LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Travabloc
(travoprost, timolol)

SE/H/2433/01/DC

This module reflects the scientific discussion for the approval of Travabloc. The procedure was finalised on 2024-12-11. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Travabloc, 40 mikrogram/ml + 5 mg/ml, Eye drops, solution.

The active substance is timolol maleate, travoprost, timolol. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Travabloc, 40 mikrogram/ml + 5 mg/ml, Eye drops, solution, is a hybrid application submitted according to Article 10(3) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is DuoTrav, 40 µg/ml+ 5 mg/ml, eye drops, solution, authorised in the union since 2006, with Novartis Europharm Limited as marketing authorisation holder.

Potential similarity with orphan medicinal products
N/A

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of travoprost/timolol 40 mcg/ml + 5 mg/ml eye drop solution are well known. As travoprost/timolol 40 mcg/ml + 5 mg/ml eye drop solution is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Travabloc is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

Conclusions on studies:
The active substances are generic substances, the use of which will not alter the concentration or distribution of the substances in the environment. Therefore, Travoprost/Timolol 40 mcg/ml + 5 mg/ml eye drop solution is not expected to pose a risk to the environment.

There are no objections to approval of Travabloc from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
No clinical study has been performed.
The pharmacokinetics characteristics of travoprost and timolol are based on literature data.

Travoprost
Absorption and Distribution
Travoprost is an ester prodrug. It is absorbed through the cornea where the isopropyl ester is hydrolysed to the active free acid. The clinical pharmacokinetics of travoprost has been investigated in different multiple dose topical ocular studies. One study was conducted in normal volunteers to characterise the steady-state pharmacokinetics of travoprost and free acid metabolite following topical ocular administration of travoprost 0.004% and travoprost 0.0015%. Another study was conducted in subjects with normal renal function or renal impairment. The objective was to characterise the steady-state pharmacokinetics of travoprost and its free acid metabolite following topical ocular administration of travoprost 0.004%. Another study was carried out in subjects with normal hepatic function or hepatic impairment. Following once daily topical ocular administration of travoprost 15 µg/mL and 40 µg/mL eye drops to healthy volunteers for 7 days, low systemic exposure to free acid was demonstrated. Peak free acid plasma concentrations of 25 pg/mL or less were observed between 10- and 30-minutes post-dose. The similarity of free acid plasma concentrations on Day 1 and Day 7 would indicate no plasma accumulation.

Metabolism
Metabolism is the major route of elimination of both travoprost and free acid. In vivo and in vitro, travoprost is rapidly hydrolysed to free acid by esterases. The metabolic pathway of the free acid parallels that of latanoprost and endogenous PGF2α, which is 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. According to the pharmacokinetics studies conducted, plasma levels declined rapidly to below the 10 pg/mL assay quantitation limit at 1 hour post-dose. Due to the low plasma concentrations and rapid elimination

following topical dosing, the elimination half-life of the free acid in man could not be determined.

Timolol

Absorption
Following topical administration of timolol 0.5% solution twice daily to the eye in a limited number of individuals, mean peak plasma concentrations were 0.46 or 0.35 ng/mL following the morning or afternoon dose, respectively. In individuals receiving topical timolol 0.5% as the gel-forming ophthalmic solution once daily in the morning, mean peak plasma concentrations following the dose were 0.28 ng/mL.
Following topical application to the eye of a 0.25 or 0.5% solution of the drug, reduction in IOP usually occurs within 15–30 minutes, reaches a maximum within 1– 5 hours, and persists about 24 hours.
The peak concentration (Cmax) of ophthalmic timolol in plasma of eight patients (1.14 ± 0.34 ng/mL) was measured in most subjects within 15 minutes after drug administration. The mean area under the curve from zero to infinitum (AUC0-inf) was 6.46 ± 2.49 ng/mL per hour after intravenous and 4.78 ± 1.90 ng/mL per hour after ocular administration. The systemic bioavailability (F) of the eyedrop was 78.0 ±24.5%.
Systemic absorption of 20 microliters of 0.5% timolol instilled unilaterally in the lower conjunctival cul-de-sac was studied in 6 volunteers. At 3 minutes one subject, at 5 minutes three and at 8 minutes all but one showed measurable (greater than or equal to 215 pg/mL) timolol concentrations in the plasma.

Intraocular pharmacokinetics
Ocular and systemic absorption of 40 μL of topical 0.5% timolol was studied in 57 patients using radioligand binding techniques. The mean concentration of timolol in aqueous humour of the treated eye was 1.9 ± 0.8 μg/mL 74 minutes after instillation of the drug. About 18 hours after drug instillation the aqueous humour concentration of timolol was 105.5 ± 60.9 ng/mL. Timolol was found in 15 (42%) contralateral eyes. Concentration of timolol in the contralateral eye increased from 0.04 ± 0.08 ng/mL at 50 minutes to 0.3 ± 0.2 ng/mL at 134 minutes and was 0.2 ± 0.4 ng/mL at 18 hours after instillation. Timolol concentrations in the aqueous humour of the treated eye appeared to be high enough to occupy beta 1- and beta 2-receptors completely (100%) at 74 minutes and at 18 hours after drug instillation. Timolol concentrations in the contralateral eye were high enough to occupy up to 33.0 ± 24.7% of the beta 2-receptors and up to 51.7 ± 35.1% of beta 2-receptors. High drug concentrations and complete beta-receptor occupancy in the aqueous humour of the treated eye after topical timolol are in agreement with the long-lasting ocular hypotensive effects. The low drug concentrations and partial receptor occupancy in the contralateral eye may also be of some clinical significance.
The concentration of timolol in aqueous humour after one single drop of timolol ophthalmic solution was studied in 19 patients. Relatively high concentrations were found (mean: 626 ng/mL), but the individual differences were great (range: 0 ng/mL- 2080 ng/mL). Possible explanations are discussed. No detectable levels of timolol were found in plasma (detection level greater than or equal to 1 ng/mL).
Samples of aqueous humour were removed from 26 eyes at the start of cataract extraction. Two drops of timolol 0.5% had been instilled into the conjunctival sac 12-71 minutes before operation. Analysis by gas chromatography showed a mean timolol concentration of 55.46 ng/mg, with a range of 8 to 100 ng/mg.

Systemic distribution and metabolism
Approximately 80% of timolol is metabolized in the liver to inactive metabolites. Timolol is 10–60% bound to plasma proteins, depending on the assay method employed. The drug is distributed into milk.
The pharmacokinetics of timolol, after oral administration of single 20 mg doses to healthy subjects was studied. Extra-renal elimination (metabolic and biliary) represented the main route of elimination, with a renal to body clearance ratio of 0.123. This level paralleled the percentage of unaltered timolol excreted in urine 24 hour after its administration.

The disposition profile of timolol was investigated in normal individuals after a single oral dose. Timolol follows first-order kinetics and may be adequately described by a one-compartment model. After the single oral doses, extrapolated volume of distribution was 1.81 ± 0.15 L/kg and the total plasma clearance was 557 ± 61 mL/min. The area under the curve from zero to infinity and the peak concentration observed were dose dependent. A linear relationship was found between timolol plasma concentrations and beta-adrenergic blocking effects (per cent inhibition), as estimated from exercise-induced tachycardia.

Elimination and excretion
Timolol has a plasma half-life (t½) of 3–4 hours; t½ is essentially unchanged in patients with moderate renal insufficiency. The unchanged drug and its metabolites are excreted in urine. Only small amounts of the drug are removed by hemodialysis.
The pharmacokinetics after oral administration of single 20 mg doses of timolol to healthy subjects was studied. Individual variation was observed in bioavailability; the peaks plasma concentration (Cmax) of 50 to 103 ng/mL being achieved at different times (0.5-3h). The residual level after 12 hours differed greatly between the subjects (0.8 to 7.2 ng/mL). The mean half-life of the terminal elimination phase was 2.62 ± 0.17 hours.
The disposition profile of timolol was investigated in normal individuals after a single oral dose. Overall elimination half-life was 3.2 ± 0.2 hours, with an observed peak time of 2.0 ± 0.2 hours. Approximately 20 per cent of elimination from the human body was dependent on the kidney.

Pharmacokinetic conclusion
Travabloc 40 mikrogram/ml + 5 mg/ml, Eye drops, solution is a locally applied product which exerts its effect at the site of application. For local acting products abridged applications should be regarded as hybrid applications.
No bioequivalence study has been conducted to support the application. This is acceptable since this is a locally applied product provided as an aqueous solution, which is of the same type of solution and the composition is essentially similar to the reference product, Duotrav, 40 ug/ml + 5 mg/ml, eye drops solution (Guideline on the Investigation of the Bioequivalence, CPMP/ EWP/ QWP/ 1401/ 98 Rev. 1/ Corr **). The biowaiver is therefore considered acceptable.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted.
The application is based on bibliographic data and is submitted in accordance with article 10(3) hybrid application in directive 2001/83/EC as bioequivalence cannot be demonstrated through bioavailability studies. Therefore, no additional data is necessary, and the Clinical Overview is regarded as adequate.
The SmPC is in line with the reference medical product with minor proposed amendments.

Risk Management Plan
The MAH 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 Travabloc.

Part II Safety specification
Summary of safety concerns from RMP Part II: Module SVIII.

Important identified risks	None
Important potential risks	None
Missing information	None

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 1, signed 17/07/2023 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a 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 user testing the PL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Travabloc 40 mikrogram/ml + 5 mg/ml, Eye drops, solution is a locally applied product which exerts its effect at the site of application.
No bioequivalence study has been conducted to support the application. This is acceptable since this is a locally applied product provided as an aqueous solution, which is of the same type of solution as the reference product with the composition being essentially similar to the reference product.
The biowaiver is therefore considered acceptable.
The quality of the hybrid product, Travabloc, is found adequate and there are no objections to approval of Travabloc, from a non-clinical and clinical point of view and the product information is considered acceptable.

The benefit/risk is considered positive, and the application is therefore recommended for approval.
There are no conditions pursuant to Article 21a or specific obligations pursuant to article 22 of Directive 2001/83/EC.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Travabloc, 40 mikrogram/ml + 5 mg/ml, Eye drops, solution was positively finalised on 2024-12-11.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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