EU RISK MANAGEMENT PLAN (EU-RMP)

Active substance(s) (INN or common name):	Travoprost
Pharmaco-therapeutic group (ATC Code):	Ophthalmologicals-antiglaucoma preparations and miotics-prostaglandin analogues (S01EE04)
Name of Marketing Authorisation Holder or Applicant:	PharmaSwiss Česká republika s.r.o.
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)	Travoprost PharmaSwiss 40 micrograms/mL eye drops, solution

Data lock point for this RMP	16 Dec 2014	Version number	1.0
Date of final sign off	16 Dec 2014		

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List of Abbreviations

Abbreviation	Definition
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GVP	Good Pharmacovigilance Practices
INN	International Non-proprietary Name
OAG	Open-angle glaucoma
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

PART I Product(s) Overview

Part	Module/annex	Date last updated for submission (sign off date)	Version number of RMP when last submitted/or Not applicable
Part II Safety Specification	SV Post authorisation experience	Not applicable	
	SVIII Summary of safety concerns	Not applicable	
Part III Pharmacovigilance Plan			Not applicable
Part IV Plan for post-authorisation efficacy studies			Not applicable
Part V Risk Minimisation Measures		Not applicable	
Part VI Summary of RMP		Not applicable	
Part VII Annexes	ANNEX 2 Current or proposed SmPC/PL	Not applicable	
	ANNEX 3 Worldwide marketing status by country	Not applicable	
	ANNEX 4 Synopsis of on-going and completed clinical trial programme	Not applicable	
	ANNEX 5 Synopsis of pharmacoepidemiological study programme	Not applicable	
	ANNEX 6 Protocols for proposed and on-going studies in Part III	Not applicable	
	ANNEX 7 Specific adverse event follow-up forms	Not applicable	
	ANNEX 8 Protocols for studies in Part IV	Not applicable	

Part	Module/annex	Date last updated for submission (sign off date)	Version number of RMP when last submitted/or Not applicable
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	Not applicable	
	ANNEX 10 Details of proposed additional risk minimisation activities	Not applicable	
	ANNEX 11 Mock up examples	Not applicable	
	ANNEX 12 Other supporting data	Not applicable	

QPPV name Dr. MD, PhD, MBA

QPPV signature .....

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Overview of versions:

Version number of last agreed RMP:

Version number	Not applicable
Agreed within	Not applicable

Current RMP versions under evaluation:

RMP version number	Submitted on	Submitted within
Not applicable		

Invented name(s) in the European Economic Area (EEA)	Travoprost PharmaSwiss 40 micrograms/mL eye drops, solution
Authorisation procedure	Decentralised Procedure
Brief description of the product including: • chemical class • summary of mode of action • important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines)	The medicinal product Travoprost PharmaSwiss contains the active substance travoprost, a prostaglandin F2a analogue, which is a highly selective full agonist with a high affinity for the prostaglandin F receptor. Travoprost reduces the intraocular pressure by increasing the outflow of aqueous humour *via* trabecular meshwork and uveoscleral pathways. Reduction of the intraocular pressure in humans starts about 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.
Indication(s) in the EEA	
Current (if applicable)	Not applicable
Proposed (if applicable)	Decrease of elevated intraocular pressure in adult patients with ocular hypertension or open-angle glaucoma.
Posology and route of administration in the EEA	
Current (if applicable)	Not applicable
Proposed (if applicable)	*Use in adults, including elderly population* The dose is one drop of Travoprost PharmaSwiss in the conjunctival sac of the affected eye(s) once daily. Optimal effect is obtained if the dose is administered in the evening. 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. 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 medicinal product with Travoprost PharmaSwiss, the other medicinal product should be discontinued and Travoprost PharmaSwiss should be started the following day. *Hepatic and renal impairment* Travoprost PharmaSwiss 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 is necessary in these patients. *Paediatric population* The efficacy and safety of Travoprost PharmaSwiss in children below the age of 18 years have not been established and its use is

	not recommended in these patients until further data become available. Method of Administration For ocular use. The patient should remove the protective overwrap (if there is one) immediately prior to initial use. After cap is removed, Travoprost PharmaSwiss preservative-free eye drops solution, multi-dose container is ready for 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.
Pharmaceutical form(s) and strengths	
Current (if applicable)	Not applicable
Proposed (if applicable)	Eye drops, solution. Clear, colourless solution. Each mL of solution contains 40 micrograms of travoprost.

Country and date of first authorisation worldwide	Not available	Not available
Country and date of first launch worldwide	Not available	Not available
Country and date of first authorisation in the EEA	Not available	Not available

Is the product subject to additional monitoring in the EU? Yes ☐ No ☒

PART II Safety Specification

SI Epidemiology of indication(s) and target population(s)

Based on the Good Pharmacovigilance Practices (GVP) Module V – Risk management systems, section V.C.3.1.a., for new applications submitted under Article 10(1) of Directive 2001/83/EC, RMP module SI may be omitted.

SII Non-clinical part of the Safety Specification

Based on the GVP Module V – Risk management systems, section V.C.3.1.a., for new applications submitted under Article 10(1) of Directive 2001/83/EC, RMP module SII may be omitted.

SIII Clinical trial exposure

Based on the GVP Module V – Risk management systems, section V.C.3.1.a., for new applications submitted under Article 10(1) of Directive 2001/83/EC, RMP module SIII may be omitted.

SIV Populations not studied in clinical trials

Based on the GVP Module V – Risk management systems, section V.C.3.1.a., for new applications submitted under Article 10(1) of Directive 2001/83/EC, RMP module SIV may be omitted.

SV Post-authorisation experience

The medicinal product Travoprost PharmaSwiss has not yet been authorised in any country worldwide. Therefore, this module of the RMP is currently not applicable.

SVI Additional EU requirements for safety specification

Based on the GVP Module V – Risk management systems, section V.C.3.1.a., for new applications submitted under Article 10(1) of Directive 2001/83/EC, RMP module SVI may be omitted.

SVII Identified and potential risks

Based on the GVP Module V – Risk management systems, section V.C.3.1.a., for new applications submitted under Article 10(1) of Directive 2001/83/EC, RMP module SVII may be omitted.

SVIII Summary of safety concerns

Table 1 Summary of safety concerns

Important identified risks	Change in eye colour Periorbital, eye lid and/or eyelashes changes Iritis/uveitis Macular oedema Teratogenicity
Important potential risks	None
Missing information	Safety in paediatric patients Safety during breastfeeding Use in patients with active intraocular inflammation Use in patients with neovascular, angle-closure, narrow-angle or congenital glaucoma, with thyroid eye disease, in open-angle glaucoma of pseudophakic patients and in pigmentary or pseudoexfoliative glaucoma

PART III Pharmacovigilance Plan

Not applicable

PART IV Plans for post-authorisation efficacy studies

Not applicable

PART V Risk Minimisation Measures

V.1 Risk minimisation measures by safety concern

Table 2 Risk minimisation measures for change in eye colour

<table>
<tr><td colspan="2">Change in eye colour</td></tr>
<tr><td>Objective(s) of the risk minimisation measures</td><td>To inform about this risk and associated risk factors using routine risk minimisation activities.</td></tr>
<tr><td rowspan="3">Routine risk minimisation measures</td><td>Proposed text in the Summary of Product Characteristics (SmPC)
<u>Section 4.4</u> - Special warnings and precautions for use
<u>Eye colour change</u>
Travoprost PharmaSwiss 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 be become more brownish. After discontinuation of therapy, no further increase in brown iris pigment has been observed.
<u>Section 4.8</u> – Undesirable effects
<table>
<tr><td>System Organ Class</td><td>Frequency</td><td>Adverse Reaction</td></tr>
<tr><td>Eye disorders</td><td>Common</td><td>iris hyperpigmentation</td></tr>
</table>
</td></tr>
<tr><td>Comment
Similar text is included in the Package Leaflet (PL) in language more appropriate for the lay audience.</td></tr>
<tr><td>Other routine risk minimisation measures:
Prescription only medicine</td></tr>
<tr><td rowspan="2">Additional risk minimisation measure(s)</td><td>Objective and justification
Not applicable</td></tr>
<tr><td>Proposed actions/components and rationale
None</td></tr>
<tr><td colspan="2">Effectiveness of risk minimisation measures</td></tr>
<tr><td>How effectiveness of risk minimisation measures for safety concern will be measured</td><td>Effectiveness will be measured by means of routine pharmacovigilance activities, including signal detection, follow-up requests etc.</td></tr>
<tr><td>Criteria for judging</td><td>Comparison of product information versus individual case safety reports</td></tr>
</table>

Change in eye colour	
the success of the proposed risk minimisation measures	
Planned dates for assessment	Assessment will be performed during medical review of case reports and during signal detection evaluation activities
Results of effectiveness measurement	Results will be presented regularly in periodic safety update report (PSUR) and RMP updates.
Impact of risk minimisation	Not applicable.
Comment	None

Table 3 Risk minimisation measures for periorbital, eye lid and/or eyelashes changes

<table>
<tr><td colspan="2">Periorbital, eye lid and/or eyelashes changes</td></tr>
<tr><td>Objective(s) of the risk minimisation measures</td><td>To inform about this risk and associated risk factors using routine risk minimisation activities.</td></tr>
<tr><td>Routine risk minimisation measures</td><td>
Proposed text in the SmPC
<u>Section 4.4</u> - Special warnings and precautions for use
<u>Periorbital and eye lid changes</u>
In controlled clinical trials, periorbital and/or eyelid skin darkening in association with the use of travoprost has been reported in 0.4% of patients. Periorbital and lid changes including deepening of the eyelid sulcus have also been observed with prostaglandin analogues.
Travoprost PharmaSwiss 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.
<u>Section 4.8</u> – Undesirable effects
<table>
<tr><td>System Organ Class</td><td>Frequency</td><td>Adverse Reaction</td></tr>
<tr><td rowspan="2">Eye disorders</td><td>Uncommon</td><td>growth of eyelashes, eyelash discolouration</td></tr>
<tr><td>Rare</td><td>anterior chamber pigmentation, eyelash thickening</td></tr>
</table>
Comment
Similar text is included in the PL in language more appropriate for the lay audience.
Other routine risk minimisation measures:
Prescription only medicine
</td></tr>
</table>

Periorbital, eye lid and/or eyelashes changes	
Additional risk minimisation measure(s)	**Objective and justification** Not applicable
	Proposed actions/components and rationale None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for safety concern will be measured	Effectiveness will be measured by means of routine pharmacovigilance activities, including signal detection, follow-up requests etc.
Criteria for judging the success of the proposed risk minimisation measures	Comparison of product information versus individual case safety reports
Planned dates for assessment	Assessment will be performed during medical review of case reports and during signal detection evaluation activities
Results of effectiveness measurement	Results will be presented regularly in PSUR and RMP updates.
Impact of risk minimisation	Not applicable.
Comment	None

Table 4 Risk minimisation measures for iritis/uveitis

<table>
<tr><td colspan="2">Iritis/uveitis</td></tr>
<tr><td>Objective(s) of the risk minimisation measures</td><td>To inform about this risk and associated risk factors using routine risk minimisation activities.</td></tr>
<tr><td>Routine risk minimisation measures</td><td>Proposed text in the SmPC
<u>Section 4.4</u> - Special warnings and precautions for use
<u>Iritis/uveitis</u>
In patients with known predisposing risk factors for iritis/uveitis, Travoprost PharmaSwiss should be used with caution.
<u>Section 4.8</u> – Undesirable effects
<table>
<tr><td>System Organ Class</td><td>Frequency</td><td>Adverse Reaction</td></tr>
<tr><td>Eye disorders</td><td>Uncommon</td><td>uveitis, iritis</td></tr>
</table>
Comment
Similar text is included in the PL in language more appropriate for the lay audience.
Other routine risk minimisation measures:
Prescription only medicine</td></tr>
<tr><td>Additional risk minimisation</td><td>Objective and justification</td></tr>
</table>

Iritis/uveitis	
measure(s)	Not applicable
	Proposed actions/components and rationale None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for safety concern will be measured	Effectiveness will be measured by means of routine pharmacovigilance activities, including signal detection, follow-up requests etc.
Criteria for judging the success of the proposed risk minimisation measures	Comparison of product information versus individual case safety reports
Planned dates for assessment	Assessment will be performed during medical review of case reports and during signal detection evaluation activities
Results of effectiveness measurement	Results will be presented regularly in PSUR and RMP updates.
Impact of risk minimisation	Not applicable.
Comment	None

Table 5 Risk minimisation measures for macular oedema

<table>
<tr><td colspan="2">Macular oedema</td></tr>
<tr><td>Objective(s) of the risk minimisation measures</td><td>To inform about this risk and associated risk factors using routine risk minimisation activities.</td></tr>
<tr><td rowspan="3">Routine risk minimisation measures</td><td>Proposed text in the SmPC
<u>Section 4.4</u> - Special warnings and precautions for use
<u>Aphakic patients</u>
Macular oedema has been reported during treatment with prostaglandin F2a analogues. Caution is recommended when using Travoprost PharmaSwiss 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.
<u>Section 4.8</u> – Undesirable effects
<table>
<tr><td>System Organ Class</td><td>Frequency</td><td>Adverse Reaction</td></tr>
<tr><td>Eye disorders</td><td>Not known</td><td>macular oedema</td></tr>
</table></td></tr>
<tr><td>Comment
Similar text is included in the PL in language more appropriate for the lay audience.</td></tr>
<tr><td>Other routine risk minimisation measures:
Prescription only medicine</td></tr>
<tr><td rowspan="2">Additional risk minimisation measure(s)</td><td>Objective and justification
Not applicable</td></tr>
<tr><td>Proposed actions/components and rationale
None</td></tr>
<tr><td colspan="2">Effectiveness of risk minimisation measures</td></tr>
<tr><td>How effectiveness of risk minimisation</td><td>Effectiveness will be measured by means of routine pharmacovigilance activities,</td></tr>
</table>

Macular oedema	
measures for safety concern will be measured	including signal detection, follow-up requests etc.
Criteria for judging the success of the proposed risk minimisation measures	Comparison of product information versus individual case safety reports
Planned dates for assessment	Assessment will be performed during medical review of case reports and during signal detection evaluation activities
Results of effectiveness measurement	Results will be presented regularly in PSUR and RMP updates.
Impact of risk minimisation	Not applicable.
Comment	None

Table 6 Risk minimisation measures for teratogenicity

Teratogenicity	
Objective(s) of the risk minimisation measures	To inform about this risk and associated risk factors using routine risk minimisation activities.
Routine risk minimisation measures	**Proposed text in the SmPC** **Section 4.4 - Special warnings and precautions for use** Contact with the skin Skin contact with Travoprost PharmaSwiss must be avoided as transdermal absorption of travoprost has been demonstrated in rabbits. 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. **Section 4.6- Fertility, pregnancy and lactation** Women of child-bearing potential/contraception Travoprost PharmaSwiss must not be used in women of child bearing age/potential 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. Travoprost PharmaSwiss should not be used during pregnancy unless clearly necessary. **Section 5.3 – Preclinical safety data** Reproduction toxicity studies 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.

Teratogenicity	
	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).
	Comment Similar text is included in the PL in language more appropriate for the lay audience.
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s)	**Objective and justification** Not applicable
	Proposed actions/components and rationale None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for safety concern will be measured	Effectiveness will be measured by means of routine pharmacovigilance activities, including signal detection, follow-up requests etc.
Criteria for judging the success of the proposed risk minimisation measures	Comparison of product information versus individual case safety reports
Planned dates for assessment	Assessment will be performed during medical review of case reports and during signal detection evaluation activities
Results of effectiveness measurement	Results will be presented regularly in PSUR and RMP updates.
Impact of risk minimisation	Not applicable.
Comment	None

Table 7 Risk minimisation measures for safety in paediatric patients

Safety in paediatric patients	
Objective(s) of the risk minimisation measures	To acknowledge the limitation of knowledge in this special population.
Routine risk minimisation measures	**Proposed text in the SmPC** **<u>Section 4.2</u> - Posology and method of administration** *Paediatric population* The efficacy and safety of Travoprost PharmaSwiss in children below the age of 18 years have not been established and its use is not recommended in these patients until further data become available.
	Comment

Safety in paediatric patients	
	Similar text is included in the PL in language more appropriate for the lay audience.
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s)	**Objective and justification** Not applicable
	Proposed actions/components and rationale None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for safety concern will be measured	Effectiveness will be measured by means of routine pharmacovigilance activities, including signal detection, follow-up requests etc.
Criteria for judging the success of the proposed risk minimisation measures	Comparison of product information versus individual case safety reports
Planned dates for assessment	Assessment will be performed during medical review of case reports and during signal detection evaluation activities
Results of effectiveness measurement	Results will be presented regularly in PSUR and RMP updates.
Impact of risk minimisation	Not applicable.
Comment	None

Table 8 Risk minimisation measures for safety during breastfeeding

Safety during breastfeeding	
Objective(s) of the risk minimisation measures	To acknowledge the limitation of knowledge in this special population.
Routine risk minimisation measures	**Proposed text in the SmPC** **Section 4.6- Fertility, pregnancy and lactation** Breastfeeding It is unknown whether travoprost from the eye drops is excreted in human breast milk. Animal studies have shown excretion of travoprost and metabolites in breast milk. The use of Travoprost PharmaSwiss by breast-feeding mothers is not recommended.
	Comment Similar text is included in the PL in language more appropriate for the lay audience.
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s)	**Objective and justification** Not applicable

Safety during breastfeeding	
	Proposed actions/components and rationale None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for safety concern will be measured	Effectiveness will be measured by means of routine pharmacovigilance activities, including signal detection, follow-up requests etc.
Criteria for judging the success of the proposed risk minimisation measures	Comparison of product information versus individual case safety reports
Planned dates for assessment	Assessment will be performed during medical review of case reports and during signal detection evaluation activities
Results of effectiveness measurement	Results will be presented regularly in PSUR and RMP updates.
Impact of risk minimisation	Not applicable.
Comment	None

Table 9 Risk minimisation measures for use in patients with active intraocular inflammation

Use in patients with active intraocular inflammation	
Objective(s) of the risk minimisation measures	To acknowledge the limitation of knowledge in this special population.
Routine risk minimisation measures	**Proposed text in the SmPC** **<u>Section 4.4</u> - Special warnings and precautions for use** There is no experience of travoprost 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. Travoprost PharmaSwiss should therefore be used with caution in patients with active intraocular inflammation.
	Comment Similar text is included in the PL in language more appropriate for the lay audience.
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s)	**Objective and justification** Not applicable
	Proposed actions/components and rationale None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for safety concern will be measured	Effectiveness will be measured by means of routine pharmacovigilance activities, including signal detection, follow-up requests etc.

Use in patients with active intraocular inflammation	
Criteria for judging the success of the proposed risk minimisation measures	Comparison of product information versus individual case safety reports
Planned dates for assessment	Assessment will be performed during medical review of case reports and during signal detection evaluation activities
Results of effectiveness measurement	Results will be presented regularly in PSUR and RMP updates.
Impact of risk minimisation	Not applicable.
Comment	None

Table 10 Risk minimisation measures for use in patients with neovascular, angle-closure, narrow-angle or congenital glaucoma, with thyroid eye disease, in open-angle glaucoma of pseudophakic patients and in pigmentary or pseudoexfoliative glaucoma

Use in patients with neovascular, angle-closure, narrow-angle or congenital glaucoma, with thyroid eye disease, in open-angle glaucoma of pseudophakic patients and in pigmentary or pseudoexfoliative glaucoma	
Objective(s) of the risk minimisation measures	To acknowledge the limitation of knowledge in this special population.
Routine risk minimisation measures	**Proposed text in the SmPC** **<u>Section 4.4</u> - Special warnings and precautions for use** There is no experience of Travoprost PharmaSwiss 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. Travoprost PharmaSwiss should therefore be used with caution in patients with active intraocular inflammation.
	Comment Similar text is included in the PL in language more appropriate for the lay audience.
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s)	**Objective and justification** Not applicable
	Proposed actions/components and rationale None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for safety concern will be measured	Effectiveness will be measured by means of routine pharmacovigilance activities, including signal detection, follow-up requests etc.
Criteria for judging the success of the proposed	Comparison of product information versus individual case safety reports

Use in patients with neovascular, angle-closure, narrow-angle or congenital glaucoma, with thyroid eye disease, in open-angle glaucoma of pseudophakic patients and in pigmentary or pseudoexfoliative glaucoma	
risk minimisation measures	
Planned dates for assessment	Assessment will be performed during medical review of case reports and during signal detection evaluation activities
Results of effectiveness measurement	Results will be presented regularly in PSUR and RMP updates.
Impact of risk minimisation	Not applicable.
Comment	None

V.2 Risk minimisation measure failure (if applicable)

Not applicable

V.3 Summary table of risk minimisation measures

Table 11 Summary table of risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Change in eye colour	Text included in the SmPC: – Warning of the potential irreversible change in eye colour during therapy with travoprost is included in section 4.4. – Listed in section 4.8 of known undesirable effects of therapy. Similar text is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable
Periorbital, eye lid and/or eyelashes changes	Text included in the SmPC: – Warnings of the potential changes of eye area are included in section 4.4. – Listed in section 4.8. Similar text is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable
Iritis/uveitis	Text included in the SmPC: – Information about the risk of iritis/uveitis is included in section 4.4. – Listed in section 4.8. Similar text is included in the PL in language more	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	appropriate for the lay audience. Prescription only medicine	
Macular oedema	Text included in the SmPC: – Information about the risk of macular oedema development is included in section 4.4. – Listed in section 4.8. Similar text is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable
Teratogenicity	Text included in the SmPC: – Risks associated with unintentional skin contact, and the effects on pregnancy are included in section 4.4. – All known effects on pregnancy are described in section 4.6. – Preclinical safety data relevant to developmental and foetal toxicity are included in section 5.3. Similar text is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable
Safety in paediatric patients	Text included in the SmPC: – Information about missing data on safety and efficacy of Travoprost PharmaSwiss in paediatric population is included in section 4.2. Similar text is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable
Safety during breastfeeding	Text included in the SmPC: – Section 4.6 includes all available information about use of Travoprost PharmaSwiss during breastfeeding. Similar text is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable
Use in patients with active intraocular inflammation	Text included in the SmPC: – Warning about the missing data on use of Travoprost PharmaSwiss in patients with active intraocular inflammation is included in section 4.4. Similar text is included in the PL in language more	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	appropriate for the lay audience. Prescription only medicine	
Use in patients with neovascular, angle-closure, narrow-angle or congenital glaucoma, with thyroid eye disease, in open-angle glaucoma of pseudophakic patients and in pigmentary or pseudoexfoliative glaucoma	Text included in the SmPC: – Warning about the missing data on use of Travoprost PharmaSwiss in patients with other forms of glaucoma or ocular hypertension is included in section 4.4. Similar text is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable

PART VI Summary of activities in the risk management plan by product

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Table 12 Summary table of safety concerns

Important identified risks	Change in eye colour Periorbital, eye lid and/or eyelashes changes Iritis/uveitis Macular oedema Teratogenicity
Important potential risks	None
Missing information	Safety in paediatric patients Safety during breastfeeding Use in patients with active intraocular inflammation Use in patients with neovascular, angle-closure, narrow-angle or congenital glaucoma, with thyroid eye disease, in open-angle glaucoma of pseudophakic patients and in pigmentary or pseudoexfoliative glaucoma

VI.1.2 Table of on-going and planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan (if applicable)

Not applicable

VI.1.3 Summary of Post-authorisation efficacy development plan (if applicable)

Not applicable

VI.1.4 Summary table of risk minimisation measures

Table 13 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Change in eye colour	Text included in the SmPC: – Warning of the potential irreversible change in eye colour during therapy with travoprost is included in section 4.4. – Listed in section 4.8 of known undesirable effects of therapy. Similar text is included in the PL in language more appropriate for the lay audience.	Not applicable

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	Prescription only medicine	
Periorbital, eye lid and/or eyelashes changes	Text included in the SmPC: – Warnings of the potential changes of eye area are included in section 4.4. – Listed in section 4.8. Similar text is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable
Iritis/uveitis	Text included in the SmPC: – Information about the risk of iritis/uveitis is included in section 4.4. – Listed in section 4.8. Similar text is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable
Macular oedema	Text included in the SmPC: – Information about the risk of macular oedema development is included in section 4.4. – Listed in section 4.8. Similar text is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable
Teratogenicity	Text included in the SmPC: – Risks associated with unintentional skin contact, and the effects on pregnancy are included in section 4.4. – All known effects on pregnancy are described in section 4.6. – Preclinical safety data relevant to developmental and foetal toxicity are included in section 5.3. Similar text is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable
Safety in paediatric patients	Text included in the SmPC: – Information about missing data on safety and efficacy of Travoprost PharmaSwiss in paediatric population is included in section 4.2. Similar text is included in the PL in language more appropriate for the lay audience.	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Prescription only medicine	
Safety during breastfeeding	Text included in the SmPC: – Section 4.6 includes all available information about use of Travoprost PharmaSwiss during breastfeeding. Similar text is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable
Use in patients with active intraocular inflammation	Text included in the SmPC: – Warning about the missing data on use of Travoprost PharmaSwiss in patients with active intraocular inflammation is included in section 4.4. Similar text is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable
Use in patients with neovascular, angle-closure, narrow-angle or congenital glaucoma, with thyroid eye disease, in open-angle glaucoma of pseudophakic patients and in pigmentary or pseudoexfoliative glaucoma	Text included in the SmPC: – Warning about the missing data on use of Travoprost PharmaSwiss in patients with other forms of glaucoma or ocular hypertension is included in section 4.4. Similar text is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Glaucoma is a major cause of blindness worldwide.[1, 2] The estimated number of people living with glaucoma is predicted to increase from 44.7 million in 2010 to 58.6 million in 2020.[3] An elevated intraocular pressure known as ocular hypertension is an important risk factor for the development of glaucoma.

An open-angle glaucoma (OAG) is the most common form of glaucoma.[4] While annually is noted 40-60 new cases of OAG per 100,000 persons in individuals over 55 years, the number increases to 200-220 new cases in individuals over 75.[5, 6] The mean occurrence of OAG is approximately 1.96% within the population.[7] It has been estimated that 4-10% of the population older than 40 years may have elevated intraocular pressure without detectable signs of glaucomatous damage.[8, 9]

Glaucoma and ocular hypertension have not been associated with significantly increased risk of death unless associated with other serious conditions like cardiovascular diseases.[8, 10]

VI.2.2 Summary of treatment benefits

In a clinical trial, patients with OAG or ocular hypertension who were treated with travoprost once-daily in the evening demonstrated 8 to 9 mmHg reductions (approximately 33%) in intraocular pressure from 24 to 26 mmHg baseline.

Data on adjunctive administration of travoprost with timolol 0.5% and limited data with brimonidine 0.2% were collected during clinical trials that showed an additive effect of travoprost with these glaucoma medications.

VI.2.3 Unknowns relating to treatment benefits

No clinical data are available on adjunctive use of travoprost with ocular hypotensive medications other than timolol and brimodinine.

There is no experience with travoprost in patients with active intraocular inflammation.

VI.2.4 Summary of safety concerns

Table 14 Important identified risks

Important Identified Risk	What is known	Preventability
Change in eye colour	Prostaglandins and prostaglandin analogues, i.e. substances including travoprost, are known to cause usually permanent change in colour of the iris. The longterm consequences of this effect are unknown.	This effect cannot be prevented by any preventive measures. All patients must be informed about the possibility of eye colour change before the initiation of the therapy with Travoprost PharmaSwiss.
Changes to area surrounding the socket of the eye, to eye lid and/or eyelashes (Periorbital, eye lid and/or eyelashes changes)	Similarly to the change in eye colour, travoprost may cause the change in colour of the eye area (darkening of the skin or discolouration) or in length, thickness and colour of the eyelashes. The longterm consequences of these effects are unknown.	These effects cannot be prevented by any preventive measures. All patients must be informed about the possibility of these changes before the initiation of the therapy with Travoprost PharmaSwiss.
Inflammation of the iris/Inflammation of the middle layer of the eye (Iritis/uveitis)	Travoprost is known to cause inflammatory conditions of the eye known as iritis and uveitis.	Patients with known risk factors for the development of iritis or uveitis should be treated by Travoprost PharmaSwiss with caution
Accumulation of fluid within the	Condition called macular oedema	Caution is recommended when

Important Identified Risk	What is known	Preventability
retina at the macular area (Macular oedema)	has been reported during treatment with prostaglandin analogues, including travoprost.	Travoprost PharmaSwiss is used in patients lacking the natural lens of the eye or in patients to whom the natural lens was replaced with an intraocular lens. Caution is also advisable in patients with predisposing factors for macular oedema.
Harmful effects on the unborn child (Teratogenicity)	Travoprost as the other prostaglandins and prostaglandin analogues has harmful effects on pregnancy and/or the foetus/new-born child.	Travoprost PharmaSwiss must not be used in women of childbearing potential unless effective method of contraception is used. Travoprost PharmaSwiss should not be used during pregnancy unless clearly necessary.

Table 15 Important potential risks

Important Potential Risk	What is known (including reason why it is considered a potential risk)
None	

Table 16 Missing information

Missing Information	What is known
Safety in paediatric population	Travoprost has not been studied in children and adolescents. Use of Travoprost PharmaSwiss is not recommended in this population.
Safety during breastfeeding	It is unknown whether travoprost is excreted into breast milk as in case of animal models. The safety of travoprost use during breastfeeding for the child or mother is unknown.
Use in patients with active intraocular inflammation	There is no experience with use of travoprost during active intraocular inflammation and Travoprost PharmaSwiss should be used only with caution.
Use in patients with neovascular, angle-closure, narrow-angle or congenital glaucoma, with thyroid eye disease, in open-angle glaucoma of pseudophakic patients and in pigmentary or pseudoexfoliative glaucoma)	There is no experience with use of travoprost in patients with other forms of glaucoma than included in the therapeutic indication of Travoprost PharmaSwiss and caution is therefore required.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in

the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post-authorisation development plan (if applicable)

Not applicable

VI.2.7 Summary of changes to the risk management plan over time

Not applicable

PART VII Annexes to the risk management

Table 17 List of annexes

Annex No	
1	Interface between EU-RMP and EudraVigilance
2	SmPC and PL
3	Worldwide marketing authorisation status by country (including EEA)
4	Synopsis of on-going and completed trial programme
5	Synopsis of on-going and completed pharmacoepidemiological study programme
6	Protocols for proposed and on-going studies in categories 1-3 in Part III.
7	Specific adverse event follow-up forms
8	Protocols for proposed and on-going studies in RMP part IV
9	Synopsis of newly available study reports for RMP parts III-IV
10	Details of proposed additional risk minimisation activities
11	Mock up examples in English of the material provided to healthcare professionals and patients as a requirement of Annex II of the Commission Decision or as a requirement of national authorisation
12	Other supporting data (including referenced material)

Annex 1 Interface between EU-RMP and EudraVigilance

Interface is available in electronic format only.

Annex 2 SmPC and PL

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

[PRODUCT NAME] Preservative-free 40 micrograms/mL eye drops solution, multi dose container

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains micrograms of travoprost.

Excipient(s) with known effect:

Each mL of solution contains g of macrogol glycerol hydroxyl stearate 40 (see section 4.4.)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.
Clear, colourless aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Decrease of elevated intraocular pressure in adult patients with ocular hypertension or open-angle glaucoma (see section 5.1).

4.2 Posology and method of administration

Posology
Use in adults, including elderly population
The dose is one drop of [PRODUCT NAME] Preservative-free in the conjunctival sac of the affected eye(s) once daily. Optimal effect is obtained if the dose is administered in the evening.

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 medicinal product with [PRODUCT NAME] Preservative-free, the other medicinal product should be discontinued and [PRODUCT NAME] Preservative-free should be started the following day.

Hepatic and renal impairment
[PRODUCT NAME] Preservative-free 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 is necessary in these patients (see section 5.2).

Paediatric population
The efficacy and safety of [PRODUCT NAME] Preservative-free in children below the age of 18 years have not been established and its use is not recommended in these patients until further data become available.

Method of Administration

For ocular use.
For patients who wear contact lenses, please refer to section 4.4.

[PRODUCT NAME] preservative-free eye drops solution, multidose container is a sterile solution that does not contain a preservative. The solution from the multi-dose container is to be used for 28 days after opening for administration to the affected eye(s). Since sterility can be maintained after the multi-dose container is opened, the remaining content must not be discarded before the 28 days after opening.

Patients should be instructed to wash their hands before use and avoid allowing the container to come into contact with the eye or surrounding structures as this could cause injury to the eye.

The patient should remove the protective overwrap (if there is one) immediately prior to initial use. After cap is removed, [PRODUCT NAME] preservative-free eye drops solution, multi-dose container is ready for 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Eye colour change
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 be become more brownish. After discontinuation of therapy, no further increase in brown iris pigment has been observed.

Periorbital and eye lid changes
In controlled clinical trials, periorbital and/or eyelid skin darkening in association with the use of travoprost has been reported in 0.4% of patients. Periorbital and lid changes including deepening of the eyelid sulcus have also been observed with prostaglandin analogues.

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

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

species specific.

There is no experience of travoprost 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. [PRODUCT NAME] should therefore be used with caution in patients with active intraocular inflammation.

Aphakic patients
Macular oedema has been reported during treatment with prostaglandin F2a analogues. Caution is recommended when using travoprost 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.

Iritis/uveitis
In patients with known predisposing risk factors for iritis/uveitis, travoprost should be used with caution.

Contact with the skin
Skin contact with travoprost must be avoided as transdermal absorption of travoprost has been demonstrated in rabbits.

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.

Contact lenses
Patients must be instructed to remove contact lenses prior to application of [PRODUCT NAME] Preservative-free and wait 15 minutes after instillation of the dose before reinsertion.

Excipients
[PRODUCT NAME] Preservative-free contains macrogol glycerol hydroxyl stearate 40 which may cause skin reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/contraception
Travoprost must not be used in women of child bearing age/potential 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.
[PRODUCT NAME] Preservative-free should not be used during pregnancy unless clearly necessary.

Breastfeeding
It is unknown whether travoprost from the eye drops is excreted in human breast milk. Animal studies have shown excretion of travoprost and metabolites in breast milk. The use of [PRODUCT NAME] Preservative-free by breast-feeding mothers is not recommended.

Fertility
There are no data on the effects of travoprost on human fertility. Animal studies showed no effect of travoprost on fertility at doses more than 250 times the maximum recommended human ocular dose.

4.7 Effects on ability to drive and use machines

Travoprost has no or negligible influence on the ability to drive and use machines, however as with any eye drop, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile
In clinical trials with travoprost, the most common adverse reactions were ocular hypearemia and iris hyperpigmentation, occurring in approximately 2 0 % and 6 % of patients respectively.

Tabulated list of adverse reactions
The following adverse reactions are classified according to the following convention: very common (>1 /1 0), common (>1 / 1 0 0 to <1 /1 0), uncommon (>1 /1 , 0 0 0 to <1 /1 0 0), rare (>1 /1 0 , 0 0 0 to<1 /1 ,0 0 0), very rare <1 /1 0 ,0 0 0), or not known (frequency cannot be estimated from the available data). Within each frequency group, adverse reactions are presented in decreasing order of seriousness. The adverse reactions were obtained from clinical studies and post marketing data with travoprost.

System Organ Class	Frequency	Adverse Reactions
Infections and infestations	Rare	herpes simplex, keratitis herpetic
Immune system disorders	Uncommon	hypersensitivity, seasonal allergy
Psychiatric disorders	Not known	depression, anxiety
Nervous system disorder	Uncommon	headache, dizziness, visual field defect
	Rare	dysgeusia
Eye disorders	Very common	ocular hyperaemia
	Common	iris hyperpigmentation, eye pain, ocular discomfort, dry eye, eye pruritus, eye irritation
	Uncommon	corneal erosion, uveitis, iritis, anterior chamber inflammation, keratitis, punctate keratitis, photophobia, eye discharge, blepharitis, erythema of eyelid, periorbital oedema, eyelids pruritus, visual acuity reduced, vision blurred, lacrimation increased, conjunctivitis, ectropion cataract, eyelid margin crusting, growth of eyelashes, eyelash discolouration, asthenopia
	Rare	iridocyclitis, eye inflammation, photopsia,

		eczema eyelids, conjunctival oedema, halo vision, conjunctival follicles, hypoaesthesia eye, meibomianitis, anterior chamber pigmentation, mydriasis, eyelash thickening
	Not known	macular oedema, sunken eyes
Ear and labyrinth disorders	Not known	vertigo, tinnitus
Cardiac disorders	Uncommon	palpitations
	Rare	heart rate irregular, heart rate decreased
	Not known	chest pain, bradycardia, tachycardia
Vascular disorders	Rare	blood pressure diastolic decreased, blood pressure systolic increased, hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	Uncommon	dyspnoea, asthma, nasal congestion, throat irritation
	Rare	respiratory disorder, oropharyngeal pain, cough, dysphonia
	Not known	asthma aggravated
Gastrointestinal disorders	Rare	peptic ulcer reactivated, gastrointestinal disorder, constipation, dry mouth
	Not known	diarrhoea, abdominal pain, nausea
Skin and subcutaneous tissue disorders	Uncommon	skin hyperpigmentation (periocular), skin discolouration, hair texture abnormal, hypertrichosis
	Rare	dermatitis allergic, dermatitis contact, erythema, rash, hair colour changes, madarosis
	Not known	pruritus, hair growth abnormal
Musculoskeletal and connective tissue disorders	Rare	musculoskeletal pain
	Not known	arthralgia
Renal and urinary disorders	Not known	dysuria, urinary incontinence
General disorders and administration site conditions	Rare	asthenia
Investigations	Not known	prostatic specific antigen increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No cases of overdose have been reported. A topical overdose is not likely to occur or to be associated with toxicity. A topical overdose of travoprost may be flushed from the eye(s) with lukewarm water. Treatment of a suspected oral ingestion is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Ophthalmologicals-antiglaucoma preparations and miotics-prostaglandin analogues
ATC code: S01E E04

Mechanism of action
Travoprost, a prostaglandin F_{2a} analogue, is a highly selective full agonist which 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 the intraocular pressure in man starts about 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.

Clinical efficacy and safety
Data on adjunctive administration of travoprost with timolol and limited data with brimonidine were collected during clinical trials that showed an additive effect of travoprost with these glaucoma medications. No clinical data are available on adjunctive use with other ocular hypotensive medications.

5.2 Pharmacokinetic properties

Absorption
Travoprost is an ester prodrug. It is absorbed through the cornea where the isopropyl ester is hydrolysed to the active free acid. Studies in rabbits have shown peak concentrations of 20 ng/g of the free acid in aqueous humour one to two hours after topical dosing of travoprost. Aqueous humour concentrations declined with a half-life of approximately 1.5 hours.

Distribution
Following topical ocular administration of travoprost to healthy volunteers, low systemic exposure to active free acid was demonstrated. Peak active free acid plasma concentrations of 25 pg/ml or less were observed between 10 and 30 minutes post-dose. Thereafter, plasma levels declined rapidly to below the 10 pg/ml assay quantitation limit before 1 hour post-administration. Due to the low plasma concentrations and rapid elimination following topical dosing, the elimination half-life of active free acid in man could not be determined.

Biotransformation
Metabolism is the major route of elimination of both travoprost and the active free acid. The systemic metabolic pathways parallel those of endogenous prostaglandin F_{2a} 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.

Elimination
Travoprost free acid and its metabolites are mainly excreted by the kidneys. 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 is necessary in these patients.

5.3 Preclinical safety data

In ocular toxicity studies in monkeys, administration of travoprost at a dose of 0.45 microgram, twice a day, was shown to induce increased palpebral fissure. 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 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 ^{3}H-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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogolglycerol hydroxystearate 40
Boric acid
Mannitol
Sodium chloride
Propylene glycol
Sodium hydroxide (for pH-adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

1 year

After first opening, this medicine does not require any special storage conditions.

Before opening, keep bottle in overwrap pouch (if available) in order to protect from moisture.

[PRODUCT NAME] Preservative-Free eye drops solution, multi-dose container
should be used no longer than 28 days after first opening of the multi – dose container.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

In a cardboard box is included a 5 ml white multi dose ophthalmic container containing 2.5ml of the ophthalmic solution.
The multi – dose container can be available in an overwrap, inside the carton box.

[PRODUCT NAME] Preservative-free eye drops solution, multi-dose container is available in the following packaging configurations:
1 x 2.5 ml (single 2.5-ml multi dose container)
3 x 2.5 ml (three 2.5-ml multi dose containers)
Cartons containing 1 or 3 number of bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBERS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

Package Leaflet

Travoprost PharmaSwiss 40 micrograms/mL eye drops, solution

Travoprost

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet, See section 4.

What is in this leaflet

1. What Travoprost PharmaSwiss is and what it is used for

Travoprost PharmaSwiss contains travoprost, one of a group of medicines called prostaglandin analogues. It works by reducing the pressure in the eye. It may be used on its own or with other drops e.g. beta-blockers, which also reduce pressure.
Travoprost PharmaSwiss is used to reduce high pressure in the eye in adults. This pressure can lead to an illness called glaucoma.

2. What you need to know before you use Travoprost PharmaSwiss

Do not use Travoprost PharmaSwiss
If you are allergic to travoprost or any of the other ingredients of this medicine (listed in section 6).

Ask your doctor for advice if this applies to you.

Warning and Precautions

- Travoprost PharmaSwiss may increase the length, thickness, colour and/or number of your eyelashes. Changes in the eyelids including unusual hair growth or in the tissues around the eye have also been observed.
- Travoprost PharmaSwiss may change the colour of your iris (the coloured part of your eye). This change may be permanent. A change in the colour of the skin around the eye may also occur.
- If you have had cataract surgery, talk to your doctor before you use Travoprost PharmaSwiss.
- If you have current or previous history of an eye inflammation (iritis and uveitis), talk to your doctor before you use Travoprost PharmaSwiss.
- Travoprost PharmaSwiss may rarely cause breathlessness or wheezing or increase the symptoms of asthma. If you are concerned about changes in your breathing pattern when using Travoprost PharmaSwiss advise your doctor as soon as possible.
- Travoprost may be absorbed through the skin. If any of the medicinal product comes into contact with the skin, it should be washed off straight away. This is especially important in women who are pregnant or are attempting to become pregnant.
- If you wear soft contact lenses, do not use the drops with your lenses in. After using the drops wait 15 minutes before putting your lenses back in.

Children and adolescents

Use of Travoprost PharmaSwiss is not recommended to those under 18 years of age.

Other medicines and Travoprost PharmaSwiss

Tell your doctor or pharmacist if you are taking or have recently taken or used any other medicines.

Pregnancy, breast feeding and fertility

Do not use Travoprost PharmaSwiss if you are pregnant. If you think that you may be pregnant speak with your doctor right away. If you could become pregnant you must use adequate contraception whilst you use Travoprost PharmaSwiss.

Do not use Travoprost PharmaSwiss if you are breast feeding. Travoprost PharmaSwiss may get into your milk.

Ask your doctor for advice before taking any medicine

Driving and using machines

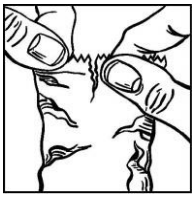
You may find that your vision is blurred for a time just after you use Travoprost PharmaSwiss. Do not drive or use machines until this has worn off.

Travoprost PharmaSwiss contains hydrogenated castor oil and propylene glycol which may cause skin reactions and irritation.

3. How to use Travoprost PharmaSwiss

Always use this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
The recommended dose is

One drop in the affected eye or eyes, once a day - in the evening.
Only use Travoprost PharmaSwiss in both eyes if your doctor told you to. Use it for as long as your doctor told you to.



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Only use Travoprost PharmaSwiss for dropping in your eyes.

- Immediately before using a bottle for the first time, tear open the overwrap pouch, take the bottle out (picture 1) and write the date of opening on the carton in the space provided
- Wash your hands
- Twist off the cap
- After cap is removed, if tamper evident snap collar is loose, remove before using the product.
- Hold the bottle, pointing down, between your thumb and fingers
- Tilt your head back. Pull down your eyelid with a clean finger, until there is a 'pocket' between the eyelid and your eye. The drop will go in here (picture 2)
- Bring the bottle tip close to the eye. Use a mirror if it helps
- Do not touch your eye or eyelid, surrounding areas or other surfaces with the dropper. It could infect the drops

- Gently squeeze the bottle to release one drop of Travoprost PharmaSwiss at a time. (picture 3)
- After using Travoprost PharmaSwiss, keep the eyelid closed, apply gentle pressure by pressing a finger into the corner of your eye, by the nose (picture 4) for at least 1 minute. This helps to stop Travoprost PharmaSwiss getting into the rest of the body
- If you use drops in both eyes, repeat the steps for your other eye
- Close the bottle cap firmly immediately after use
- Only use one bottle at a time. Do not open the pouch until you need to use the bottle.

If a drop misses your eye, try again.

If you are using other eye preparations such as eye drop or eye ointment, wait for at least 5 minutes between putting in Travoprost PharmaSwiss and the other eye preparations.

If you use more Travoprost PharmaSwiss than you should

Rinse all the medicine out with warm water. Don't put in any more drops until it's time for your next regular dose.

If you forget to use Travoprost PharmaSwiss

Continue with the next dose as planned. Do not use a double dose to make up for a forgotten dose. Never use more than one drop in the affected eye(s) in a single day.

If you stop using Travoprost PharmaSwiss

Do not stop using Travoprost PharmaSwiss without first speaking to your doctor, the pressure in your eye will not be controlled which could lead to loss of sight.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You can usually carry on using the drops, unless the side effects are serious. If you're worried, talk to a doctor or pharmacist. Do not stop taking Travoprost PharmaSwiss without speaking to your doctor.

The following side effects have been seen with Travoprost PharmaSwiss

Very common side effects: may affect more than 1 in 10 people

Effects in the eye: eye redness,

Common side effects: may affect up to 1 in 10 people

Effects in the eye: changes in the colour of the iris (coloured part of the eye), eye pain, eye discomfort, dry eye, itchy eye, eye irritation.

Uncommon side effects: may affect up to 1 in 100 people

Effects in the eye: corneal disorder, eye inflammation, iris inflammation, inflammation inside the eye, eye surface inflammation with/out surface damage, sensitivity to light, eye discharge, eyelid inflammation, eyelid redness, swelling around the eye, eyelid itching, reduced vision, blurred vision, increased tear production, infection or inflammation of the conjunctiva (conjunctivitis), abnormal turning outward of the lower eyelid, clouding of the eye, eyelid crusting, growth of eyelashes, discolouration of the eyelashes, tired eyes.

General side effects: increased allergic symptoms, headache, dizziness, irregular heart beat, shortness of breath, asthma, stuffy nose, throat irritation, darkening of skin around the eye (s), skin darkening, abnormal hair texture, excessive hair growth.

Rare: may affect up to 1 in 1,000 people

Effects in the eye: perception of flashing lights, eczema of the eyelids, eye swelling, halo vision, decreased eye sensation, inflammation of the glands of the eyelids, pigmentation inside the eye, increase in pupil size, change in the texture of the eyelashes.

General side effects: eye viral infection, bad taste, irregular or decreased heart rate, increased or decreased blood pressure, cough, voice changes, gastrointestinal discomfort or ulcer, constipation, dry mouth, redness or itching of the skin, rash, hair colour change, loss of eyelashes, musculoskeletal pain, generalised weakness.

Not known: frequency cannot be estimated from the available data

Effects in the eye: inflammation of the back of the eye, eyes appear more inset.

General side effects: depression, anxiety, sensation of false movement, ringing in ears, chest pain, worsening of asthma, diarrhea, abdominal pain, nausea, itching, abnormal hair growth, joint pain, painful or involuntary urination, increase in prostate cancer marker.

<u>Reporting of side effects</u>

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Travoprost PharmaSwiss

Keep this medicine out of the sight and reach of children.

Do not use Travoprost PharmaSwiss after the expiry date which is stated on the bottle and the box after 'Exp'. The expiry date refers to the last day of the month.

This medicine does not require any special storage conditions.

You must throw away the bottle 4 weeks after you first opened it, to prevent infections, and use a new bottle. Write down the date you opened it in the space on the carton box.
Do not throw away medicine via wastewater or in household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Travoprost PharmaSwiss contains
The active substance is travoprost 40 micrograms/ml.
The other ingredients are:Polyquaternium-1, polyoxyethylene hydrogenated castor oil 40 , propylene glycol, sodium chloride, boric acid, mannitol and purified water.Tiny amounts of hydrochloric acid or sodium hydroxide are added to keep acidity levels (pH levels) normal.

What Travoprost PharmaSwiss looks like and contents of the pack
Travoprost PharmaSwiss is a liquid (a clear, colourless solution) supplied in a pack containing a 4 ml plastic bottle with a screw cap. Each bottle contains 2.5 mL of travoprost eye drops and each bottle is placed in a pouch.

Pack sizes : 1 or 3 bottles.
Not all pack sizes may be marketed

Annex 3 Worldwide marketing authorisation by country (including EEA)

A3.1 Licensing status in the EEA

Not applicable

A3.2 Licensing status in the rest of the world

Not applicable

Annex 4 Synopsis of on-going and completed clinical trial programme

Not applicable

Annex 5 Synopsis of on-going and completed pharmacoepidemiological study programme

Not applicable

Annex 6 Protocols for proposed and on-going studies in categories 1-3 in Part III

Not applicable

Annex 7 Specific adverse event follow-up forms

Not applicable

Annex 8 Protocols for proposed and on-going studies in RMP part IV

Not applicable

Annex 9 Synopsis of newly available study reports for RMP parts III-IV

Not applicable

Annex 10 Details of proposed additional risk minimisation activities

Not applicable

Annex 11 Mock up examples in English of the material provided to healthcare professionals and patients as a requirement of Annex II of the Commission Decision or as a requirement of national authorisation

Not applicable

Annex 12 Other supporting data (including referenced material)

Not applicable

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