

**Public Assessment Report**

**Decentralised Procedure**

**TRAVOPROST PH&T**

***40 mcg/ml, eye drop, solution***

**Applicant: PH&T SPA (Italy)**

**Italian Marketing Authorisation Number: 043123**

**European procedure number: IT/H/0373/001/DC**

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**Module 1**

**Information about the Initial Procedure**

|  |  |
| --- | --- |
| **Product Name** | **IT/H/0373/001/DC:**  Travoprost PH&T |
| **Type of application** | Article 10.3 of Directive 2001/83/EC as amended |
| **Active Substance** | Travoprost |
| **Form** | Eye drops solution |
| **Strength** | 40 mcg/ml |
| **MA Holder** | PH&T Spa.  Via Marostica 1 Milano Italy |
| **Reference Member State (RMS)** | IT |
| **Concerned Memember States (CMS)** | RO |
| **Procedure number** | IT/H/0373/001/DC |
| **Timetable** | End of procedure: Day 210 –3/11/2014 |

Module 2

Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Italian version of the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level would be available on the AIFA website once the marketing Authorization will be granted.

Here is reported the English version of the SMPC approved at European level.

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TRAVOPROST PH&T 40 micrograms/ml eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 40 micrograms of travoprost.

Excipients with known effect: each ml of solution contains Benzalkonium chloride 0.15 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

*Use in adults, including the elderly population*

The dose is one drop of TRAVOPROST PH&T 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 TRAVOPROST PH&T, the other medicinal product should be discontinued and TRAVOPROST PH&T should be started the following day.

*Hepatic and renal impairment*

Travoprost has been studied in patients with mild to severe hepatic impairment and in patients with mild to severe renal impairment (creatinine clearance as low as 14 ml/min). No dosage adjustment is necessary in these patients (see section 5.2).

*Paediatric population*

The efficacy and safety of TRAVOPROST PH&T in patients below the age of 18 years have not been established and its use is not recommended in these patients until further data become available.

Method of administration

For ocular use.

The patient should remove the protective overwrap immediately prior to initial use. To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle.

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

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 PH&T 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 PH&T 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 PH&T 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 PH&T 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 PH&T 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 PH&T should be used with caution.

Contact with the skin

Skin contact with TRAVOPROST PH&T 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 TRAVOPROST PH&T and wait 15 minutes after instillation of the dose before reinsertion.

TRAVOPROST PH&T may rarely cause dyspnea or wheezing or increase the symptoms of asthma.

Excipients

TRAVOPROST PH&T contains benzalkonium chloride which is commonly used as a preservative in ophthalmic preparation. Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy, may cause eye irritation and is known to discolour soft contact lenses. Close monitoring is required with frequent or prolonged use of TRAVOPROST PH&T in dry eye patients, or in conditions where the cornea is compromised. Contact lenses may absorb benzalkonium chloride and these should be removed before applying TRAVOPROST PH&T but may be reinserted after 15 minutes (see section 4.2).

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 PH&T 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 PH&T should not be used during pregnancy unless clearly necessary.

Breastfeeding

It is unknown whether travoprost from eye drops is excreted in human breast milk. Animal studies have shown excretion of travoprost and metabolites in breast milk. The use of TRAVOPROST PH&T by breast-feeding mothers is not recommended.

Fertility

There are no data on the effects of TRAVOPROST PH&T 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 PH&T 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 machine.

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 20% and 6% of patients respectively.

Tabulated list of adverse reactions

The following adverse reactions are classified according to the following convention: very common (≥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(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 Classification | Frequency | Preferred Term |
| 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, connective tissue and bone disorders | Rare | musculoskeletal pain |
| Not known | arthralgia |
| Renal and urinary disorders | Not known | dysuria, urinary incontinence |
| General disorders and administrative 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 PH&T 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 7

Mechanism of action

Travoprost, a prostaglandin F2α 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

In a clinical trial, patients with open-angle glaucoma or ocular hypertension who were treated with travoprost (polyquaternium-preserved) dosed 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. No clinical data are available on adjunctive use with other ocular hypotensive medications.

Secondary pharmacology

Travoprost significantly increased optic nerve head blood flow in rabbits following 7 days of topical ocular administration (1.4 micrograms, once-daily).

Travoprost preserved with polyquaternium-1 induced minimal ocular surface toxicity, compared to eye drops preserved with benzalkonium chloride, on cultured human corneal cells and following topical ocular administration in rabbits.

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 F2α 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 (see section 4.2).

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 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Macrogol-15-Hydroxystearate

Trometamol

Boric acid (E284)

EDTA disodium

Mannitol (E421)

Sodium hydroxide and/or hydrochloric acid (to adjust pH)

Water for injection

6.2 Incompatibilities

None known.

Specific *in vitro* interaction studies were performed with travoprost and medicinal products containing thiomersal. No evidence of precipitation was observed.

6.3 Shelf life

2 years.

Discard 4 weeks after first opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

A plastic polypropylene (PP) bottle with a low density polyethylene dropper (LDPE) and a high density polyethylene (HDPE) screw cap.

Each bottle contains 2.5 ml of eye drops solution.

Pack sizes: 1 x 2.5 ml bottle.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

PH&T S.p.A.

Via Marostica, 1

20146 – Milano

Italy

8. MARKETING AUTHORISATION NUMBERS

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation : [To be completed nationally]

Date of last renewal: [To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Module 3

Package Leaflets

In accordance with Directive 2010/84/EU, the Italian version of the package leaflet for products granted Marketing Authorisations at a national level would be available on the AIFA website once the marketing Authorization will be granted.

Here is reported the English version of the PIL approved at European level.

1.3.1 Package leaflet: Information for the user

TRAVOPROST PH&T 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 your pharmacist.

- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

- If you get any side effects, talk toyour 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 PH&T is and what it is used for

2. What you need to know before you use TRAVOPROST PH&T

3. How to use TRAVOPROST PH&T

4. Possible side effects

5. How to store TRAVOPROST PH&T

6. Contents of the pack and other information

1. What TRAVOPROST PH&T is and what it is used for

TRAVOPROST PH&T contains travoprost, one of a group of medicines called prostaglandin analogues. It works by reducing the pressure in the eye.

TRAVOPROST PH&T eye drops are used to reduce high pressure in the eye. This pressure can lead to an illness called glaucoma.

2. What you need to know before you use TRAVOPROST PH&T

Do not use TRAVOPROST PH&T

• 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 PH&T 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 PH&T 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 PH&T.

• If you have current or previous history of an eye inflammation (iritis and uveitis), talk to your doctor before you use TRAVOPROST PH&T.

• TRAVOPROST PH&T 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 PH&T advise your doctor as soon as possible.

• TRAVOPROST PH&T may be absorbed through the skin. If any of the 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.

• Caution is recommended when using TRAVOPROST PH&T in patients without lens, or with artificial lens with a rupture of posterior lens capsule or with implant of lens in anterior chamber, or in patients with known risk factors for retinal cystoid macular oedema (which is a condition in which fluids collect on or under the central area of the retina).

• 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 PH&T is not recommended to those under 18 years of age.

Other medicines and TRAVOPROST PH&T

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

Pregnancy, breast feeding and fertility

Do not use TRAVOPROST PH&T if you are pregnant. If you think that you may be pregnant or are planning to have a baby,ask your doctor for advice before taking this medicine.

If you could become pregnant you must use adequate contraception whilst you use TRAVOPROST PH&T.

Do not use TRAVOPROST PH&T if you are breast feeding, TRAVOPROST PH&T may get into your breast 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 PH&T. Do not drive or use machines until this has worn off.

Important information about some of the ingredients

TRAVOPROST PH&T contains benzalkoniumchloride which may cause eye irritation and is known to discolour soft contact lenses. Close monitoring is required with frequent or prolonged use of TRAVOPROST PH&T in dry eye patients, or in conditions where the cornea is compromised. Contact lenses may absorb benzalkonium chloride and these should be removed before applying TRAVOPROST PH&T but may be reinserted after 15 minutes.

3. How to use TRAVOPROST PH&T

Always use TRAVOPROST PH&T exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The recommended dose is 1 drop in the affected eye or eyes, once a day-in the evening.

Only use TRAVOPROST PH&T in both eyes if your doctor told you to. Use it for as long as your doctor told you to.

Only use TRAVOPROST PH&T for dropping in your eyes.



1 2 3

• Immediately before using a bottle for the first time, write the date of opening on the label in the space provided

• Wash your hands

• Twist off the cap

• 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 1)

• 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 PH&T at a time (picture 2).

• After using TRAVOPROST PH&T, keep the eyelid closed, apply gentle pressure by pressing a finger into the corner of your eye, by the nose (picture 3) for at least 1 minute. This helps to stop TRAVOPROST PH&T getting into the rest of the body

• If you take 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.

If a drop misses your eye, try again.

If you use more TRAVOPROST PH&T than you should,

rinse it all out with warm water. Do not put in any more drops until it is time for your next regular dose.

If you forget to use TRAVOPROST PH&T,

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 PH&T

Do not stop using TRAVOPROST PH&T without speaking to your doctor, the pressure in your eye will not be controlled which could lead to loss of sight.

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.

If you are using other eye drops, leave at least 5 minutes between putting in TRAVOPROST PH&T and the other drops.

If you have any further questions on the use of this product ask a doctor or pharmacist.

4. Possible side effects

Like all medicines, TRAVOPROST PH&T can cause side effects although not everybody gets them.

Possible side effects are listed below on the basis of how often they occur:

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 irritation
* dry eye
* itchy eye
* eye pain
* eye discomfort

Uncommon side effects

*(May affects 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,
* eyelidinflammation
* 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:*

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

Rare side effects

*(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

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report any side effects directly to 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 PH&T

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

Do not use this medicine 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 each bottle label and box.

Do not throw away any medicines via wastewater or in household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. Contents of the pack and other information

What TRAVOPROST PH&T contains

* The active substance is travoprost 40 micrograms/ml.
* The other ingredients areBenzalkonium chloride, Macrogol-15-Hydroxystearate,Trometamol, Boric acid (E284), EDTA disodium, Mannitol (E421) , Water for injection. Tiny amounts of hydrochloric acid or sodium hydroxide are added to keep acidity levels (pH levels) normal.

What TRAVOPROST PH&T looks like and the contents of the pack

TRAVOPROST PH&T is a liquid (a clear, colourless solution) supplied in a pack containing a 2.5 ml plastic bottle with a screw cap.

The Marketing Authorisation Holder Manufacturer

PH&T SpA RAFARM S.A.

Via Marostica, 1 ThesiPousi-HatziAgiouLouka

20146 Milano Paiania-Attiki,

Italy TK 19002, P.O. 37, Greece

This medicinal product is authorised in the Member States of the EEA under the following names:

Italy: Travoprost PH&T 40 micrograms/ml eye drops, solution

Romania: Travoprost PH&T 40 micrograms/ml eye drops, solution

This leaflet was last revised in

[To be completed nationally]

Module 4

Labelling

**INNER LABELLING**

**1.3.1 Labelling**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**BOTTLE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION**

TRAVOPROST PH&T 40 micrograms/ml eye drops.

Travoprost

**Ocular use**

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

<Open here>

**3. EXPIRY DATE**

Exp:

Discard 4 weeks after first opening.

Opened:

**4. BATCH NUMBER**

Lot:

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

2.5 ml

**6. OTHER**

**OUTER LABELLING**

PARTICULARS TO APPEAR ON THE OUTER PACKAGIN

**C**ARTON FOR SINGLE BOTTLE 2.5 ml

1. NAME OF THE MEDICINAL PRODUCT

TRAVOPROST PH&T 40 micrograms/ml eye drops, solution

2. STATEMENT OF ACTIVE SUBSTANCE

1 ml of solution contains 40 micrograms of travoprost

3. LIST OF EXCIPIENTS

Benzalkonium chloride, Macrogol-15-Hydroxystearate,Trometamol, Boric acid (E284), EDTA disodium, Mannitol (E421), Sodium hydroxide and/or hydrochloric acid (to adjust pH), Water for injection. See the package leaflet for further details.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, solution

1 x 2.5 ml

5. METHOD AND ROUTE OF ADMINISTRATION

Ocular use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and the reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp:

Discard 4 weeks after first opening.

Opened:

Opened (1):

Opened (2)

Opened (3)

9. SPECIAL STORAGE CONDITIONS

10 SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PH&T S.p.A.

Via Marostica, 1

20146 – Milano

Italy

12. MARKETING AUTHORISATION NUMBERS

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16 INFORMATION IN BRAILLE

TRAVOPROST PH&T

Module 5

Scientific discussion during the initial procedure

1. Introduction

Based on the review of the data on quality, safety and efficacy, the member states involved in the procedure considered that the applications for Travoprost PH&T 40 mcg/ml eye drops solution (MA No 043123; Procedure No IT/H/0373/001/DC) could be approved. This product is aprescription-only medicine indicated for the treatment of ocular hypertension and open-angle glaucoma.

This application was submitted using the Decentralised Procedure (DCP), with the Italy (IT) as Reference Member State (RMS) and Romania as Concerned Member State (CMS). This application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, the reference product is marketed in Europe under the trade name Travatan 40 micrograms/ml eye drops, solution (Alcon Laboratories Ltd., UK, marketing authorisation no.: EU/1/01/199/001-002).

Travoprost PH&T eye drops solutioncontains the active ingredientTravoprost which is a prostaglandine for local use (ATC-code: S01EE04) and it is indicated for decrease of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

It is recommended that one drop of Travoprost PH&T T in the conjunctival sac of the affected eye(s) is taken once daily, usually in the evening.

The therapeutic equivalence has been demonstrated between the test product Travoprost PH&T and the reference product Travatan (Alcon Laboratories Limited), containing Travoprost40 mcg/ml. The study was conducted in healthy, adult, human subjects under fasting condition. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

1. About the product

|  |  |
| --- | --- |
| **Proposed name of the medicinal product in the RMS** | Travoprost PH&T |
| **Name of the drug substances (INN name):** | Travoprost |
| **Pharmaco-therapeutic group (ATC Code):** | S01EE04 |
| **Pharmaceutical form(s) and strength(s):** | Eye drops solution |
| **Reference Number(s) for the Decentralised Procedure** | IT/H/0373/001/DC |
| **Reference Member State:** | IT |
| **ConcernedMemberStates:** | RO |
| **Marketing Authorisation Numbers** | AIC No: 043123 |
| **Name and address of the Authorization Holder** | PH&T Spa. Via Marostica 1 Milano Italy |

1. Scientific Overview and discussion

III.1 Quality aspects

**ACTIVE SUBBSTANCE – Travoprost**

DCI: Travoprost

Chemical name: (5Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3R)-3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid 1-methylethyl ester;

Other names:

(+)-16-[3-(trifluoromethyl)phenoxy]-17, 18, 19, 20-tetranorprostaglandin F2α isopropyl ester;

(+)-9α, 11α, 15-trihydroxy-16-(3-trifluoromethylphenoxy)-17, 18, 19, 20-tetranor-5-*cis*-13- *trans*-prostadienoic acid isopropyl ester.

CAS Reg. No.: [157283-68-6]

Structural formula:



Molecular formula: C26H35F3O6

Relative Molecular mass: 500.6

Physical form: Colourless or yellow pasty oil, clear or slightly opalescent.

Solubility: Very soluble in acetonitrile, methanol, octanol, chloroform. Practically insoluble in water.

Isomerism: Specific rotation from +52.0° to +58.0°, at 365 nm (USP <781S>).

Travoprost Reference Standard is supplied by U.S. Pharmacopoeia: analytical controls are also referred to USP monograph, and are overall adequately drawn up.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed (tight, light resistant containers under a nitrogen atmosphere).

**DRUG PRODUCT**

**Other Ingredients**

Other ingredients are: BAK,macrogol-15 hydroxystearate, trometamol, boric acid, EDTA disodium, mannitolNaOH 1N, HCl 1N, WFI. All the excipients, except NaOH and HCl, comply with their respective European Pharmacopeia monographs. The qualitative formulation was developed and each of the excipients was selected for its intended use based on development studies. They are included in the formulation at suitable levels and for recognized purposes.

All the excipients are free from any risk of TSE.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**

The establishment of the pharmaceutical equivalence was achieved by comparative studies (batches analysis and drop size study) between batches of Travoprost PH&T and Travatan.

Suitable pharmaceutical development data have been provided for this application.

**Manufacturing Process**

Satisfactory batch formula has been provided for the manufacture of the medicinal product, along with an appropriate description of the manufacturing process. The manufacturing process has been validatedon three industrial batches.

**Control of Finished Product**

The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**

The drug product is filled into sterile 5 ml PP vials equipped with a LDPE dropper and HDPE screw safety cap and packed into cardboard cartons with Patient Information Leaflet.

Satisfactory specifications and statements of compliance to the current European regulations concerning materials in contact with foodstuff have been provided.

**Stability**

Finished product stability studies were performed in accordance to current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months has been proposed and an in-use period of 4weeks after first opening.

III.2 Non-clinical aspects

Travoprost is a generic application for travoprost for ophthalmic use, under the trade nameTravoprost PH&T 40 micrograms/ml.

Pharmacodynamic, pharmacokinetic and toxicological properties of travoprost are well known. However taking into account that, for this product the quali-quantitative formula in excipients is slightly different from the current Travatan formula, the applicant has performed, in adding to data literature, two new pre-clinical study to verify the similarity of the test and reference product in terms of efficacy and safety. The results of both the study indicated that are non statistically significant differences.

**Ecotoxicity/environmental risk assessment (ERA)**

Since TRAVOPROST is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Clinical aspects

## Introduction

Based on the review of the quality, safety and efficacy data, the Member States involved in the procedure have granted a marketing authorisation for TRAVOPROST PH&T 40 micrograms/ml eye drops, solution for the following therapeutic indication:

**Decrease of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.**

The application was made in accordance with Article 10(3) of Directive 2001/83/EC because “Travoprost 40 mcg/ml eye drop solution”, is the hybrid form of the reference product “Travatan 40 mcg/ml eye drop solution”, a locally applied and locally acting medicinal product.

Travatan has been marketed by Alcon Laboratories Limited in Europe since November 2001.

Initially Travatan contained benzalkoniun chloride (BAK) as preservative system and cremophor RH40 as solubilizer; the preservative system was then changed with Polyqaternium-1. Since Travoprost PR and Travatan contain different quali-quantitative composition in excipients a clinical trial was therefore conducted to demonstrate the therapeutic equivalence between the two medicinal products.

## Pharmacokinetics

No new pharmacokinetics studies were performed.

## Pharmacodynamics

No new pharmacodinamic studies were performed. Travoprost is a prostaglandin F2α analogue and reduces the intraocular pressure by increasing the outflow of aqueous humour via trabecular meshwork and uveoscleral pathways. Reduction of the intraocular pressure starts about 2 hours after administration and maximum effect is reached after 12 hours. Moreover, Travoprost increased optic nerve head blood flow in animal models.

## Clinical efficacy

The efficacy of travoprost is well-known. No new efficacy data have been submitted except for those reported in equivalence study.

Bioequivalence studies

A clinical trial (“Evaluation of the therapeutic equivalence of Travoprost PR and Travatan. Double blind randomized clinical trial in subjects affected by glaucoma or intraocular hypertension”) was conducted to demonstrate the therapeutic equivalence between Travoprost PR and Travatan.

The trial enrolled patients affected by primary open angle glaucoma (POAG) or intraocular hypertension (OHT), treatment-naïve or already treated, with ocular pressure (IOP) >21 mm Hg. Patients were randomisedto one of the following treatments: Travoprost PR eye drops, solution 40 mcg/mL orTratavatan eye drops, solution 40 mcg/mL; both administered as one drop of in the affected eyes(s) every evening.

Primary outcome was the change in IOP from baseline to 12 weeks in the two study groups.

Study results showed that both Travoprost PR and Travatan, administered to patients affected by POAG and OHT, were able to reduce the mean IOP values from baseline to 12 weeks of follow-up: -7.79 (+3.51) in Travoprost PR group and -8.84 (+3.08) in Travatan group, in ITT analysis; in PP analysis, mean reduction were -8.25(+2.55) versus -8.95 (+2.99), respectively.

Both treatments produced a >30% reduction from baseline to week 12 follow-up of daily mean IOP values. Mean % change from baseline were as follows: 34.40% (+14.19) in Travoprost PR group and 38.26% (+11.8) in Travatan PR group in ITT analyses; -36.24% (+9.61) versus -38.65% (+11.53), respectively, in PP population.With reference to safety profile the differences between two treatments groups for adverse events, severe adverse events or an adverse event leading to discontinuation were not statistically significant.

Conjunctiva hyperaemia was the most frequent eye disorders in both treatment group, reported between adverse events: 10.3% in the Travoprost PR group and 8.1% in the Travatan group. Moreover, it was the most frequent reason for discontinuation to adverse events.

## Clinical safety

Safety profile is well known as reference product initially contained BAK-preservative system. Equivalence trial did not show unexpected safety issues. Considering the scientific debate of local tolerability of BAK-preserved topic ocular medication, attention should be addressed to local tolerability issue; nevertheless it remains a well-known adverse event.

**PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN**

The Applicant has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Travoprost. However, the RMP reported at the end of this procedure has been accepted with a post-approval commitment: Applicant is requested to submit an updated RMP version including the risk during lactation within 30 days.

- Summary table of safety concerns as approved in RMP ( risk during lactation which should be reported yet):



- Summary of Planned Risk Minimisation Activities as approved in RMP:

Concerning the current RMP version, the proposed routine risk minimisation measures are evaluated as sufficient; as a consequence, no additional risk minimisation measures have been set in this RMP.

**SUMMARIES OF PRODUCT CHARACTERISTICS (Sm.PCs), PATIENT INFORMATION LEAFLETS (PILs) AND LABELLING**

The SmPCs, PILs and labelling are acceptable from a clinical perspective. The SmPCs are consistent with those for the originator products. The PILs are consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with current guidance.

The packed leaflet has been evaluated via user consultation study in accordance with the requirements of articles 59(3) and 61(1) of directive 2001/83/EC. The language used for the purpose of the user testing PIL was English.

IV Overall conclusions and benefit-risk assessment

This Application is related to the request of the Applicant PH&T SPAfor the Marketing Authorisation of a medicinal product containing Travoprost in eye drop solution. The application was made in accordance with Article 10(3) of Directive 2001/83/EC because “Travoprost PH&T 40 mcg/ml eye drop solution”, is the hybrid form of the reference product “Travatan 40 mcg/ml eye drop solution”, a locally applied and locally acting medicinal product.

Travatan has marketed by Alcon Laboratories Limited in Europe since November 2001.

The quality characteristics Travoprost PH&T 40 mcg/ml eye drop solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

Based on the legislation requirements related to these kind of application (“Hybrid application”) data from a clinical equivalence study were provided.

The therapeutic equivalence has been demonstrated between the test product Travoprost PH&T and the reference product Travatan (Alcon Laboratories Limited), containing travoprost40 mcg/ml.

The efficacy and safety profiles of travoprost are well known; two new preclinical studies and a therapeutic equivalence study were submitted in accordance to the legislation requirements. No new or unexpected safety concerns arose from the clinical equivalence study.

The SmPCs, PILs and labelling are satisfactory, and consistent with those for the reference products, where appropriate, along with current guidelines.

**BENEFITI RISK ASSESSMENT**

The quality of the productTravoprost PH&T 40 mcg/ml eye drop solution is acceptable, and no new non-clinical or clinical safety concerns have been identified.

The therapeutic equivalence has been demonstrated between the test product Travoprost PH&T and the reference product Travatan (Alcon Laboratories Limited), containing Travoprost40 mcg/ml.

Extensive clinical experience with Travoprost is considered to have demonstrated the therapeutic value of the products.

The benefit/risk balance is, therefore, considered to be positive.