SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DuoTrav40micrograms/mL+5mg/mLeyedrops,solution

2. QUALITATIVEANDQUANTITATIVECOMPOSITION

EachmL ofsolutioncontains40 microgramsoftravoprost and5 mgoftimolol (astimolol maleate).

Excipient(s) with known effect

EachmLofsolutioncontainspolyquaternium-1(POLYQUAD)10microgram,propyleneglycol 7.5 mgandpolyoxyethylenehydrogenatedcastoroil401 mg(seesection4.4).

Forthefulllistofexcipients,seesection6.1.

3. PHARMACEUTICALFORM

Eyedrops,solution(eyedrops).

Clear, colourless solution.

4. CLINICALPARTICULARS

4.1 Therapeuticindications

DuoTravisindicatedinadultsforthedecreaseofintraocularpressure(IOP)inpatientswith open-angleglaucomaorocularhypertensionwhoareinsufficientlyresponsivetotopicalbeta blockers or prostaglandin analogues (see section 5.1).

4.2 Posologyandmethodofadministration

Posology

Use inadults,includingtheelderly
Thedose isone dropofDuoTravintheconjunctivalsac oftheaffectedeye(s)once daily,inthe morning or evening. It should be administered at the same time each day.

Ifadoseismissed,treatment should becontinued withthenextdoseasplanned.Thedoseshould not exceed one drop in the affected eye(s) daily.

Specialpopulations
Hepaticand renalimpairment
Nostudieshave beenconductedwithDuoTravorwith timolol5 mg/mL eye dropsinpatientswith hepatic or renal impairment.

Travoprost has been studied in patients with mild to severe hepatic impairment and in patients with mildtosevererenalimpairment (creatinineclearanceaslowas14 mL/min).Nodoseadjustment was necessary in these patients.

Patientswithhepaticorrenalimpairment areunlikelytorequiredose adjustment withDuoTrav(see section 5.2).

Paediatricpopulation
The safetyandefficacyof DuoTravinchildrenandadolescentsbelowthe age of18 yearshave not been established. No data are available.

Methodofadministration

Forocularuse.

The patient should remove the protective overwrap immediately prior toinitial use. To prevent contaminationofthedroppertipand solution, care must be takennottotouchtheeyelids, surrounding areas or other surfaces with the dropper tip of the bottle.

Whennasolacrimalocclusion isused ortheeyelidsareclosed for2 minutes, systemic absorptionis reduced. Thismayresult inadecrease insystemic sideeffectsandanincreaseinlocalactivity (see section 4.4).

If more thanone topicalophthalmicmedicinalproductisbeingused, the medicinalproductsmust be administered at least 5 minutes apart (see section 4.5).

WhensubstitutinganotherophthalmicantiglaucomamedicinalproductwithDuoTrav, the other medicinal product should be discontinued and DuoTrav should be started the following day.

Patientsmust be instructed toremove soft contactlensespriortoapplicationofDuoTrav andwait 15 minutes after instillation of the dose before reinsertion (see section 4.4).

4.3 Contraindications

Hypersensitivitytothe active substances, ortoanyoftheexcipients listed insection 6.1. Hypersensitivity to other beta blockers.
Reactiveairwaydisease includingbronchialasthma, orahistoryofbronchialasthma, severe chronic obstructive pulmonary disease.
Sinus bradycardia, sick sinus syndrome, including sino-atrial block, second- or third-degree atrioventricularblocknot controlled withpacemaker.Overtcardiacfailure,cardiogenicshock. Severe allergic rhinitis and corneal dystrophies.

4.4 Specialwarningsandprecautionsforuse

Systemiceffects

Likeothertopicallyapplied ophthalmicagents,travoprost andtimololareabsorbed systemically.Due to the beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking medicinal productsmay occur. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. For information on how to reduce systemic absorption, see section 4.2.

Cardiacdisorders

In patients with cardiovasculardiseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta blockers should be criticallyassessed and therapy with otheractive substancesshould beconsidered.Patientswithcardiovasculardiseasesshould be watched for signs of deterioration of these diseases and of adverse reactions.

Due totheirnegativeeffect onconductiontime, beta blockersshould onlybe givenwithcautionto patients with first-degree heart block.

Vasculardisorders

Patientswithsevere peripheralcirculatorydisturbance/disorders (i.e.severe formsofRaynaud's disease or Raynaud's syndrome) should be treated with caution.

Respiratorydisorders

Respiratoryreactions, includingdeathduetobronchospasminpatientswithasthma, have been reported following administration of some ophthalmic beta blockers.

DuoTravshould be usedwithcautioninpatientswithmild/moderatechronic obstructivepulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Hypoglycaemia/diabetes

Beta blockersshould be administered withcautioninpatientssubjecttospontaneoushypoglycaemia or in patients with labile diabetes, as beta blockers may mask the signs and symptoms of acute hypoglycaemia.

Muscleweakness

Beta-adrenergicblockingmedicinalproductshavebeen reportedtopotentiatemuscleweakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis and generalisedweakness).

Cornealdiseases

Ophthalmic betablockersmayinducedrynessofeyes. Patientswithcornealdiseasesshould betreated with caution.

Choroidaldetachment

Choroidaldetachment hasbeenreportedwithadministrationofaqueoussuppressant therapy(e.g. timolol, acetazolamide) after filtration procedures.

Otherbeta-blockingagents

The effectonintra-ocular pressure or theknowneffectsof systemic beta blockademaybe potentiated when timolol is given to patients already receiving a systemic beta-blocking medicinal product. The responseofthesepatientsshould becloselyobserved.Theuseoftwotopical beta-adrenergic blocking agents is not recommended (see section 4.5).

Surgicalanaesthesia

Beta-blockingophthalmologicalpreparationsmayblock systemic beta-agonisteffects,e.g.of adrenaline. The anaesthetist should be informed when the patient is receiving timolol.

Hyperthyroidism

Betablockersmaymaskthesignsofhyperthyroidism.

Skincontact

Prostaglandinsand prostaglandin analoguesare biologicallyactive substancesthat may be absorbed through the skin. Women who are pregnant or attempting to become pregnant should exercise appropriate precautionstoavoiddirectexposure tothecontentsofthe bottle. Intheunlikelyeventof coming in contact witha substantial portion of the contents of the bottle, thoroughly cleanse the exposed area immediately.

Anaphylacticreactions

Whiletakingbeta blockers, patientswith ahistoryofatopyora historyofsevere anaphylacticreaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual dose of adrenaline used totreat anaphylactic reactions.

Concomitanttherapy

Timolol mayinteract withothermedicinal products(seesection4.5). The

use of two local prostaglandins is not recommended.

Oculareffects

Travoprost may graduallychange the eye colour by increasing the number of melanosomes (pigment granules)inmelanocytes.Beforetreatmentisinstituted,patientsmust be informedofthe possibilityof a permanent change in eye colour. Unilateral treatment canresult in permanent heterochromia. The long-term effects on the melanocytes and any consequences thereof are currently unknown. The change iniriscolour occursslowly and may not be noticeable for monthsto years. The change ineye 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 inpatients with browneyes. Typically,the brownpigmentationaroundthe pupil spreadsconcentricallytowardsthe 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.

Incontrolledclinical trials, periorbitaland/oreyelidskindarkeninginassociationwiththe use of travoprost has been reported.

Periorbitalandlidchanges,includingdeepeningoftheeyelidsulcus, have beenobservedwith prostaglandinanalogues.

Travoprost may graduallychange 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/ornumberoflashes. The mechanismofeyelashchangesandtheir long-termconsequencesare currently unknown.

Travoprost hasbeenshowntocause slight enlargement ofthe palpebralfissure instudiesinthe monkey. However, thiseffect wasnot observed duringthe clinicaltrialsandisconsideredtobe species specific.

There is no experience of DuoTrav in inflammatory ocular conditions, nor in neovascular, angle-closure,narrow-angleorcongenitalglaucoma, and onlylimitedexperienceinthyroideye disease,inopen-angleglaucoma ofpseudophakicpatientsandinpigmentaryorpseudoexfoliative glaucoma.

Macular oedema has been reported during treatment with prostaglandin $F_{2\alpha}$ analogues. Caution is recommended whenusingDuoTravinaphakicpatients, pseudophakicpatientswithatornposterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema.

Inpatientswithknownpredisposingrisk factorsforiritis/uveitis, andinpatientswithactive intraocular inflammation, DuoTrav can be used with caution.

Excipients

DuoTravcontainspropyleneglycolwhichmaycauseskinirritation.

DuoTravcontainspolyoxyethylenehydrogenatedcastoroil40whichmaycauseskinreactions.

Patientsmust be instructed toremove contactlensespriortoapplicationofDuoTravand wait 15 minutes after instillation of the dose before reinsertion (see section 4.2).

4.5 Interactionwithothermedicinalproductsandotherformsofinteraction

Nospecificdruginteractionstudieshavebeenperformedwithtravoprostortimolol.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blockersolutionisadministeredconcomitantlywithoralcalciumchannel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics or guanethidine.

The hypertensive reactiontosuddenwithdrawal ofclonidine canbepotentiated whentakingbeta blockers.

Potentiated systemicbetablockade(e.g.decreased heart rate,depression)hasbeen reporteddurin combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.

Mydriasisresultingfromconcomitantuseofophthalmicbeta blockersand adrenaline(epinephrine) has been reported occasionally.

Beta blockersmayincreasethe hypoglycaemiceffect ofantidiabetic medicinalproducts.Betablockers can mask the signs and symptoms of hypoglycaemia (see section 4.4).

4.6 Fertility,pregnancyandlactation

Womenofchildbearingpotential/contraception

DuoTravmust not beusedinwomenofchild-bearingage/potential unlessadequatecontraceptive measures are in place (see section 5.3).

Pregnancy

Travoprosthasharmfulpharmacologicaleffectsonpregnancyand/orthefoetus/newbornchild.

Thereare noorlimitedamount ofdatafromthe use ofDuoTravortheindividual componentsin pregnant women. Timolol should not be used during pregnancy unless clearly necessary.

Epidemiological studieshavenot revealed malformativeeffectsbut showa risk forintrauterinegrowth retardation when beta blockers are administered bythe oral route. 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.

DuoTravshould not beusedduringpregnancyunlessclearlynecessary. Forinformationonhowto reduce systemic absorption, see section 4.2.

Breast-feeding

It is unknown whether travoprost from eye drops is excreted in human breast milk. Animal studies haveshownexcretionoftravoprost and metabolitesinbreast milk. Timolol isexcretedinbreast milk and has the potential to cause serious adverse reactions in the breast-fed infant. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta blockade in the infant. For information on how to reduce systemic absorption, see section 4.2.

TheuseofDuoTravbybreast-feedingwomenisnot recommended. Fertility

There are nodata onthe effects of DuoTrav on human fertility. Animal studies showed no effect of travoprost onfertilityatdosesupto75timesthe maximumrecommended humanoculardose, whereas no relevant effect of timolol was noted at this dose level.

4.7 Effectsonabilitytodriveanduse machines

DuoTrav has minor influence on the ability todrive and use machines. As with any eye drops, 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. DuoTrav may also cause hallucinations, dizziness, nervousness and/or fatigue (see section 4.8) which may affectthe abilitytodrive anduse machines.Patientsshould be advisednottodrive and use machines if these symptoms occur.

4.8 Undesirableeffects

Summaryofthe safetyprofile

Inclinical studiesinvolving2,170patientstreated with DuoTravthe most frequentlyreported treatment-related adverse reaction was ocular hyperaemia (12.0%).

Tabulatedsummaryofadversereactions

The adverse reactionslistedinthetablebelow were observed inclinicalstudiesorwithpost-marketing experience. They are ranked accordingto systemorgan class and classified according to the following convention: verycommon (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), or not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in decreasing order of seriousness.

Systemorganclass	**Frequency**	**Adversereactions**
Immunesystemdisorders	Uncommon	Hypersensitivity
Psychiatricdisorders	Rare	Nervousness
	Notknown	Hallucinations*,Depression
Nervoussystemdisorders	Uncommon	Dizziness,headache
	Not known	Cerebrovascularaccident,syncope,paraesthesia
Eyedisorders	Verycommon	Ocularhyperaemia
	Common	Punctatekeratitis,eyepain,visualdisturbance, vision blurred, dry eye, eye pruritus, ocular discomfort, eye irritation
	Uncommon	Keratitis, iritis, conjunctivitis, anterior chamber inflammation,blepharitis,photophobia,visualacuity reduced, asthenopia, eye swelling, lacrimation increased, erythema of eyelid, growth of eyelashes, eye allergy, conjunctival oedema, eyelid oedema
	Rare	Corneal erosion, meibomianitis, conjunctival haemorrhage,eyelidmargincrusting,trichiasis, distichiasis
	Not known	Macularoedema,eyelidptosis, lidsulcusdeepened, iris hyperpigmentation, corneal disorder
Cardiacdisorders	Uncommon	Bradycardia
	Rare	Arrhythmia,heartrateirregular
	Not known	Cardiacfailure,tachycardia,chestpain,palpitations
Vasculardisorders	Uncommon	Hypertension,hypotension
	Not known	Oedemaperipheral
Respiratory,thoracicand mediastinal disorders	Uncommon	Dyspnoea,postnasaldrip
	Rare	Dysphonia,bronchospasm,cough,throatirritation, oropharyngeal pain, nasal discomfort
	Not known	Asthma
Gastrointestinaldisorders	Notknown	Dysgeusia
Hepatobiliarydisorders	Rare	Alanineaminotransferaseincreased,aspartate aminotransferase increased
Skinandsubcutaneoustissue disorders	Uncommon	Dermatitiscontact,hypertrichosis,skin hyperpigmentation (periocular)
	Rare	Urticaria,skindiscolouration,alopecia
	Not known	Rash
Musculoskeletal and connectivetissuedisorders	Rare	Paininextremity
Renaland urinarydisorders	Rare	Chromaturia
General disorders and administrationsiteconditions	Rare	Thirst,fatigue

*adversereactionsobservedwithtimolol.

Additionaladverse reactionsthat have beenseen withone oftheactivesubstancesand maypotentially occur with DuoTrav:

Travoprost

Systemorganclass	**MedDRApreferredterm**
Immunesystemdisorders	Seasonalallergy
Psychiatricdisorders	Anxiety,insomnia
Eyedisorders	Uveitis, conjunctival follicles, eye discharge, periorbital oedema, eyelids pruritus, ectropion, cataract, iridocyclitis, ophthalmic herpes simplex, eye inflammation, photopsia, eczema eyelids,halovision,hypoaesthesiaeye,anterior chamber pigmentation, mydriasis, eyelash hyperpigmentation, eyelash thickening, visual fielddefect
Earandlabyrinthdisorders	Vertigo,tinnitus
Vasculardisorders	Bloodpressurediastolicdecreased,blood pressuresystolicincreased
Respiratory,thoracicandmediastinaldisorders	Asthmaaggravated,rhinitisallergic,epistaxis, respiratory disorder, nasal congestion, nasal dryness
Gastrointestinaldisorders	Pepticulcerreactivated,gastrointestinal disorder,diarrhoea,constipation,drymouth, abdominal pain, nausea, vomiting
Skinandsubcutaneoustissue disorders	Skin exfoliation, hair texture abnormal, dermatitis allergic, hair colour changes, madarosis,pruritus,hairgrowthabnormal, erythema
Musculoskeletalandconnectivetissuedisorders	Musculoskeletalpain,arthralgia
Renalandurinarydisorders	Dysuria,urinaryincontinence
Generaldisordersandadministrationsite conditions	Asthenia
Investigations	Prostaticspecificantigenincreased

Timolol

Like other topicallyapplied ophthalmic medicinal products, timolol is absorbed into the systemic circulation. This may cause undesirable effects similar to those seen with systemic beta-blocking agents. Additionallistedadverse reactionsinclude reactionsseenwithintheclassofophthalmic beta blockers. The incidence of systemic ADRsaftertopical ophthalmic administrationislower than for systemic administration. For information on howto reduce systemic absorption, see section 4.2.

Systemorganclass	**MedDRApreferredterm**
Immunesystemdisorders	Systemic allergic reactions including angioedema,urticaria,localisedandgeneralised rash,pruritus,anaphylaxis
Metabolismandnutritiondisorders	Hypoglycaemia
Psychiatricdisorders	Hallucinations,insomnia,nightmares,memory loss
Nervoussystemdisorders	Cerebralischaemia,increasesinsignsand symptomsofmyasthenia gravis
Eyedisorders	Signsandsymptomsofocularirritation(e.g. burning, stinging, itching, tearing, redness), choroidal detachment following filtration surgery (see section 4.4), decreased corneal sensitivity,diplopia
Cardiacdisorders	Oedema,congestiveheartfailure, atrioventricularblock,cardiacarrest
Vasculardisorders	Raynaud'sphenomenon,cold handsandfeet
Gastrointestinaldisorders	Nausea,dyspepsia,diarrhoea,drymouth, abdominalpain,vomiting
Skinandsubcutaneoustissue disorders	Psoriasiformrashorexacerbationofpsoriasis
Musculoskeletalandconnectivetissuedisorders	Myalgia
Reproductivesystemandbreastdisorders	Sexualdysfunction,decreasedlibido
Generaldisordersandadministrationsite conditions	Asthenia

4.9 Overdose

AtopicaloverdosewithDuoTravisnotlikelytooccurortobeassociatedwithtoxicity.

Incase ofaccidentalingestion, symptomsofoverdose fromsystemic betablockademayinclude bradycardia, hypotension, bronchospasm and heart failure.

IfoverdosewithDuoTravoccurs,treatment should besymptomatic and supportive.Timololdoesnot dialyse readily.

5 PHARMACOLOGICALPROPERTIES

5.1 Pharmacodynamicproperties

Pharmacotherapeuticgroup:Ophthalmologicals;Antiglaucomapreparationsandmiotics,ATCcode: S01ED51.

Mechanismofaction

DuoTravcontainstwoactivesubstances: travoprost andtimolol maleate.Thesetwo componentslower intraocular pressure by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound alone.

Travoprost, a prostaglandin$F_{2\alpha}$analogue, is a full agonist which is highly selectiveand has a high affinity for the prostaglandin FP receptor, and reduces the intraocular pressure by increasing the outflowofaqueoushumourvia trabecularmeshwork and uveoscleralpathways. ReductionofIOP in man starts within approximately2hours after administration andmaximum effect is reachedafter 12 hours. Significant lowering of intraocular pressure can be maintained for periods exceeding 24hourswitha singledose.

Timolol is a non-selective adrenergic blocking agent that has no intrinsic sympathomimetic, direct myocardialdepressant ormembrane-stabilisingactivity.Tonographyand fluorophotometrystudiesin man suggest that its predominant actionis related to reduced aqueous humour formationand a slight increase in outflow facility.

Secondarypharmacology

Travoprost significantlyincreased optic nervehead blood flowinrabbitsfollowing7 daysoftopical ocular administration (1.4 micrograms once daily).

Pharmacodynamiceffects

Clinical effects
In a twelve-month controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of25 to 27 mmHg, the mean IOP-lowering effect of DuoTrav dosed oncedailyinthemorning was8 to10 mmHg. The non-inferiorityofDuoTravascompared to latanoprost 50 micrograms/mL + timolol 5 mg/mL in the meanIOP reduction was demonstrated across all time-points at all visits.

Ina three-monthcontrolledclinicalstudyinpatientswith open-angleglaucoma orocular hypertension and baselinemeanIOP of27 to30 mmHg, the meanIOP-loweringeffect ofDuoTravdosedoncedaily in the morning was 9 to12 mmHg, and was up to 2 mmHg greaterthanthat of travoprost 40micrograms/mLdosedoncedailyinthe eveningand2 to3mmHggreaterthanthatoftimolol 5 mg/mL dosed twicedaily. Astatistically superior reductionin morning mean IOP (08:00, 24 hours afterthelastdose ofDuoTrav)wasobserved comparedtotravoprost at allvisitsthroughoutthe 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 oncedailyinthemorning was7 to9 mmHg. MeanIOP reductionswere non-inferior, although numericallylower, tothose achieved by concomitant therapy with travoprost 40 micrograms/mL dosed oncedailyin the evening and timolol 5 mg/mL dosed once dailyin the morning.

Ina 6-weekcontrolledclinical studyinpatientswithopen-angle glaucoma orocularhypertensionand baseline mean IOP of 24 to26 mmHg, the mean IOP-lowering effect of DuoTrav (polyquaternium-1-preserved)dosed oncedailyinthe morningwas8 mmHgand equivalenttothatof DuoTrav (benzalkonium chloride-preserved).

Inclusion criteria were common across the studies, with the exception of the IOP entry criteria and response topreviousIOP therapy.Theclinicaldevelopment ofDuoTravincludedbothpatientsnaive and on therapy. Insufficient responsiveness to monotherapy was not an inclusion criterion.

Existingdata suggest thateveningdosingmight have some advantages asregardsmeanIOP reduction. Consideration shouldbe given to patient convenience and their likely compliance whenrecommending morning vs. evening dosing.

5.2 Pharmacokineticproperties

Absorption

Travoprost andtimolol areabsorbed throughthecornea.Travoprost isa prodrugthat undergoesrapid esterhydrolysisinthecorneatothe active freeacid. Followingonce-dailyadministrationofDuoTrav PQinhealthysubjects(N=22)for5days,travoprost free acid wasnot quantifiableinplasma samples fromthe majority of subjects(94.4%) and generally wasnot detectable one hour after dosing. When measurable (≥0.01 ng/mL, the assay limit of quantitation), concentrations ranged from 0.01to0.03ng/mL.Themeantimololsteady-stateC_{max}was1.34ng/mlandT$_{max}$wasapproximately 0.69hoursafteronce-dailyadministrationofDuoTrav.

Distribution

Travoprost freeacidcanbe measuredintheaqueoushumourduringthe first fewhoursinanimalsand 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 12hoursafterocularadministrationofDuoTrav.

Biotransformation

Metabolismisthe majorroute ofeliminationofbothtravoprost and the active freeacid.Thesystemic metabolic pathways parallel those of endogenous prostaglandin $F_{2\alpha}$ which are characterised by reduction of the 13-14 double bond, oxidation of the15-hydroxyl and β-oxidative cleavages of the upper side chain.

Timolol is metabolised by two pathways. One route yields anethanolamine side chain on the thiadiazole ring and the other gives an ethanolic side chainon the morpholine nitrogen and a second similarsidechainwithacarbonyl groupadjacent tothenitrogen.The plasma $t_{1/2}$of timololis4 hours after ocular administration of DuoTrav.

Elimination

Travoprost freeacidand itsmetabolitesare mainlyexcreted bythekidneys. Lessthan2% ofanocular dose of travoprost was recovered in urine as free acid. Timolol and its metabolitesare primarily excreted bythekidneys. Approximately20% ofa timololdose isexcretedinthe urine unchangedand the remainder excreted in urine as metabolites.

5.3 Preclinicalsafetydata

In monkeys, administrationofDuoTravtwice dailywasshowntoinduceincreasedpalpebralfissure and to increase irispigmentation similarto that observed with ocularadministration of prostanoids.

DuoTravpreserved withpolyquaternium-1induced minimal ocularsurfacetoxicity, comparedtoeye drops preserved with benzalkonium chloride, on cultured human corneal cells and following topical ocular administration in rabbits.

Travoprost

Topical ocularadministrationoftravoprost tomonkeysatconcentrationsofupto0.012%tothe right eye, twice daily for one year resulted in no systemic toxicity.

Reproductiontoxicitystudieswithtravoprost have beenundertakeninrats, miceand rabbitsusingthe systemic route. Findings are related to FP receptor agonist activityin uterus with early embryolethality, post-implantationlossand foetotoxicity.Inpregnant rats, systemic administrationof travoprost at dosesmore than 200 timesthe clinicaldose during the period of organogenesisresulted in an increased incidence of malformations. Low levels of radioactivity were measured in amniotic fluid and foetal tissues of pregnant rats administered ^{3}H-travoprost. Reproduction and development studies have demonstrated a potent effect on foetal loss with a high rate observed inrats and mice (180 pg/mL and 30 pg/mL plasma, respectively) at exposures1.2 to6 timestheclinical exposure (up to 25 pg/mL).

Timolol

Non-clinicaldatarevealed nospecial hazard forhumanswithtimolol based onconventionalstudiesof safety pharmacology, repeated 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).

6 PHARMACEUTICALPARTICULARS

6.1 Listofexcipients

Polyquaternium-1
Mannitol (E421)
Propyleneglycol(E1520)
Polyoxyethylenehydrogenatedcastoroil40 (HCO-40)
Boric acid
Sodiumchloride
Sodiumhydroxideand/orhydrochloricacid (forpHadjustment) Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelflife

2years.

Discard4weeksafterfirst opening.

6.4 Specialprecautionsforstorage

Donotstoreabove30°C.

6.5 Natureandcontentsofcontainer

2.5 mLoval polypropylene(PP)orlow-densitypolyethylene(LDPE)bottleandPPorLDPE dispensing plug with PP screw cap, presented in an overwrap.

Packsizesof1bottle.
.

6.6 Specialprecautionsfordisposal

Nospecialrequirements.

7 MARKETINGAUTHORISATIONHOLDER

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8 MARKETINGAUTHORISATIONNUMBER(S)

A4-3210

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