הודעה על החמרה (מידע בטיחות)

תאריך: 18.06.2013

שם תכשיר באנגלית: DUOTRAV

מספר רישום: 144333176400

שם בעל הרישום: Lapidot Medical Import and Marketing Ltd.

עלון לרופא

פרטים על השינוי/ים המבוקש/ים		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
Qualitative and quantitative composition	1 ml of solution contains 40 micrograms of travoprost and 5 mg of timolol (as timolol maleate). Excipients: benzalkonium chloride 0.15 mg, polyoxyethylene hydrogenated castor oil 40 (HC0-40) 5 mg (see section 4.4) For a full list of excipients, see section 6.1.	1 ml of solution contains 40 micrograms of travoprost and 5 mg of timolol (as timolol maleate). Excipients: Each ml of solution contains polyquaternium-1 (POLYQUAD) 10 microgram, propylene glycol 5 mg, ~~benzalkonium chloride 0.15 mg~~, polyoxyethylene hydrogenated castor oil 40 ~~(HC0-40) 5~~ 1 mg (see section 4.4). For a full list of excipients, see section 6.1.

Posology Use in adults, including the elderly population The dose is one drop of DuoTrav in the conjunctival sac of the affected eye(s) once daily, in the morning or evening. It should be administered at the same time each day. **Special Populations** Hepatic and renal impairment No studies have been conducted with DuoTrav or with timolol 5 mg/ml 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. Patients with hepatic or renal impairment are unlikely to require dose adjustment with DuoTrav (see section 5.2). Paediatric population The safety and efficacy of DuoTrav in children and adolescents below the age of 18 years have not been established. No data are available. Method of administration For ocular use. 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. When using ~~N~~nasolacrimal occlusion or ~~gently~~ closing the eyelids for 2 minutes, the systemic absorption is reduced. ~~after administration is recommended.~~ ~~This may reduce the systemic absorption of medicinal products administered via the ocular route and~~ This may result in a decrease in systemic adverse reactions and an increase in local activity. If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart (see section 4.5). If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily. When substituting another ophthalmic antiglaucoma agent with DuoTrav, the other agent should be discontinued and DuoTrav should be started the following day. Patients must be instructed to remove soft contact lenses prior to application of DuoTrav and wait15 minutes after instillation of the dose before reinsertion. ~~Paediatric patients~~ ~~The efficacy and safety of DuoTrav in patients below the age of 18 years have not been established and its use is not recommended in these patients until further data become available.~~ ~~Use in hepatic and renal impairment~~ ~~No studies have been conducted with DuoTrav or with timolol 5 mg/ml 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.~~	Use in adults, including the elderly The dose is one drop of DuoTrav in the conjunctival sac of the affected eye(s) once daily, in the morning or evening. It should be administered at the same time each day. Nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions. If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart (see section 4.5). If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily. When substituting another ophthalmic antiglaucoma agent with DuoTrav, the other agent should be discontinued and DuoTrav should be started the following day. Paediatric patients The efficacy and safety of DuoTrav in patients below the age of 18 years have not been established and its use is not recommended in these patients until further data become available. Use in hepatic and renal impairment No studies have been conducted with DuoTrav or with timolol 5 mg/ml 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. For ocular use. 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.	Posology and method of administration

~~For ocular use~~. ~~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.~~		
Hypersensitivity to travoprost, timolol, or to any of the excipients. Hypersensitivity to other beta-blockers. Reactive airway disease including ~~B~~bronchial asthma, or a history of bronchial asthma, or severe chronic obstructive pulmonary disease. Sinus bradycardia, sick sinus syndrome,including sino-atrial block, second or third degree atrioventricular block not controlled with pace-maker. ~~o~~Overt cardiac failure, or cardiogenic shock. Severe allergic rhinitis and bronchial hyper reactivity; corneal dystrophies.~~; hypersensitivity to other beta-blockers.~~	Hypersensitivity to travoprost, timolol, or to any of the excipients. Bronchial asthma, a history of bronchial asthma or severe chronic obstructive pulmonary disease. Sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, or cardiogenic shock. Severe allergic rhinitis and bronchial hyper reactivity; corneal dystrophies; hypersensitivity to other beta-blockers.	Contra-indications

Systemic effects Like other topically applied ophthalmic agents, travoprost and timolol are absorbed systemically. Due to the beta-adrenergic component, timolol, the same types of cardiovascular and pulmonary adverse reactions as seen with systemic beta adrenergic blocking agents may occur. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2. *Cardiac disorders* ~~Cardiac failure should be adequately controlled before beginning therapy with timolol.~~ 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 the therapy with other active substances should be considered. Patients with a history of ~~severe~~ cardiac disease should be watched for signs of deterioration of these diseases and of adverse reactions (such as cardiac failure) and have their pulse rates checked. Cardiac reactions, including death in association with cardiac failure, have been reported following administration of timolol maleate. Due to its 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 ~~and cardiac reactions~~, including death due to bronchospasm in patients with asthma ~~and, rarely, death in association with cardiac failure~~, have been reported following administration of timolol maleate. DuoTrav should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk. *Hypoglycaemia/diabetes* Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) as beta-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycaemia. *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 agents* The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two local beta-adrenergic blocking agents is not recommended.	Systemic effects Like other topically applied ophthalmic agents, travoprost and timolol are absorbed systemically. Due to the beta-adrenergic component, timolol, the same types of cardiovascular and pulmonary adverse reactions as seen with systemic beta adrenergic blocking agents may occur. Cardiac failure should be adequately controlled before beginning therapy with timolol. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure and have their pulse rates checked. Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failure, have been reported following administration of timolol maleate. Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) as beta-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycaemia. They may also mask the signs of hyperthyroidism and cause worsening of Prinzmetal angina, severe peripheral and central circulatory disorders and hypotension. Prostaglandins and prostaglandin analogues are biologically active materials 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 adrenergic blocking agents, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions. Concomitant therapy Timolol may interact with other medicinal products (see section 4.5). The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when DuoTrav is given to patients already receiving an oral beta-blocking agent. The use of two local beta-adrenergic blocking agents or two local prostaglandins is not recommended. Ocular effects Travoprost 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.	Special warnings and precautions for use

Surgical anaesthesia Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol. Beta-blockers ~~They~~ may also mask the signs of hyperthyroidism and cause worsening of Prinzmetal angina, severe peripheral and central circulatory disorders and hypotension. *Skin contact* Prostaglandins and prostaglandin analogues are biologically active materials 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 ~~adrenergic blocking agents~~, 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 doses of adrenaline used to treat anaphylactic reactions. *Concomitant therapy* Timolol may interact with other medicinal products (see section 4.5). The use of two local prostaglandins is not recommended. ~~The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when DuoTrav is given to patients already receiving an oral beta-blocking agent. The use of two local beta-adrenergic blocking agents or two local prostaglandins is not recommended.~~ *Ocular effects* Travoprost 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. 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 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. 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 DuoTrav 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 pseudoexfoliative glaucoma. Caution is recommended when using DuoTrav 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, DuoTrav can be used with caution. DuoTrav contains benzalkonium chloride which may cause irritation and is known to discolour soft contact lenses. Contact with soft contact lenses is to be avoided. Patients must be instructed to remove contact lenses prior to application of DuoTrav and wait 15 minutes after instillation of the dose before reinsertion. Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since DuoTrav contains benzalkonium chloride, close monitoring is required with frequent or prolonged use. DuoTrav contains polyoxyethylene hydrogenated castor oil 40 which may cause skin reactions.	

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 DuoTrav 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 pseudoexfoliative glaucoma. Caution is recommended when using DuoTrav 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, DuoTrav can be used with caution. *Excipients* ~~DuoTrav contains benzalkonium chloride which may cause irritation and is known to discolour soft contact lenses. Contact with soft contact lenses is to be avoided.~~ ~~Patients must be instructed to remove contact lenses prior to application of DuoTrav and wait 15 minutes after instillation of the dose before reinsertion.~~ ~~Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since DuoTrav contains benzalkonium chloride, close monitoring is required with frequent or prolonged use.~~ DuoTrav contains propylene glycol which may cause skin irritation. DuoTrav contains polyoxyethylene hydrogenated castor oil 40 which may cause skin reactions. Patients must be instructed to remove contact lenses prior to application of DuoTrav and wait 15 minutes after instillation of the dose before reinsertion.		
No specific drug interaction studies have been performed with travoprost or timolol. There is a potential for additive effects results in hypotension and/or marked bradycardia when ~~eye drops with timolol~~ ophthalmic beta blockers solution ~~are~~ is administered concomitantly with oral calcium channel blockers, guanethidine or beta-blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides or parasympathomimetics. The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers. Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents. Beta-blockers can mask the signs and symptoms of hypoglycaemia (see section 4.4).	No interaction studies have been performed. There is a potential for additive effects results in hypotension and/or marked bradycardia when eye drops with timolol are administered concomitantly with oral calcium channel blockers, guanethidine or beta-blocking agents, antiarrhythmics, digitalis glycosides or parasympathomimetics. The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers. Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents. Beta-blockers can mask the signs and symptoms of hypoglycaemia (see section 4.4).	Interaction with other medicinal products and other forms of interaction

Women of childbearing potential/contraception DuoTrav must not be used in women who may become pregnant unless adequate contraceptive measures are in place (see section 5.3). Pregnancy Travoprost has harmful pharmacological effects on pregnancy and/or the foetus/new-born child. There are no adequate data for the use of timolol in pregnant women. Timolol should not be used during pregnancy unless clearly necessary. ~~Well controlled~~ eEpidemiological studies ~~with systemic use of beta-blockers did not indicate~~ have not revealed malformative effects but show a risk for intra uterine growth retardation when beta-blockers are administered by the oral route.~~,but some pharmacological effects such as bradycardia have been observed in foetuses or neonates~~. ~~Data on a limited number of exposed pregnancies indicate no adverse effects of timolol in eye drops on pregnancy or on the health of the foetus/newborn child but bradycardia and arrhythmia have been reported in one case in the foetus of a woman treated with timolol eye drops. To date, no other relevant epidemiological data are available~~. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If DuoTrav is administered until delivery, the neonate should be carefully monitored during the first days of life. DuoTrav should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2. ~~Lactation~~ Breastfeeding It is unknown whether travoprost from eye drops is excreted in human breast milk. Animal studies have shown excretion of travoprost and metabolites in breast milk. Timolol is excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk ~~the calculated dose of timolol for the infant would be too low~~ to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see section 4.2. The use of DuoTrav by breast-feeding women is not recommended. Fertility There are no data on the effects of DuoTrav on human fertility. Animal studies showed no effect of travoprost or timolol on fertility at doses more than 250 times the maximum recommended human ocular dose.	Women of childbearing potential/contraception DuoTrav must not be used in women who may become pregnant unless adequate contraceptive measures are in place (see section 5.3). Pregnancy Travoprost has harmful pharmacological effects on pregnancy and/or the foetus/new-born child. Well controlled epidemiological studies with systemic use of beta-blockers did not indicate malformative effects, but some pharmacological effects such as bradycardia have been observed in foetuses or neonates. Data on a limited number of exposed pregnancies indicate no adverse effects of timolol in eye drops on pregnancy or on the health of the foetus/newborn child but bradycardia and arrhythmia have been reported in one case in the foetus of a woman treated with timolol eye drops. To date, no other relevant epidemiological data are available. DuoTrav should not be used during pregnancy unless clearly necessary. Lactation It is unknown whether travoprost from eye drops is excreted in human breast milk. Animal studies have shown excretion of travoprost and metabolites in breast milk. Timolol is excreted in breast milk. However, at therapeutic doses of timolol in eye drops the calculated dose of timolol for the infant would be too low to produce clinical beta-blockade. The use of DuoTrav by breast-feeding women is not recommended.	Pregnancy and lactation

In clinical studies involving ~~721~~ 938 patients, DuoTrav (benzalkonium chloride-preserved) was administered once-daily. ~~No serious ophthalmic or systemic undesirable effects related to DuoTrav were reported~~. The most frequently reported treatment-related undesirable effect was ocular hyperaemia (15.0%). Almost all patients (~~98%~~ 96%) who experienced ocular hyperaemia did not discontinue therapy as a result of this event. The following adverse reactions listed in the table below were observed in clinical studies or with post-marketing experience. They are ranked according to system organ class and classified according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), or not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in decreasing order of seriousness. **DuoTrav (benzalkonium chloride-preserved)** **System Organ Class, Frequency, ~~Preferred Term~~ Adverse Reactions** **Cardiac disorders** Common: heart rate irregular, heart rate decreased Uncommon: arrhythmia Not known: cardiac failure, tachycardia **Nervous system disorders** Common: dizziness, headache Not known: cerebrovascular accident, syncope, Paraesthesia **Eye disorders** Very common: eye irritation, ocular discomfort , ocular hyperaemia Common: punctate keratitis, ~~anterior chamber cell~~, anterior chamber ~~flare~~ inflammation, eye pain, photophobia, eye swelling, conjunctival haemorrhage, corneal staining, ~~ocular discomfort~~, abnormal sensation in eye, visual acuity reduced, visual disturbance, vision blurred, dry eye, eye pruritus, conjunctivitis ~~allergic~~, lacrimation increased, eyelid irritation, erythema of eyelid, blepharitis, asthenopia, growth of eyelashes Uncommon: corneal erosion, keratitis, eyelid pain, eye allergy, conjunctival oedema, eyelid oedema, eyelids pruritus Rare: iritis Not known: macular oedema, ~~iritis~~, conjunctivitis, eyelid ptosis, corneal disorder **Respiratory, thoracic and mediastinal disorders** Common: bronchospasm Uncommon: dyspnoea, cough, oropharyngeal pain, throat irritation, nasal discomfort, postnasal drip Not known: asthma **Renal and urinary disorders** Uncommon: chromaturia **Skin and subcutaneous tissue disorders** Common: urticaria, skin hyperpigmentation (periocular) Uncommon: dermatitis contact Rare: alopecia Not known: rash, ~~alopecia~~ **Musculoskeletal and connective tissue disorders** Common: pain in extremity **Vascular disorders** Common: blood pressure increased, blood pressure decreased	In clinical studies involving 721 patients, DuoTrav was administered once-daily. No serious ophthalmic or systemic undesirable effects related to DuoTrav were reported. The most frequently reported treatment-related undesirable effect was ocular hyperaemia (15.0%). Almost all patients (98%) who experienced ocular hyperaemia did not discontinue therapy as a result of this event. The following adverse reactions listed in the table below were observed in clinical studies or with post-marketing experience. They are ranked according to system organ class and classified according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), or not known (cannot be estimated from the available data. Within each frequency grouping, undesirable effects are presented in decreasing order of seriousness. **System Organ Class, Frequency, Preferred Term** **Cardiac disorders** Common: heart rate irregular, heart rate decreased Uncommon: arrhythmia Not known: cardiac failure, tachycardia **Nervous system disorders** Common: dizziness, headache Not known: cerebrovascular accident, syncope, Paraesthesia **Eye disorders** Very common: eye irritation, ocular hyperaemia Common: punctate keratitis, anterior chamber cell, anterior chamber flare, eye pain, photophobia, eye swelling, conjunctival haemorrhage, corneal staining, ocular discomfort, abnormal sensation in eye, visual acuity reduced, visual disturbance, vision blurred, dry eye, eye pruritus, conjunctivitis allergic, lacrimation increased, eyelid irritation, erythema of eyelid, blepharitis, asthenopia, growth of eyelashes Uncommon: corneal erosion, keratitis, eyelid pain, eye allergy, conjunctival oedema, eyelid oedema, eyelids pruritus Not known: macular oedema, iritis, conjunctivitis, eyelid ptosis, corneal disorder **Respiratory, thoracic and mediastinal disorders** Common: bronchospasm Uncommon: dyspnoea, cough, throat irritation, postnasal drip Not known: asthma **Renal and urinary disorders** Uncommon: chromaturia **Skin and subcutaneous tissue disorders** Common: urticaria, skin hyperpigmentation (periocular) Uncommon: dermatitis contact Not known: rash, alopecia **Musculoskeletal and connective tissue disorders** Common: pain in extremity **Vascular disorders** Common: blood pressure increased, blood pressure decreased	Undesirable effects

General disorders and administration site conditions Uncommon: thirst Not known: chest pain **Hepatobiliary disorders** Uncommon: alanine aminotransferase increased, aspartate aminotransferase increased **Psychiatric disorders** Common: nervousness Not known: depression In 3 clinical trials involved in the development of DuoTrav (polyquaternium-1-preserved), 372 patients/subjects were exposed for up to 12 months. The most frequently reported treatment-related undesirable effect with DuoTrav (polyquaternium-1-preserved) was hyperaemia of the eye (11.8%), which included ocular or conjunctival hyperaemia. The majority of patients (91%) who experienced hyperaemia of the eye did not discontinue therapy as a result of this reaction. The following adverse reactions listed in the table below were observed in the clinical studies. **DuoTrav (polyquaternium-1-preserved)** **System Organ Classification, Frequency, Adverse Reactions** **Immune system disorders** Umcommon: hypersensitivity **Nervous system disorders** Uncommon: Headache Eye disorders Common: eye pain, ocular discomfort, dry eye, eye pruritus, ocular hyperaemia Uncommon: punctate keratitis, iritis, photophobia, vision blurred, conjunctivitis,meibomianitis, eyelid margin crusting, asthenopia, lacrimation increased, growth of eye lashes **Cardiac disorders** Uncommon: bradycardia **Vascular disorders** Uncommon: hypotension **Skin and subcutaneous tissue disorders** Uncommon: skin discolouration, hair growth abnormal **General disorders and administration site conditions** Uncommon: fatigue **Investigations** Uncommon: heart rate decreased Additional adverse events that have been seen with one of the components and may potentially occur with DuoTrav: ***Travoprost****:* Eye disorders: uveitis, conjunctival disorder, conjunctival follicles, eyelid margin crusting, iris hyperpigmentation Skin and subcutaneous tissue disorders: skin exfoliation	**General disorders and administration site conditions** Uncommon: thirst Not known: chest pain **Hepatobiliary disorders** Uncommon: alanine aminotransferase increased, aspartate aminotransferase increased **Psychiatric disorders** Common: nervousness Not known: depression Additional adverse events that have been seen with one of the components and may potentially occur with DuoTrav: **Travoprost**: Eye disorders: uveitis, conjunctival disorder, conjunctival follicles, eyelid margin crusting, iris hyperpigmentation Skin and subcutaneous tissue disorders: skin exfoliation **Timolol**: Cardiac disorders: cardiac arrest, atrioventricular block, palpitations Nervous system disorders: cerebral ischaemia, myasthenia gravis, Eye disorders: diplopia Respiratory, thoracic and mediastinal disorders: respiratory failure, nasal congestion Gastrointestinal disorders: diarrhoea, nausea Metabolism and nutrition disorders: hypoglycaemia General disorders and administration site conditions: asthenia	

Timolol: Like other topically applied ophthalmic drugs, timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Additional listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see 4.2. Immune system disorders: Systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylaxis. Cardiac disorders: chest pain, cardiac arrest, atrioventricular block, palpitations, oedema, congestive heart failure Nervous system disorders: cerebral ischaemia, increases in signs and symptoms of myasthenia gravis, Eye disorders: signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, redness), choroidal detachment following filtration surgery (see 4.4 Special warnings and special precautions for use), decreased corneal sensitivity,diplopia Respiratory, thoracic and mediastinal disorders: respiratory failure, nasal congestion, bronchospasm (predominantly in patients with pre-existing bronchospastic disease) Gastrointestinal disorders: diarrhoea, nausea, dysgeusia, dyspepsia, dry mouth, abdominal pain, vomiting Metabolism and nutrition disorders: hypoglycaemia General disorders and administration site conditions: asthenia Psychiatric disorders: Insomnia, nightmares, memory loss Vascular disorders: Raynaud's phenomenon, cold hands and feet Skin and subcutaneous tissue disorders: Psoriasiform rash or exacerbation of psoriasis Musculoskeletal and connective tissue disorders: Myalgia Reproductive system and breast disorders: Sexual dysfunction, decreased libido		
A topical overdose with travoprost is not likely to occur or to be associated with toxicity. The most common symptoms of a systemic timolol overdose are bradycardia, hypotension, bronchospasm and heart failure. If overdose with DuoTrav occurs, treatment should be symptomatic. Timolol does not dialyse readily.	If overdose with DuoTrav occurs, treatment should be symptomatic. Timolol does not dialyse readily.	Overdose

Pharmacotherapeutic group: Ophthalmologicals-antiglaucoma preparations and miotics-beta-blocking agents-timolol, combinations. ATC code: S01ED51 Mechanism of action DuoTrav contains two active substances: travoprost and timolol maleate. These two components lower intraocular pressure by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound alone. Travoprost, a prostaglandin F2 α analogue, is a full agonist which is highly selective and has a high affinity for the prostaglandin FP receptor, and 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. Significant lowering of 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. Secondary pharmacology Travoprost significantly increased optic nerve head blood flow in rabbits following 7 days of topical ocular administration (1.4 micrograms, once-daily). Pharmacodynamic effects *Clinical effects* In a twelve-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 25 to 27 mmHg, the mean IOP-lowering effect of DuoTrav dosed once-daily in the morning was 8 to 10 mmHg. The non-inferiority of DuoTrav as compared to latanoprost 50 micrograms/ml + timolol 5 mg/ml in the mean IOP reduction was demonstrated across all time-points at all In a three-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 27 to 30 mmHg, the mean IOP-lowering effect of DuoTrav dosed once-daily in the morning was 9 to 12 mmHg, and was up to 2 mmHg greater than that of travoprost 40 micrograms/ml dosed once-daily in the evening and 2 to 3 mmHg greater than that of timolol 5 mg/ml dosed twice daily. A statistically superior reduction in morning mean IOP (8AM-24 hours after the last dose of DuoTrav) was observed compared to travoprost at all visits throughout the study. In two three-month, controlled clinical studies in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 23 to 26 mmHg, the mean IOP-lowering effect of DuoTrav dosed once-daily in the morning was 7 to 9 mmHg. Mean IOP reductions were non-inferior, although numerically lower, to those achieved by concomitant therapy with travoprost 40 micrograms/ml dosed once-daily in the evening and timolol 5 mg/ml dosed once-daily in the morning.	Pharmacotherapeutic group: Ophthalmologicals-antiglaucoma preparations and miotics-beta-blocking agents-timolol, combinations. ATC code: S01ED51 Mechanism of action DuoTrav contains two active substances: travoprost and timolol maleate. These two components lower intraocular pressure by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound alone. Travoprost, a prostaglandin F2_ analogue, is a full agonist which is highly selective and has a high affinity for the prostaglandin FP receptor, and 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. Significant lowering of 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. Secondary pharmacology Travoprost significantly increased optic nerve head blood flow in rabbits following 7 days of topical ocular administration (1.4 micrograms, once-daily). Pharmacodynamic effects *Clinical effects* In a twelve-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 25 to 27 mmHg, the mean IOP-lowering effect of DuoTrav dosed once-daily in the morning was 8 to 10 mmHg. The non-inferiority of DuoTrav as compared to latanoprost 50 micrograms/ml + timolol 5 mg/ml in the mean IOP reduction was demonstrated across all time-points at all visits.In a three-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 27 to 30 mmHg, the mean IOP-lowering effect of DuoTrav dosed once-daily in the morning was 9 to 12 mmHg, and was up to 2 mmHg greater than that of travoprost 40 micrograms/ml dosed once-daily in the evening and 2 to 3 mmHg greater than that of timolol 5 mg/ml dosed twice daily. 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In a 6-week, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 24 to 26 mmHg, the mean IOP-lowering effect of DuoTrav (polyquaternium-1-preserved) dosed once-daily in the morning was 8 mmHg and equivalent to that of DuoTrav (benzalkonium chloride-preserved). Inclusion criteria were common across the studies, with the exception of the IOP entry criteria and response to previous IOP therapy. The clinical development of DuoTrav included both patients naive and on therapy. Insufficient responsiveness to monotherapy was not an inclusion criteria. Existing data suggest that evening dosing might have some advantages in the mean IOP reduction. Consideration should be given to patient convenience and their likely compliance when recommending morning vs. evening dosing.	Mean IOP reductions were non-inferior, although numerically lower, to those achieved by concomitant therapy with travoprost 40 micrograms/ml dosed once-daily in the evening and timolol 5 mg/ml dosed once-daily in the morning. Inclusion criteria were common across the studies, with the exception of the IOP entry criteria and response to previous IOP therapy. The clinical development of DuoTrav included both patients naive and on therapy. Insufficient responsiveness to monotherapy was not an inclusion criteria. Existing data suggest that evening dosing might have some advantages in the mean IOP reduction. Consideration should be given to patient convenience and their likely compliance when recommending morning vs. evening dosing.	

Absorption Travoprost and timolol are absorbed through the cornea. Travoprost is a prodrug that undergoes rapid ester hydrolysis in the cornea to the active free acid. Following once-daily administration of DuoTrav in healthy subjects (N=~~15~~ 22) for ~~3~~ 5 days, travoprost free acid was not quantifiable in plasma samples from the majority of subjects (~~80~~ 94.4%) and was not detectable in any samples one hour after dosing. When measurable (≥0.01 ng/ml, the assay limit of quantitation), concentrations ranged from ~~0.011~~ 0.01 to ~~0.020~~ 0.03 ng/ml. The mean timolol steady-state Cmax was ~~0.692~~ 1.34 ng/ml and Tmax was approximately ~~1~~ 0.69 hour after once-daily administration of DuoTrav. 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 DuoTrav. 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 DuoTrav. ~~Metabolism~~ 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 F2 α 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 giving an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl group adjacent to the nitrogen. The plasma t1/2 of timolol is 4 hours after ocular administration of DuoTrav. ~~Excretion~~ 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.	Absorption Travoprost and timolol are absorbed through the cornea. Travoprost is a prodrug that undergoes rapid ester hydrolysis in the cornea to the active free acid. Following once-daily administration of DuoTrav in healthy subjects (N=15) for 3 days, travoprost free acid was not quantifiable in plasma samples from the majority of subjects (80%) and was not detectable in any samples one hour after dosing. When measurable (≥ 0.01 ng/ml, the assay limit of quantitation), concentrations ranged from 0.011 to 0.020 ng/ml. The mean timolol steady-state Cmax was 0.692 ng/ml and Tmax was approximately 1 hour after once-daily administration of DuoTrav. 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 DuoTrav. 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 DuoTrav. Metabolism Metabolism is the major route of elimination of both travoprost and the active free acid. The systemic metabolic pathways parallel those of endogenous prostaglandin F2 α 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 giving an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl group adjacent to the nitrogen. The plasma t1/2 of timolol is 4 hours after ocular administration of DuoTrav. Excretion 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.	Pharmaco-kinetic properties

In monkeys, administration of DuoTrav twice–daily was shown to induce increased palpebral fissure and to increase iris pigmentation similar to that observed with ocular administration of prostanoids. DuoTrav preserved with polyquaternium-1 induced minimal ocular surface toxicity, compared to eye drops preserved with benzalkonium chloride, on cultured human corneal cells and following topical ocular administration in rabbits. Travoprost Topical ocular administration of travoprost to monkeys at concentrations of up to 0.012% to the right eye, twice daily for one year resulted in no systemic toxicity. Reproduction toxicity studies with travoprost have been undertaken in rat, mice and rabbit by systemic route. Findings are related to FP receptor agonist activity in uterus with early embryolethality, post-implantation loss, foetotoxicity. In pregnant rat, systemic administration of travoprost at doses more than 200 times the clinical dose during the period of organogenesis resulted in an increased incidence of malformations. Low levels of radioactivity were measured in amniotic fluid and foetal tissues of pregnant rats administered 3H-travoprost. Reproduction and development studies have demonstrated a potent effect on foetal loss with a high rate observed in rats and mice (180 pg/ml and 30 pg/ml plasma, respectively) at exposures 1.2 to 6 times the clinical exposure (up to 25 pg/ml). Timolol Non-clinical data revealed no special hazard for humans with timolol based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenic potential. Reproduction toxicity studies with timolol showed delayed foetal ossification in rats with no adverse effects on postnatal development (7000 times the clinical dose) and increased foetal resorptions in rabbits (14000 times the clinical dose).	In monkeys, administration of DuoTrav twice–daily was shown to induce increased palpebral fissure and to increase iris pigmentation similar to that observed with ocular administration of prostanoids. Travoprost Topical ocular administration of travoprost to monkeys at concentrations of up to 0.012% to the right eye, twice daily for one year resulted in no systemic toxicity. Reproduction toxicity studies with travoprost have been undertaken in rat, mice and rabbit by systemic route. Findings are related to FP receptor agonist activity in uterus with early embryolethality, post-implantation loss, foetotoxicity. In pregnant rat, systemic administration of travoprost at doses more than 200 times the clinical dose during the period of organogenesis resulted in an increased incidence of malformations. Low levels of radioactivity were measured in amniotic fluid and foetal tissues of pregnant rats administered 3H-travoprost. Reproduction and development studies have demonstrated a potent effect on foetal loss with a high rate observed in rats and mice (180 pg/ml and 30 pg/ml plasma, respectively) at exposures 1.2 to 6 times the clinical exposure (up to 25 pg/ml). Timolol Non-clinical data revealed no special hazard for humans with timolol based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenic potential. Reproduction toxicity studies with timolol showed delayed foetal ossification in rats with no adverse effects on postnatal development (7000 times the clinical dose) and increased foetal resorptions in rabbits (14000 times the clinical dose).	Preclinical safety data
~~Benzalkonium chloride~~ Polyquaternium-1 Mannitol (E421) ~~Trometamol~~ Propylene glycol (E1520) Polyoxyethylene hydrogenated castor oil 40 (HCO-40) Boric acid ~~Disodium edentate~~ Sodium chloride Sodium hydroxide and/ or hydrochloric acid (for pH adjustment) Purified water	Benzalkonium chloride Mannitol Trometamol Polyoxyethylene hydrogenated castor oil 40 (HCO-40) Boric acid Disodium edetate Hydrochloric acid (for pH adjustment) Purified water	List of excipients
~~Luxemburg Pharmaceuticals~~ LAPIDOT MEDICAL IMPORT AND MARKETING LTD 8 Hashita st., Caesarea Industrial Park 38900, Israel	Luxemburg Pharmaceuticals 8 Hashita st., Caesarea Industrial Park 38900, Israel	License Holder

עלון לצרכן

פרטים על השינוי/ים המבוקש/ים		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
מתי אין להשתמש בתכשיר?	אל תשתמשי בתרופה כאשר הינך בהריון או מתכננת להרות. אין להשתמש בתרופה אם הינך סובל/ת מבעיות נשימה חמורות כגון אסטמה או חסימה ריאתית כרונית חמורה. אין להשתמש בתרופה במקרים של האטה בקצב הלב, אי ספיקת לב או הפרעות בקצב הלב. אין להשתמש אם הנך סובל/ת מעכירות פני השטח של העין.	אין להשתמש בתרופה אם: • אם הינך בהריון או מתכננת להרות • אם הינך סובל או סבלת בעבר מבעיות נשימה חמורות כגון אסטמה או חסימה ריאתית כרונית חמורה (לדוגמא ברונכיטיס) או בעיות נשימה אחרות. • במקרים של האטה בקצב הלב, אי ספיקת לב או הפרעות בקצב הלב. • אם הינך סובל מעכירות פני השטח של העין. • במקרים של נזלת אלרגית חמורה או קדחת השחת. • אם ידועה רגישות לאחד ממרכיבי התרופה או לחוסמי בטא או פרוסטגלנדינים אחרים.

אזהרות:	**אין להשתמש בתרופה מבלי להיוועץ ברופא לפני התחלת הטיפול** אם הינך מניקה, אם הינך סובלת או סבלת בעבר מליקוי בתפקוד: מערכת הנשימה (כגון אסטמה), הלב ו/או כלי דם, לחץ דם נמוך, עיניים, בלוטת התריס (תיראואיד), מערכת העצבים, סוכרת (ראה ב"אזהרות"), חולשת שרירים.	**אזהרות מיוחדות הנוגעות לשימוש בתרופה** **אין להשתמש בתרופה מבלי להיוועץ ברופא לפני התחלת הטיפול אם:** • הינך מניקה • עברת ניתוח קטרקט בעבר • הינך סובל או סבלת בעבר מליקוי בתפקוד: ○ מערכת הנשימה (כגון אסטמה, חסימה ריאתית כרונית) ○ הלב ו/או כלי דם (מחלת לב כלילית, אי ספיקת לב, הפרעות בקצב הלב, (בעיות בזרימת הדם כגון מחלת ריינו (Raynaud's disease)). ○ לחץ דם נמוך ○ עיניים ○ בלוטת התריס (תיראואיד) ○ מערכת העצבים ○ סוכרת (ראה ב"אזהרות") ○ חולשת שרירים. **<u>אזהרות:</u>** • אם הינך רגיש ~~למזון כלשהו או~~ לתרופה כלשהי, עליך להודיע על כך לרופא לפני נטילת התרופה. • בתקופת הטיפול בתרופה זו יש לערוך בדיקות לחץ תוך עיני. • אם הינך עומד לעבור ניתוח (כולל דנטלי), יש להודיע לרופא המנתח על נטילת התרופה. • ~~התכשיר מכיל חומר משמר בשם בנזלקוניום כלוריד, העלול להיספג על ידי עדשות מגע רכות.~~ אם הנך מרכיב עדשות מגע רכות אין להשתמש בתכשיר זה כאשר העדשות נמצאות בתוך העיניים. ~~אתה מרכיב עדשות מגע רכות.~~ יש להסיר את העדשות לפני השימוש בתכשיר, וניתן להחזירן כעבור לא פחות מ- 15 דקות מהזלפת התרופה לעין. • התכשיר מכיל שמן קיק (castor oil) העלול לגרום לגירוי בעור. • אם הינך סובל מתגובה אלרגית חמורה כלשהי (פריחה עורית, אדמומיות וגירוד של העין) בזמן השימוש בדואוטרב, ללא קשר לגורם, טיפול באדרנלין עלול להיות פחות יעיל. לכן, בעת קבלת טיפול אחר, ספר לרופא כי הינך משתמש בדואוטרב. • במשך הטיפול עלול להופיע שינוי בצבע הקשתית (החלק הצבעוני של העין) שינוי זה עלול להיות בלתי הפיך. • תתכנה גם תופעות של הארכת הריסים, שינוי בצבעם, התעבות הריסים, שינוי במספר הריסים, צמיחת שיער לא רגילה על העפעף. • אם מתפתח זיהום בעין במשך הטיפול או היא מקבלת חבלה או אם הינך עובר ניתוח בעין יש להיוועץ ברופא לגבי המשך הטיפול. • לתשומת לב חולי סכרת: שימוש בדואוטרב עלול למסך את הופעת התסמינים המלווים רמת סוכר נמוכה בדם (היפוגליקמיה) כגון רעד או סחרחורת. • טרבופרוסט עלול להיספג דרך העור ולכן אין להשתמש בו בנשים הרות או המנסות להיכנס להיריון. אם התרופה באה במגע עם העור, יש לשטוף אותה באופן מיידי.

תגובות בין תרופתיות:	אם הינך נוטל/ת תרופה נוספת, או אם גמרת זה עתה הטיפול בתרופה אחרת כולל תרופות ללא מרשם, עליך לדווח לרופא המטפל כדי למנוע סיכונים או אי-יעילות הנובעים מתגובות בין-תרופתיות. במיוחד, לגבי: תכשירים אחרים לטיפול בעין ותרופות ללב וללחץ דם – ממשפחת חוסמי ביטא, חוסמי תעלות סידן, תרופות לטיפול באסטמה, דיגוקסין, גואנטידין, תרופות אנטיאריטמיות, תכשירים פארסימפטומימטיים, תכשירים להורדת רמת הסוכר.	**אם אתה לוקח, או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח.** במיוחד יש ליידע את הרופא או הרוקח אם אתה לוקח: • תכשירים אחרים לטיפול בעין • תרופות ללב וללחץ דם – ממשפחת חוסמי ביטא, חוסמי תעלות סידן, כיניידין • תרופות לטיפול באסטמה • דיגוקסין • גואנטידין • תרופות אנטיאריטמיות • תכשירים פאראסימפטומימטיים • תכשירים ~~להורדת רמת הסוכר~~ לטיפול בסכרת תכשירים נוגדי דיכאון (פלואוקסטין).
הריון והנקה:		אין להשתמש בתרופה אם הינך בהריון. טרבופרוסט עלול להיספג דרך העור ולכן אין להשתמש בו בנשים הרות או המנסות להיכנס להיריון. אם התרופה באה במגע עם העור, יש לשטוף אותה באופן מיידי. אין להשתמש בתרופה מבלי להיוועץ ברופא לפני התחלת הטיפול אם הינך מניקה.
מידע חשוב אודות חלק מהמרכיבים של התרופה		דואוטרב מכילה hydrogenated castor oil ו- propylene glycol אשר עלולים לגרום לתגובות וגירוי בעור.
תופעות לוואי:	בנוסף לפעילות הרצויה של התרופה, בזמן השימוש בה עלולות להופיע השפעות לוואי כגון: עצבנות, סחרחורת, כאב ראש, גירויי בעיניים, היפראמיה של העיניים, דלקת קרנית ממוקדת, כאבי עיניים, רגישות לאור, נפיחות בעיניים, דימום לחמית, צביעת קרנית, יובש בעיניים, אי נוחות בעין, הרגשה של גוף זר בעין, טשטוש ראייה, גרד בעיניים, רגישות יתר של לחמית, דמיעה מוגברת, גירוי ואדמומיות בעפעפיים, עייפות העיניים, שינויי קצב לב, שינויי לחץ דם, עווית הסמפונות (bronchospasm), אורטיקריה, התקהות העור מסביב לעיניים, כאבי גפיים. עליה במספר או בקצב גדילת הריסים. **<u>תופעות המחייבות התייחסות מיוחדת:</u>** שינויי קצב לב, שינויי לחץ דם, קוצר או קשיי בנשימה: הפסק/י הטיפול ופנה/י לרופא. עצבנות, סחרחורת, עין אדומה, דלקת ושינוי כל שהוא בעפעף, טשטוש בראיה, דלקת כלשהי-בעין, עיניים יבשות, תחושת צריבה, שינויים בצבע הקשתית, דלקת הקרנית, רגישות לאור, שטפי דם בעין: המשך/י בטיפול ופנה/י לרופא מיד! חוסר נוחות בעיניים, תחושה של עצם זר בעין, כאב וגירוד: המשך בטיפול ופנה לרופא. בכל מקרה שבו הינך מרגיש/ה תופעות לוואי שלא ציינו בעלון זה, או אם חל שינוי בהרגשתך הכללית עליך להתייעץ עם הרופא מיד.	בדומה לכל תרופה, השימוש ב**דואוטרב** עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. יתכן ולא תסבול מאף אחת מהן. **<u>תופעות המחייבות התייחסות מיוחדת:</u>** שינויי קצב לב, שינויי לחץ דם, קוצר או קשיי בנשימה: הפסק/י הטיפול ופנה/י לרופא. עצבנות, סחרחורת, עין אדומה, דלקת ושינוי כל שהוא בעפעף, טשטוש בראיה, דלקת כלשהי-בעין, עיניים יבשות, תחושת צריבה, שינויים בצבע הקשתית, דלקת הקרנית, רגישות לאור, שטפי דם בעין: המשך/י בטיפול ופנה/י לרופא מיד! חוסר נוחות בעיניים, תחושה של עצם זר בעין, כאב וגירוד: המשך בטיפול ופנה לרופא. בכל מקרה שבו הינך מרגיש/ה תופעות לוואי שלא ציינו בעלון זה, או אם חל שינוי בהרגשתך הכללית עליך להתייעץ עם הרופא מיד. **תופעות לוואי נוספות:** **מופיעות לעיתים קרובות:** גירויי בעיניים, היפראמיה של העיניים (אדמומיות), גרד בעיניים, דמיעה מוגברת, עקצוץ בעיניים, כאבי עיניים, נפיחות בעיניים, , רגישות לאור, דימום לחמית, טשטוש ראייה, ירידה בראייה, הפרעה בראייה, יובש בעיניים, אי נוחות בעין, אלרגיה בעיניים, גירוי, גרד, כאב, נפיחות ואדמומיות בעפעפיים, עייפות העיניים, עליה במספר או בקצב גדילת הריסים, אלרגיה לתרופה, עצבנות, סחרחורת, כאב ראש, שינויי קצב לב, שינויי לחץ דם, עווית הסמפונות (bronchospasm), קוצר נשימה, אורטיקריה, התקהות העור מסביב לעיניים, כאבי גפיים. **מופיעות לעיתים רחוקות:** הידללות או דלקת של שטח פנים של העין, דלקת של בלוטות העפעף, נפיחות הלחמית, היווצרות קרום בעפעפיים, גדילה מוגברת של גבות, דלקת בקשתית, שיעול, כאב או גירוי גרון, ליחה, תפקודי כבד לא תקינים, דלקת וגרד של העור, שינוי בצבע השתן, תחושת צמא, אי נוחות בתוך האף. **מופיעות לעיתים נדירות:** אבדן שיער, צניחה של העפעף, פריחה, אי ספיקת לב, כאב בחזה, שבץ, עלפון, דכאון, אסתמה, עליה בקצב הלב, נימול ועקצוץ. דלקת קרנית ממוקדת, צביעת קרנית, הרגשה של גוף זר בעין, רגישות יתר של לחמית. אם אחת מתופעות הלוואי מחמירה, או כאשר אתה סובל מתופעת לוואי שלא הוזכרה בעלון, עליך להתייעץ עם הרופא.

איך לאחסן את התרופה?	יש לשמור בטמפרטורה של 2-25 C°. אין להשתמש לאחר 4 שבועות מפתיחה. גם לפי תנאי האריזה /אחסנה המומלצים, תרופות נשמרות לתקופה מוגבלת בלבד. נא לשים לב לתאריך התפוגה של התכשיר! בכל מקרה של ספק, עליך להיוועץ ברוקח שסיפק לך את התרופה. אין לאחסן תרופות שונות באותה אריזה.	● מנע הרעלה! תרופה זו וכל תרופה אחרת יש לשמור במקום סגור מחוץ להישג ידם של ילדים ו/או תינוקות ועל ידי כך תמנע הרעלה. אל תגרום להקאה ללא הוראה מפורשת מהרופא. ● אין להשתמש בתרופה אחרי תאריך התפוגה (exp. date) המופיע על גבי האריזה. תאריך התפוגה מתייחס ליום האחרון של אותו חודש. ~~● יש לשמור בטמפרטורה של 2-25 C°.~~ ●אין לאחסן מעל 25 C°. ● אין להשתמש לאחר 4 שבועות מפתיחה.
מידע נוסף:	**כמו כן, התכשיר את המרכיבים הבלתי פעילים הבאים:** Polyoxyethylene Hydrogenated Castor Oil 40, Trometamol, Boric Acid, Mannitol, Disodium Edetate, Benzalkonium Chloride,Concentrated Hydrochloric Acid, Purified Water	נוסף על החומרים הפעילים, התרופה מכילה גם: Polyoxyethylene Hydrogenated Castor Oil 40 (HCO-40), Propylene Glycol, Boric Acid, Mannitol, Sodium Chloride, Polyquanterium-1Solution equivalent to Polyquanterium-1, Hydrochloric Acid and/or Sodium Hydroxide, Water for Injection. ~~Polyoxyethylene Hydrogenated Castor Oil 40, Trometamol, Boric Acid, Mannitol, Disodium Edetate, Benzalkonium Chloride,Concentrated Hydrochloric Acid, Purified Water.~~ כיצד נראית התרופה ומה תוכן האריזה? דואוטרב היא תמיסה צלולה, חסרת צבע המסופקת בבקבוק פלסטיק בנפח של 2.5 מ״ל.