

Module 2.4: Non-Clinical Overview

Travoprost-Timolol/Pharmathen (40 micro grams/ml and 5 mg/ml) **preservative free eye drops, solution in multi-dose container**

Formulation of Pharmathen S.A.

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2.4 Non-Clinical Overview

2.4.1 Overview of the Non-clinical Testing Strategy

2.4.2 Pharmacology

Travoprost

Timolol

2.4.2.1 Primary Pharmacodynamics

Travoprost

Timolol

Travoprost-Timolol Combination Activity

2.4.2.3 Pharmacodynamic Interactions

2.4.3 Pharmacokinetics

2.4.3.1. Analytical Methodology

Travoprost

Timolol

2.4.3.2 Pharmacokinetics Overview

Travoprost

2.4.3.3. Absorption

Travoprost

Timolol

Travoprost/Timolol combination

2.4.3.4 Distribution

Travoprost

Timolol

Travoprost – Timolol Combination

2.4.3.5 Metabolism

Travoprost

Timolol

Travoprost-Timolol Combination

2.4.3.6. Excretion

Travoprost

Timolol

Travoprost-Timolol Combination

2.4.4 Safety/Toxicology

2.4.4.1. Animal toxicology

Travoprost

Timolol

2.4.4.2 Clinical Safety

2.4.4.3 Carcinogenicity

Travoprost

Timolol

2.4.4.4 Genotoxicity

Travoprost

Timolol

2.4.4.5 Reproductive toxicity and Lactation

Travoprost

Timolol

2.4.4.6 Special studies

Travoprost

T

Timolol Local toxicity studies

Timolol Effects on lens

2.4.4.8 Travoprost/Timolol Combination Preclinical Toxicity

2.4.4.9 Impurities and Excipients

Travoprost/Timolol combination

2.4.4.10 Environmental risk assessment

Travoprost

2.4.4.9 Preservative Toxicity

2.4.5: Integrated Overview and Conclusions

2.4.6 REFERENCES

AHFS drug information 2008a. McEvoy GK, ed. Timolol. Bethesda, MD: American Society of Health-System Pharmacists, 2008: 2930-2932.

AHFS drug information 2008b. McEvoy GK, ed. Timolol Maleate. Bethesda, MD: American Society of Health-System Pharmacists, 2008: 1922-1926.

Akaishi T, Kurashima H, Odani-Kawabata N, Ishida N, Nakamura M, 2010. Effects of repeated administrations of tafluprost, latanoprost, and travoprost on optic nerve head blood flow in conscious normal rabbits. *J Ocul Pharmacol Ther*; 26(2):181-6.

Ammar DA, Noecker RJ, Kahook MY, 2010. Effects of benzalkonium chloride-preserved, polyquad-preserved, and sofZia preserved topical glaucoma medications on human ocular epithelial cells. *Adv Ther*; 27(11):837-45.

Andres-Guerrero V, Vicario-de-la-Torre M, Molina-Martínez IT, Benítez-del-Castillo JM, García-Feijoo J, Herrero-Vanrell R, 2011. Comparison of the in vitro tolerance and in vivo efficacy of traditional timolol maleate eye drops versus new formulations with bioadhesive polymers. *Invest Ophthalmol Vis Sci*; 52(6):3548-56.

Arnold JJ, Hansen MS, Gorman GS, Inoue T, Rao V, Spellen S, Hunsinger RN, Chapleau CA, Pozzo-Miller L, Stamer WD, Challa P, 2013. The effect of Rho-associated kinase inhibition on the ocular penetration of timolol maleate. *Invest Ophthalmol Vis Sci*; 54(2):1118-26.

Ayaki M, Iwasawa A, 2010. Cytotoxicity of prostaglandin analog eye drops preserved with benzalkonium chloride in multiple corneoconjunctival cell lines. *Clin Ophthalmol*; 4:919-24.

Baudouin C, Riancho L, Warnet JM, Brignole F, 2007. In vitro studies of antiglaucomatous prostaglandin analogues: travoprost with and without benzalkonium chloride and preserved latanoprost. *Invest Ophthalmol Vis Sci*; 48(9):4123-8.

Baudouin C, Labbé A, Liang H, Pauly A, Brignole-Baudouin F, 2010. Preservatives in eyedrops: the good, the bad and the ugly. *Prog Retin Eye Res*; 29(4):312-34.

Bolivar G, Teus M, Arranz-Marquez E, 2011. Effect of Acute Increases of the Intraocular Pressure on the Corneal Pachymetry in Eyes Treated with Travoprost: An Animal Study. *Curr Eye Res*; 36(11):1014-9.

Brignole-Baudouin F, Riancho L, Liang H, Baudouin C, 2011. Comparative In Vitro Toxicology Study of Travoprost Polyquad-preserved, Travoprost BAK-preserved, and Latanoprost BAK-preserved Ophthalmic Solutions on Human Conjunctival Epithelial Cells. *Curr Eye Res*;36(11):979-88.

Cheng JW, Cheng SW, Gao LD, Lu GC, Wei RL, 2012. Intraocular pressure-lowering effects of commonly used fixed-combination drugs with timolol: a systematic review and meta-analysis. *PLoS One*; 7(9):e45079.

Cho HK, Park MH, Moon JI, 2011. Effects of antiglaucoma drugs on the ocular surface in rabbits: a fixed-combination drug versus two concomitant drugs. *Jpn J Ophthalmol*; 55(6): 670-5.

Chou A, Hori S, Takase M, 1985. Ocular toxicity of beta-blockers and benzalkonium chloride in pigmented rabbits: electrophysiological and morphological studies; *Jpn J Ophthalmol*, 29, 13-23.

DuoTrav® Scientific Discussion, 2006. Scientific Discussion, EMA, 2006.

DuoTrav® Product Monograph, 2008. Travoprost and Timolol maleate Product Monograph, Alcon Canada, 2008.

DuoTrav® SPC, 2015. Summary of Product Characteristics. Alcon Surrey, UK.

Eichhold TH, Kuhlenbeck DL, Baker TR, Stella ME, Amburgey JS, deLong MA, Hartke JR, Cruze CA, Pierce SA, Wehmeyer KR, 2000. Use of short high-performance liquid chromatography columns and tandem-mass spectrometry for the rapid analysis of a prostaglandin analog, fluprostenol, in rat plasma. *J Chromatogr B Biomed Sci Appl*; 741(2):213-20.

Ellis PP, Wu PY, Riegel M., 1991. Aqueous humor pilocarpine and timolol levels after instillation of the single drug or in combination. *Invest Ophthalmol Vis Sci*; 32(3):520-2.

EMA, 2009: EMA Public Statement on Antimicrobial Preservatives in Ophthalmic Preparations for Human Use (Doc. Ref.: EMA/622721/2009).

Franks WA, Renard JP, Cunliffe IA, Rojanapongpun P, 2006. A 6-week, double-masked, parallel-group study of the efficacy and safety of travoprost 0.004% compared with latanoprost 0.005%/timolol 0.5% in patients with primary open-angle glaucoma or ocular hypertension. *Clin Ther*; 28(3):332-9.

Frishman WH, Kowalski M, Nagnur S, Warshafsky S, Sica D, 2001: Cardiovascular considerations in using topical, oral, and intravenous drugs for the treatment of glaucoma and ocular hypertension: focus on beta-adrenergic blockade; *Heart Dis*, 3, 386-97.

Fukuda M, Sasaki H, 2015. The transcorneal penetration of commercial ophthalmic formulations containing timolol maleate in rabbit eyes. *J Ocul Pharmacol Ther*. 201; 31(1):57-60.

Furrer P, Berger J, Mayer JM, Gurny R, 2001: A comparative study of the ocular tolerance of 3 timolol-based preparations: the influence of preservatives on ocular tolerance; *J Fr Ophthalmol*, 24, 13-9.

Gabelt BT, Hennes EA, Bendel MA, Constant CE, Okka M, Kaufman PL, 2009. Prostaglandin subtype-selective and non-selective IOP-lowering comparison in monkeys. *J Ocul Pharmacol Ther*; 25(1):1-8.

Gagliuso DJ, Wang RF, Mittag TW, Podos SM, 2004. Additivity of bimatoprost or travoprost to latanoprost in glaucomatous monkey eyes. *Arch Ophthalmol*; 122(9):1342-7.

Gelatt KN, MacKay EO, 2004. Effect of different dose schedules of travoprost on intraocular pressure and pupil size in the glaucomatous Beagle. *Vet Ophthalmol*; 7(1):53-7.

Goldberg I, Cunha-Vaz J, Jakobsen JE, Nordmann JP, Trost E, Sullivan EK; International Travoprost Study Group, 2001. Comparison of topical travoprost eye drops given once daily and timolol 0.5% given twice daily in patients with open-angle glaucoma or ocular hypertension. *J Glaucoma*, 10:414–22

Guenoun JM, Baudouin C, Rat P, Pauly A, Warnet JM, Brignole-Baudouin F, 2005. In vitro study of inflammatory potential and toxicity profile of latanoprost, travoprost, and bimatoprost in conjunctiva-derived epithelial cells. *Invest Ophthalmol Vis Sci*; 46(7):2444-50.

Hariharan S, Minocha M, Mishra GP, Pal D, Krishna R, Mitra AK, 2009. Interaction of ocular hypotensive agents (PGF2 alpha analogs-bimatoprost, latanoprost, and travoprost) with MDR efflux pumps on the rabbit cornea. *J Ocul Pharmacol Ther*; 25(6):487-98.

Hellberg MR, Sallee VL, McLaughlin MA, Sharif NA, Desantis L, Dean TR, Zinke PW, 2001. Preclinical efficacy of travoprost, a potent and selective FP prostaglandin receptor agonist. *J Ocul Pharmacol Ther*; 17(5):421-32.

Hollo G. 2007. The side effects of the prostaglandin analogues. *Expert Opin Drug Saf*, 6:45–52.

Inan UU, Ermis SS, Orman A, Onrat E, Yucel A, Ozturk F, Asagidag A, Celik A, 2004. The comparative cardiovascular, pulmonary, ocular blood flow, and ocular hypotensive effects of topical travoprost, bimatoprost, brimonidine, and betaxolol. *J Ocul Pharmacol Ther*; 20(4):293-310.

Kahook MY, Noecker R, 2008. Quantitative analysis of conjunctival goblet cells after chronic application of topical drops. *Adv Ther*; 25(8):743-51.

Khoh-Reiter S, Jessen BA, 2009. Evaluation of the cytotoxic effects of ophthalmic solutions containing benzalkonium chloride on corneal epithelium using an organotypic 3-D model. *BMC Ophthalmol*; 9:5.

Kurashima H, Watabe H, Sato N, Abe S, Ishida N, Yoshitomi T, 2010. Effects of prostaglandin F(2 α) analogues on endothelin-1-induced impairment of rabbit ocular blood flow: comparison among tafluprost, travoprost, and latanoprost. *Exp Eye Res*; 91(6):853-9.

Liang H, Brignole-Baudouin F, Pauly A, Riancho L, Baudouin C, 2011. Polyquad-preserved travoprost/timolol, benzalkonium chloride (BAK)-preserved travoprost/timolol, and latanoprost/timolol in fixed combinations: a rabbit ocular surface study. *Adv Ther*; 28(4):311-25.

Liu HK, Chiou GC, Garg LC, 1980. Ocular hypotensive effects of timolol in cat eyes. *Arch Ophthalmol*; 98(8):1467-9.

Liu G, Zeng T, Yu W, Yan N, Wang H, Cai SP, Pang IH, Liu X, 2011. Characterization of intraocular pressure responses of the Tibetan monkey (*Macaca thibetana*). *Mol Vis*; 17:1405-13.

Mackay EO, McLaughlin M, Plummer CE, Ben-Shlomo A, Gelatt KN, 2011. Dose response for travoprost(®) in the glaucomatous beagle. *Vet Ophthalmol*; 15 Suppl 1:31-5.

McCue BA, Cason MM, Curtis MA, Faulkner RD, Dahlin DC, 2002. Determination of travoprost and travoprost free acid in human plasma by electrospray HPLC/MS/MS. *J Pharm Biomed Anal*; 28(2):199-208.

Nagai N, Murao T, Okamoto N, Ito Y, 2010. Comparison of corneal wound healing rates after instillation of commercially available latanoprost and travoprost in rat debrided corneal epithelium. *J Oleo Sci*; 59(3):135-41.

Nasir F, Iqbal Z, Khan A, Ahmad L, Shah Y, Khan AZ, Khan JA, Khan S, 2011. Simultaneous determination of timolol maleate, rosuvastatin calcium and diclofenac sodium in pharmaceuticals and physiological fluids using HPLC-UV. *J Chromatogr B Analyt Technol Biomed Life Sci*; 879(30):3434-43.

Netland PA, Landry T, Sullivan EK, Andrew R, Silver L, Weiner A, Mallick S, Dickerson J, Bergamini MV, Robertson SM, Davis AA; Travoprost Study Group, 2001. Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. *Am J Ophthalmol*, 132:472–84.

Ohashi M, Mayama C, Ishii K, Araie M, 2007. Effects of topical travoprost and unoprostone on optic nerve head circulation in normal rabbits. *Curr Eye Res*; 32(9):743-9.

Ohashi M, Mayama C, Ishi K, Araie M, 2008. Local effect of topical FP-receptor agonists on retinal vessels of the ipsilateral posterior retina in normal rabbit eyes. *Clin Experiment Ophthalmol*; 36(8):767-74.

Okahara A, Tanioka H, Takada K, Kawazu K., 2013: Ocular toxicity of benzalkonium chloride homologs compared with their mixtures. *J Toxicol Pathol*; 26(4):343-9.

Olah Z, Veselovsky J, 2013. A decrease of the rabbit's physiologic IOP after the application of specific amino acids and double combination of antiglaucomatics mixture. *Bratisl Lek Listy*; 114(7):365-8.

Park HY, Kim JH, Lee DE, Lee JH, Park CK, 2011. Changes of the Retina and Intrinsic Survival Signals in a Rat Model of Glaucoma following Brinzolamide and Travoprost Treatments. *Ophthalmic Res*; 46(4):208-217.

Pisella PJ, Fillacier K, Elena PP, Debbasch C, Baudouin C, 2000: Comparison of the effects of preserved and unpreserved formulations of timolol on the ocular surface of albino rabbits. *Ophthalmic Res*; 32: 3-8.

Potter DE, Nicholson HT, Rowland JM, 1982. Ocular hypertensive response to beta-adrenoceptor agonists. *Curr Eye Res*; 2(10):711-9.

Schmid KL, Abbott M, Humphries M, Pyne K, Wildsoet CF, 2000. Timolol lowers intraocular pressure but does not inhibit the development of experimental myopia in chick; *Exp Eye Res*; 70, 659-66.

Schmitt CJ, Lotti VJ, LeDouarec JC, 1980. Penetration of timolol into the rabbit eye. Measurements after ocular instillation and intravenous injection. *Arch Ophthalmol*; 98(3):547-51.

Sugiyama T, Shibata M, Kajiura S, Okuno T, Tonari M, Oku H, Ikeda T, 2011. Effects of fasudil, a Rho-associated protein kinase inhibitor, on optic nerve head blood flow in rabbits. *Invest Ophthalmol Vis Sci*; 52(1):64-9.

Shafaa MW, Sabra NM, Fouad RA, 2011. The extended ocular hypotensive effect of positive liposomal cholesterol bound timolol maleate in glaucomatous rabbits. *Biopharm Drug Dispos*; 32(9):507-17.

Tan AY, LeVatte TL, Archibald ML, Tremblay F, Kelly ME, Chauhan BC, 2002. Timolol concentrations in rat ocular tissues and plasma after topical and intraperitoneal dosing. *J Glaucoma*; 11(2):134-42.

Timolol maleate, Ph.Eur.monograph, (2014): 8.2 edition, EDQM, Strassburg, France.

Timoptol® SPC, 2014. Timolol Unit Dose, Merck Sharp & Dohme Limited, Hertfordshire, 2014.

Travatan®, Prescribing Information, 2010. Alcon Laboratories, Fort Worth, Texas, USA.

Travatan® Scientific Discussion. EMEA, 2004.

Uematsu M, Kumagami T, Shimoda K, Kusano M, Teshima M, To H, Kitahara T, Kitaoka T, Sasaki H, 2011. Polyoxyethylene hydrogenated castor oil modulates benzalkonium chloride toxicity: comparison of acute corneal barrier dysfunction induced by travoprost z and travoprost. *J Ocul Pharmacol Ther*; 27(5):437-44.

Volotinen M, Hakkola J, Pelkonen O, Vapaatalo H, Mäenpää J, 2011. Metabolism of ophthalmic timolol: new aspects of an old drug. *Basic Clin Pharmacol Toxicol*; 108(5):297-303.

Whitson JT, Cavanagh HD, Lakshman N, Petroll WM, 2006. Assessment of corneal epithelial integrity after acute exposure to ocular hypotensive agents preserved with and without benzalkonium chloride. *Adv Ther*; 23(5):663-71.

Wu PY, Riegel M, Ellis PP, 1989. High-performance liquid chromatographic assay for timolol in the aqueous humor of the eye. *J Chromatogr*; 494:368-75.