PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Dorzolamide/Timolol NTC 20mg/ml + 5mg/ml, eye drops, solution
NTC Srl, Italy
dorzolamide hydrochloride/timolol maleate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.
General information on the Public Assessment Reports can be found on the website of the MEB.
To the best of the MEB’s knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1874/001/DC
Registration number in the Netherlands: RVG 106539

21 September 2011

Pharmacotherapeutic group: antiguamoa preparations and miotics, beta blocking agents
ATC code: S01ED51
Route of administration: ocular
Therapeutic indication: treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or pseudoexfoliative glaucoma when topical beta-blocker monotherapy is not sufficient.

Prescription status: prescription only
Date of authorisation in NL: 12 May 2011
Concerned Member States: Decentralised procedure with ES, PL
Application type/legal basis: Directive 2001/83/EC, Article 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.
I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Dorzolamide/Timolol NTC 20mg/ml + 5mg/ml, eye drops, solution from NTC Srl. The date of authorisation was on 12 May 2011 in the Netherlands. The product is indicated for treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or pseudoexfoliative glaucoma when topical beta-blocker monotherapy is not sufficient.

A comprehensive description of the indications and posology is given in the SPC.

Dorzolamide/Timolol NTC is comprised of two components: dorzolamide hydrochloride and timolol maleate. Each of these two components decreases elevated intraocular pressure by reducing aqueous humor secretion, but does so by a different mechanism of action. Dorzolamide hydrochloride is a potent inhibitor of human carbonic anhydrase II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Timolol maleate is a non-selective beta-adrenergic receptor blocking agent. The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that the predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed. The combined effect of these two agents results in additional intraocular pressure (IOP) reduction compared to either component administered alone.

Following topical administration, Dorzolamide/Timolol NTC reduces elevated intraocular pressure, whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. The product reduces intraocular pressure without the common side effects of miotics such as night blindness, accommodative spasm and pupillary constriction.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product COSOPT 20 mg/ml + 5 mg/ml, eye drops, solution (NL License RVG 22871) which has been registered in the Netherlands by Merck Sharpe & Dohme B.V. since 5 August 1998. COSOPT was harmonised in the EEA through MRP DK/H/0134/001. In addition, reference is made to COSOPT authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC, hybrid application, as bioequivalence cannot be demonstrated through bioavailability studies.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Dorzolamide/Timolol NTC 20mg/ml + 5mg/ml, eye drops, solution is a product for ocular use (eye drops) intended to act without systemic absorption, with qualitatively and quantitatively the same excipients as used in the reference product, it is exempted for biostudy (Guideline CPMP/239/95 on locally applied, locally acting products, containing known constituents). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a hybrid application.
II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance timolol maleate
The active substance timolol maleate is an established active substance described in the European Pharmacopoeia (Ph.Eur). The active substance is a white or almost white, crystalline powder or colourless crystals, practically soluble in water and ethanol. The substance possesses one chiral center. The active substance is the S-enantiomer. Polymorphism is not relevant for the drug product, as it is an aqueous solution.

The CEP procedure is used for timolol. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur., with additional requirements of the CEP. The specification is acceptable in view of the CEP and the various European guidelines. Certificates of analysis have been provided, demonstrating compliance with the drug substance specification.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Active substance dorzolamide hydrochloride
The active substance dorzolamide hydrochloride is an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white to off-white crystalline powder, which is soluble in water, sparingly soluble in ethanol and methanol. The drug substance presents two different polymorphic forms, which are in fact pseudopolymorphic compounds.

Manufacturing process
A four-step synthesis is used. Acceptable specifications have been adopted by the drug substance manufacturer for the starting materials, intermediates and reagents. The drug substance has been adequately characterised.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur., with additional requirements for residual solvents. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three full scaled batches stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). No significant changes of parameters were observed. The stability data supports the claimed re-test period of 3 years.

**Medicinal Product**

**Composition**

Dorzolamide/Timolol NTC is a clear, colourless to nearly colourless, slightly viscous solution (65 to 135 cP) with pH 5.5-5.8 and 240-325 mOsmol/kg. Each ml contains 22.26 mg of dorzolamide hydrochloride corresponding to 20 mg dorzolamide and 6.83 mg of timolol maleate corresponding to 5 mg timolol.

The aqueous solution is packed in white PE LD dropper containers with an HDPE cap. Each multi-dose dropper container contains 5 ml of Dorzolamide/Timolol NTC eye drops solution.

The excipients are chosen in accordance with the original product: benzalkonium chloride, hydroxyethyl cellulose, mannitol (E421), sodium citrate (E331), sodium hydroxide (E524) (for pH adjustment), water for injections. Benzalkonium chloride as preservative agent is added to the medicinal product to maintain sterility during the use after first opening and throughout the whole shelf-life.

**Pharmaceutical development**

The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation and manufacturing process have been optimised. Key physicochemical characteristics (pH, viscosity, tonicity) have been sufficiently specified and compared with the innovator product. This comparison showed that the characteristics of two products have identical properties. The method of sterilisation has been justified. No significant differences between the values of pH, identification, preservative and active substances distribution content of the solution before filtration and after filtration were observed. The drop volume was found comparable for COSOPT versus Dorzolamide/Timolol NTC.

Based on the chemical-pharmaceutical characteristics the product was demonstrated to be essentially similar to the reference product.

**Manufacturing process**

A five-step production process is described. The aseptic manufacturing process involves production of two solutions with different sterilization methods. The two solutions are mixed to a final bulk solution. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three commercial-scale batches.

**Control of excipients**

The excipients comply with Ph.Eur. requirements. These specifications are acceptable.

**Container Closure System**

The bottle and the dropper are made of LDPE and the wing screw cap is made of HDPE. All components are sterilized by irradiation in accordance with the Ph.Eur. The compatibility of the container system with the drug product is demonstrated in the pre-stability studies.

**Microbiological attributes**

The sterility is maintained by addition of benzalkonium chloride in accordance with the originator product. Challenge testing was performed on the product in compliance with the criteria of Ph. Eur. for all microorganisms tested and under operating conditions. Efficacy of the preservation has been demonstrated.

**Quality control of drug product**

The product specification includes tests for appearance, identification (timolol, dorzolamide and benzalkonium chloride), uniformity of volume, pH, viscosity, osmolality, related substances, assay (timolol, dorzolamide and benzalkonium chloride), particulate matter, sterility, microbial purity, preservative efficacy, and water loss.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three commercial-scale batches, demonstrating compliance with the release specification.

**Stability of drug product**
Stability data on the product has been provided three commercial scaled batches stored at 25 °C/60% RH (24 months) and at 40 °C/75% RH (6 months). The product was packed in a dropper container. No significant changes were seen in the stability studies. The contents of dorzolamide hydrochloride, timolol maleate and benzalkonium chloride remained well within the specified limits. The proposed shelf-life of 2 years when stored below 25ºC is justified.

**In-use stability**
The in-use stability was tested after the first use (accelerated) stability study. Results for up to 4 weeks have been provided. After first opening, the container should not be used longer than 4 weeks.

**Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies**
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

**II.2 Non-clinical aspects**
This product is a hybrid formulation of COSOPT 20 mg/ml + 5 mg/ml, which is available on the European market. Pharmacodynamic, pharmacokinetic and toxicological properties of dorzolamide hydrochloride and timolol maleate are well known. One non-clinical study has been performed with the proposed product in rabbits (see below). No additional studies are required for these applications; overview based on literature review is considered appropriate.

**Toxicology**
An acute eye irritation test was conducted with dorzolamide 2% + timolol 0.5% (study 97322). The test substance was applied in a single dose to the right eye of 3 New Zealand White rabbits (0.1 ml was applied in the conjunctival sac). The left eye was used as control. The degree of eye irritation was evaluated scoring lesions of conjunctiva, cornea, iris and lids at 1, 24, 48 and 72 hours after application. No signs of irritation were observed. The study was performed in compliance with GLP.

**Environmental risk assessment**
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of dorzolamide hydrochloride or timolol maleate released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

**II.3 Clinical aspects**
Dorzolamide hydrochloride and timolol maleate are a well-known active substances with established efficacy and tolerability.

The Guideline on requirements for locally applied, locally acting products, containing known constituents (CPMP/239/05) states that in order to demonstrate therapeutic equivalence clinical trials are in principal necessary, but other models may be used or developed. The essential physical and chemical similarity of Dorzolamide/Timolol NTC 20mg/ml + 5mg/ml, eye drops, solution with the reference product was demonstrated and therefore the exemption from biostudy can be supported. Not only the composition of the drug product is similar to the innovator product, but also other characteristics, such as viscosity, pH, tonicity and drop volume are the same. Dorzolamide/Timolol NTC may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substances of the reference medicinal product. The current product can be used instead of its reference product.

**Risk management plan**
The combination of dorzolamide and timolol was first approved in 1998, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of dorzolamide/timolol can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Cosopt, registered through MRP DK/H/0134/001.

Readability test
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 test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. A total of 21 questions were asked: 18 questions specifically addressed the key safety messages of the leaflet in a randomised order and 3 were specific to the format of the package leaflet. The questions were formulated to identify all the key safety messages in the PIL and other questions were designed around those issues that would ensure a patient’s comprehension and ability to act upon. The results of the user testing are acceptable according to the guideline on the readability, because the criterion “90% of literate adults are able to find the information requested within the package leaflet, of whom 90% can show that they understand it” is fulfilled. No weaknesses of the PIL were identified from the questions specifically addressing the key safety issues or from the open questions aiming to identify positive and negative impressions of the PIL (including lay-out). In summary, the tested package leaflet is in line with the current readability requirements. The results show that the leaflet is easy to read and understandable. The readability test has been sufficiently performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Dorzolamide/Timolol NTC 20mg/ml + 5mg/ml, eye drops, solution has a proven chemical-pharmaceutical quality and is a hybrid form of COSOPT 20 mg/ml + 5 mg/ml, eye drops, solution. COSOPT eye drops is a well-known medicinal product with an established favourable efficacy and safety profile.

Dorzolamide/Timolol NTC is a product for ocular use (eye drops) intended to act without systemic absorption, with the same excipients used in the reference product, it is exempted for biostudy.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other latanoprost and dorzolamide containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Dorzolamide/Timolol NTC 20mg/ml + 5mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 20 April 2011. Dorzolamide/Timolol NTC 20mg/ml + 5mg/ml, eye drops, solution was authorised in the Netherlands on 12 May 2011.

A European harmonised birth date has been allocated (6 March 1998) and subsequently the first data lock point for dorzolamide/timolol is February 2013. The first PSUR will cover the period from April 2011 to February 2013, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 20 April 2016.

The following post-approval commitments have been made during the procedure:

Product information
- The MAH committed to update the product information by means of an appropriate variation following the finalisation of the CSP for dorzolamide/timolol.
## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<td>AUC</td>
<td>Area Under the Curve</td>
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<td>BP</td>
<td>British Pharmacopoeia</td>
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<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>C\text{max}</td>
<td>Maximum plasma concentration</td>
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<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<tr>
<td>CSP</td>
<td>Core Safety Profile</td>
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<td>CV</td>
<td>Coefficient of Variation</td>
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<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EEA</td>
<td>European Economic Area</td>
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<td>EU</td>
<td>European Union</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GLP</td>
<td>Good Laboratory Practice</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
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<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
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<td>PAR</td>
<td>Public Assessment Report</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PIL</td>
<td>Package Leaflet</td>
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<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<td>t\text{½}</td>
<td>Half-life</td>
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<td>t\text{max}</td>
<td>Time for maximum concentration</td>
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<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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<td>USP</td>
<td>Pharmacopoeia in the United States</td>
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### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached</th>
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