FORTE.

Special populations

Use in hepatic and renal impairment

No studies have been conducted with RAVTAGON FORTE eye drops in patients with hepatic or renal impairment.

Travoprost has been studied in patients with mild to severe hepatic impairment and in patients with mild to severe renal impairment

(creatinine clearance as low as 14 mL/min). No dosage adjustment was necessary in these patients.

Paediatric population

The safety and efficacy of RAVTAGON FORTE in children and adolescents below the age of 18 years have not been established. No data are available.

Method of administration

The patient should remove the protective overwrap immediately prior to initial use.

To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle.

For ocular use.

4.3 Contraindications

- Hypersensitivity to travoprost, timolol, or to any of the excipients listed in section 6.1.
- Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second- or third-degree atrioventricular block, overt cardiac failure or cardiogenic shock.
- Hypersensitivity to other beta blockers.

4.4 Special warnings and precautions for use

Systemic effects

Travoprost and timolol are 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 medicines may occur. The incidence of systemic adverse drug reactions (ADRs) after topical ophthalmic administration is lower than for systemic administration. For information on how to reduce systemic absorption, see section 4.2.

Cardiac disorders

In patients with cardiovascular diseases (e.g., coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta blockers should be critically assessed and therapy with other active substances should be considered. Patients with history of severe cardiovascular diseases should be watched for signs of deterioration of these diseases and have their pulse rate checked.

Due to their negative effect on conduction time, beta blockers should only be given with caution to patients with first-degree heart block.

Vascular disorders

Patients with severe peripheral circulatory disturbance/disorders (i.e., 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 some ophthalmic beta blockers.

RAVTAGON FORTE should be used with caution in patients with mild/moderate chronic obstructive pulmonary disease (COPD).

Hypoglycaemia/diabetes

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

Muscle weakness

Beta-adrenergic blocking medicines have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalised weakness).

Corneal diseases

Ophthalmic beta blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Choroidal detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

Other beta-blocking medicines

The effect on intra-ocular pressure or the known effects of systemic beta blockade may be potentiated when timolol is given to patients already receiving a systemic beta-blocking medicine. The response of these patients should be closely observed. The use of two topical beta-

adrenergic blocking medicines is not recommended (see section 4.5).

Surgical anaesthesia

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects, e.g. of adrenaline. The anaesthetist should be informed when the patient is receiving timolol.

Hyperthyroidism

Beta blockers may mask the signs of hyperthyroidism.

Skin contact

Prostaglandins and prostaglandin analogues are biologically active substances that may be absorbed through the skin. Women who are pregnant or attempting to become pregnant should exercise appropriate precautions to avoid direct exposure to the contents of the bottle. In the unlikely event of coming in contact with a substantial portion of the contents of the bottle, thoroughly cleanse the exposed area immediately.

Anaphylactic reactions

While taking beta blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

Concomitant therapy

Timolol as contained in RAVTAGON FORTE may interact with other medicines (see section 4.5).

The use of two local prostaglandins is not recommended.

Ocular effects

Travoprost as contained in RAVTAGON FORTE, may gradually change the eye colour by increasing the number of melanosomes (pigment granules) in melanocytes. Before treatment is instituted, patients must be informed of the possibility of a permanent change in eye colour.

Unilateral treatment can result in permanent heterochromia. The long-term effects on the melanocytes and any consequences thereof are currently unknown. The change in iris colour occurs slowly and may not be noticeable for months to years. The change in eye colour has predominantly been seen in patients with mixed coloured irides, i.e. blue-brown, grey-brown, yellow-brown and green-brown; however, it has also been observed in patients with brown eyes. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. After discontinuation of therapy, no further increase in brown iris pigment has been observed.

In controlled clinical trials, periorbital and/or eyelid skin darkening in association with the use of travoprost has been reported.

Periorbital and lid changes, including deepening of the eyelid sulcus, have been observed with prostaglandin analogues.

Travoprost may gradually change eyelashes in the treated eye(s); these changes were observed in about half of the patients in clinical trials and include increased length, thickness, pigmentation, and/or number of lashes. The mechanism of eyelash changes and their long-term consequences are currently unknown.

Travoprost has been shown to cause slight enlargement of the palpebral fissure in studies in the monkey. However, this effect was not observed during the clinical trials and is considered to be species specific.

There is no experience of RAVTAGON FORTE in inflammatory ocular conditions, nor in neovascular, angle-closure, narrow-angle or congenital glaucoma, and only limited experience in thyroid eye disease, in open-angle glaucoma of pseudophakic patients and in pigmentary or pseudo exfoliative glaucoma.

Macular oedema has been reported during treatment with prostaglandin F_{2α} analogues. Caution is recommended when using RAVTAGON FORTE in aphakic patients, pseudophakic patients with a torn posterior lens capsule or anterior chamber lenses or in patients with known risk factors for cystoid macular oedema.

In patients with known predisposing risk factors for iritis/uveitis, and in patients with active intraocular inflammation, RAVTAGON FORTE can be used with caution.

Excipient: Benzalkonium chloride

RAVTAGON FORTE contains 0,30 mL Benzalkonium Chloride Solution (50 % aq.) (a preservative) in each millilitre eye drop solution which is equivalent to 0,15 mL Benzalkonium Chloride.

Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. You should remove contact lenses before using this medicine and put them back 15 minutes afterwards. Benzalkonium chloride may also cause eye irritation, especially if you have dry eyes or disorders of the cornea (the clear layer at the front of the eye).

Excipients: Boric acid

Do not use in a child less than 12 years old as this medicine contains boron and may impair fertility in the future.

4.5 Interaction with other medicines and other forms of interaction

No specific drug interaction studies have been performed with travoprost or timolol.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blocker solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking medicines, antidysrhythmics (including amiodarone), digoxin, parasympathomimetics or guanethidine.

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

Potentiated systemic beta blockade (e.g. decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.

Mydriasis resulting from concomitant use of ophthalmic beta blockers and adrenaline (epinephrine) has been reported occasionally.

Beta blockers may increase the hypoglycaemic effect of antidiabetic medicines. Beta blockers can mask the signs and symptoms of hypoglycaemia (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception

RAVTAGON FORTE must not be used in women of child-bearing age/potential unless adequate contraceptive measures are in place.

Pregnancy

There are no adequate data from the use of RAVTAGON FORTE in pregnant women. Animal studies with travoprost have shown reproductive toxicity. RAVTAGON FORTE should not be used during pregnancy.

Breastfeeding

Travoprost and Timolol are excreted in breast milk. Therefore, mothers breastfeeding their babies should not be treated with RAVTAGON FORTE.

Fertility

There are no data on the effects of RAVTAGON FORTE on human fertility. Animal studies showed no effect of travoprost on fertility at doses up to 75 times the maximum recommended human ocular dose, whereas no relevant effect of timolol was noted at this dose level.

4.7 Effects on ability to drive and use machines

Temporary blurred vision or other visual disturbances may occur. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machines. RAVTAGON FORTE may also cause hallucinations, dizziness, nervousness and/or fatigue (see section 4.8) which may affect the ability to drive and use machines. Patients should be advised not to drive and use machines if these symptoms occur.

4.8 Undesirable effects

a) Summary of the safety profile

In 3 reported clinical trials involved in the development of RAVTAGON FORTE (polyquaternium-1-preserved), 372 patients/subjects were exposed for up to 6 months. No serious ophthalmic or systemic side-effects related to the product were reported in any of the clinical trials. The most frequently reported treatment-related side-effect with RAVTAGON FORTE was hyperaemia of the eye, which included ocular or conjunctival hyperaemia. The majority of patients who experienced hyperaemia of the eye did not discontinue therapy as a result of this reaction.

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and post market spontaneous reports with Travoprost and Timolol eye drop, solution.

System Organ Class	Frequency		
	Frequent	Less Frequent	Not known
Immune system disorders		Hypersensitivity	
Psychiatric disorders		Nervousness	Hallucinations, depression
Nervous system disorders		Dizziness, headache	Cerebrovascular accident, syncope, paraesthesia

<p>Eye disorders</p>	<p>Eye pain, eye irritation, foreign body sensation in eyes, dry eye, eye pruritus, conjunctival hyperaemia, ocular hyperaemia, visual disturbance.</p>	<p>Punctate keratitis, photophobia, ocular discomfort, abnormal sensation in eye, blurred vision, keratoconjunctivitis sicca, conjunctivitis, allergic conjunctivitis, meibomianitis, eyelid margin crusting, eyelids pruritus, asthenopia, increased lacrimation, iris hyperpigmentation, growth of eye lashes, dark circles under eyes, iritis, anterior chamber inflammation, blepharitis, eye swelling, erythema of eyelid, eyelid oedema.</p> <p>Corneal erosion, conjunctival haemorrhage, trichiasis, distichiasis.</p>	<p>Macular oedema, eyelid ptosis, lid sulcus deepened, corneal disorder.</p>
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Cardiac disorders		Bradycardia Arrhythmia, heart rate irregular	Cardiac failure, tachycardia, chest pain, palpitations
Vascular disorders		Hypertension, hypotension	Oedema peripheral
Respiratory, thoracic and mediastinal disorders		Dyspnoea, postnasal drip Dysphonia, bronchospasm, cough, throat irritation, oropharyngeal pain, nasal discomfort	Asthma
Gastrointestinal disorders			Dysgeusia
Hepatobiliary disorders		Alanine aminotransferase increased; aspartate aminotransferase increased	
Skin and subcutaneous tissue disorders		Dermatitis contact, hypertrichosis, skin hyperpigmentation (periocular). Urticaria, skin discolouration, alopecia, abnormal hair growth.	Rash

Musculoskeletal and connective tissue disorders		Pain in extremity	
Renal and urinary disorders		Chromaturia	
General disorders and administration site conditions		Thirst, fatigue	

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications:

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

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

4.9 Overdose

If overdosage with RAVTAGON FORTE occurs, treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A.15.4 Ophthalmic preparations, other.

Pharmacotherapeutic group: Ophthalmologicals; Antiglaucoma preparations and miotics.

ATC Code: S01ED51

RAVTAGON FORTE contains two active components: travoprost and timolol maleate. These two components lower intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound alone.

Travoprost is a prostaglandin selective F2 α analogue agonist with an affinity for the prostaglandin FP receptor. It reduces the intraocular pressure by increasing the outflow of aqueous humour via trabecular meshwork and uveoscleral pathways. Reduction of IOP in man starts within approximately 2 hours after administration and maximum effect is reached after 12 hours. Low intraocular pressure can be maintained for periods exceeding 24 hours with a single dose.

Timolol is a non-selective adrenergic blocking agent that has no intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Tonography and fluorophotometry studies in man suggest that its

predominant action is related to reduced aqueous humour formation and a slight increase in outflow facility.

5.2 Pharmacokinetic properties

Absorption

Travoprost and timolol are absorbed through the cornea. Travoprost is a prodrug that undergoes ester hydrolysis in the cornea to the active free acid.

Following once-daily administration of travoprost and timolol in healthy subjects (N = 22) for 5 days, travoprost free acid was not quantifiable in plasma samples from the majority of subjects (94,4 %) and generally, was not detectable one hour after dosing. When measurable ($\geq 0,01$ ng/mL, the assay limit of quantitation), concentrations ranged from 0,01 to 0,03 ng/mL. The mean timolol steady-state C_{max} was 1,34 ng/mL and T_{max} was approximately 0,69 hours after once-daily administration of travoprost and timolol.

Distribution

Travoprost free acid can be measured in the aqueous humour during the first few hours in animals and in human plasma only during the first hour after ocular administration of travoprost and timolol.

Timolol can be measured in human aqueous humour after ocular administration of timolol and in plasma for up to 12 hours after ocular administration of travoprost and timolol.

Biotransformation

Metabolism is the major route of elimination of both travoprost and the active free acid. The systemic metabolic pathways parallel those of

endogenous prostaglandin F_{2α} which are characterised by reduction of the 13-14 double bond, oxidation of the 15-hydroxyl and β-oxidative cleavages of the upper side chain.

Timolol is metabolised by two pathways. One route yields an ethanolamine side chain on the thiadiazole ring, and the other gives an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl group adjacent to the nitrogen. The plasma t_{1/2} of timolol is 4 hours after ocular administration of travoprost and timolol.

Elimination

Travoprost free acid and its metabolites are mainly excreted by the kidneys. Less than 2 % of an ocular dose of travoprost was recovered in urine as free acid.

Timolol and its metabolites are primarily excreted by the kidneys.

Approximately 20 % of a timolol dose is excreted in the urine unchanged and the remainder excreted in urine as metabolites.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium Chloride

Mannitol

Trometamol

Macrogolglycerol Hydroxystearate

Boric acid

Disodium Edetate

Sodium Hydroxide (for pH-adjustment)

Hydrochloric Acid (for pH-adjustment)

Water for Injection

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

After opening: 28 days

6.4 Special precautions for storage

Store at or below 25 °C in original carton to protect from light.

Discard four weeks after first opening.

6.5 Nature and contents of container

RAVTAGON FORTE is available in 5 mL polypropylene (PP) bottles, low density polyethylene (LDPE) droppers and high-density polyethylene (HDPE) caps and 5 mL LDPE bottles, LDPE droppers and HDPE caps.

Each bottle contains 2,5 mL of RAVTAGON FORTE.

Pack sizes of 1 or 3 bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER

56/15.4/0727

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

02 July 2024

10. DATE OF REVISION OF THE TEXT