LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Dorzolamid/Timolol Misom
(timolol maleate, dorzolamide hydrochloride)

SE/H/2252/01/DC

This module reflects the scientific discussion for the approval of Dorzolamid/Timolol Misom. The procedure was finalised on 2023-12-18. 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 Dorzolamid/Timolol Misom, 20 mg/ml + 5 mg/ml, Eye drops, solution in single-dose container.

The active substances are timolol maleate and dorzolamide hydrochloride. 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 Dorzolamid/Timolol Misom, 20 mg/ml + 5 mg/ml, Eye drops, solution in single-dose container, 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 DK, IE, PL, RO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Cosopt 20 mg/ml + 5 mg/ml, Eye drops, solution authorised in SE since 2006, with Santen Oy as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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 active substances are well known. As active substances are widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Dorzolamide/Timolol 20mg/ml + 5mg/ml Preservative-free, Single Dose Eye drops, Solution is a generic or essentially similar product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Dorzolamide/Timolol 20mg/ml + 5mg/ml Preservative-free, Single Dose Eye drops, Solution from a non-clinical point of view.

IV. CLINICAL ASPECTS

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

Dorzolamide Hydrochloride
Unlike oral carbonic anhydrase inhibitors, topical administration of dorzolamide hydrochloride allows for the active substance to exert its effects directly in the eye at substantially lower doses and therefore with less systemic exposure. In clinical trials, this resulted in a reduction in IOP without the acid-base disturbances or alterations in electrolytes characteristic of oral carbonic anhydrase inhibitors.

When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, active substance and metabolite concentrations in red blood cells (RBCs) and plasma and carbonic anhydrase inhibition in RBCs were measured. Dorzolamide accumulates in RBCs during chronic dosing as a result of selective binding to CA-II while extremely low concentrations of free active substance in plasma are maintained. The parent active substance forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent active substance but also inhibits a less active isoenzyme (CA-I). The metabolite also accumulates in RBCs where it binds primarily to CA-I. Dorzolamide binds moderately to plasma proteins (approximately 33%). Dorzolamide is primarily excreted unchanged in the urine; the metabolite is also excreted in urine. After dosing ends, dorzolamide washes out of RBCs non-linearly, resulting in a rapid decline of active substance concentration initially, followed by a slower elimination phase with a half-life of about four months.

When dorzolamide was given orally to simulate the maximum systemic exposure after long term topical ocular administration, steady state was reached within 13 weeks. At steady state, there was virtually no free active substance or metabolite in plasma; CA inhibition in RBCs was less than that anticipated to be necessary for a pharmacological effect on renal function or respiration. Similar pharmacokinetic results were observed after chronic, topical administration of dorzolamide hydrochloride. However, some elderly patients with renal impairment (estimated CrCl 30-60 ml/min) had higher metabolite concentrations in RBCs, but no meaningful differences in carbonic anhydrase inhibition and no clinically significant systemic side effects were directly attributable to this finding.

Timolol Maleate

In a study of plasma active substance concentration in six subjects, the systemic exposure to timolol was determined following twice daily topical administration of timolol maleate ophthalmic solution 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/ml and following afternoon dosing was 0.35 ng/ml.

Discussion and overall conclusion
Dorzolamide + Timolol 20 mg/ml + 5 mg/ml eye drops, solution (in single dose container) 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, Cosopt 20 mg/ml + 5 mg/ml, eye drops, solution (Guideline on the Investigation of the Bioequivalence, CPMP/ EWP/ QWP/ 1401/ 98 Rev. 1/ Corr **) (for further information see Quality AR).

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Dorzolamid/Timolol Misom.

Safety specification
Summary table of proposed safety concerns (RMP Part II: Module SVIII).

Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan

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

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

Summary of the RMP

The Applicant has proposed a list of safety concern that is empty, and this is in accordance with the intention of GVP V (rev 2). And since there is no need for additional pharmacovigilance activities nor additional risk minimization measures for the safety concerns, it is agreed that the list of safety concern could be empty.
The submitted Risk Management Plan, version 0.1, signed 18 May 2022, 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

A user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to the text for COSOPT-S 20 mg/ml + 5 mg/ml eye drops, solution in single-dose container", DCP/MRP DK/H/0134/002. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dorzolamide/Timolol Misom, 20 mg/ml + 5 mg/ml eye drops, solution (in single dose container) 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 and the composition is essentially similar to the reference product.
The quality of the hybrid product, Dorzolamid/Timolol Misom, is found adequate. There are no objections to approval of Dorzolamid/Timolol Misom, from a non-clinical and clinical point of view.
The product information is acceptable.
The benefit/risk is considered positive, and the application is therefore recommended for approval.

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 Dorzolamid/Timolol Misom, 20 mg/ml + 5 mg/ml, Eye drops, solution in single-dose container was positively finalised on 2023-12-18.

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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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