Public Assessment Report

Scientific discussion

Carteolol hydrochloride Thea 20 mg/ml eye drops, solution

(carteolol hydrochloride)

NL/H/4035/001/DC

Date: 4 December 2018

This module reflects the scientific discussion for the approval of Carteolol hydrochloride Thea 20 mg/ml eye drops, solution. The procedure was finalised at 22 August 2018. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.
## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<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>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<td>CMS</td>
<td>Concerned Member State</td>
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<tr>
<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>ERA</td>
<td>Environmental Risk Assessment</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>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PL</td>
<td>Package Leaflet</td>
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<td>RH</td>
<td>Relative Humidity</td>
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<td>RMP</td>
<td>Risk Management Plan</td>
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<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Carteolol hydrochloride Thea 20 mg/ml eye drops, solution, from Laboratoires Théa.

The product is indicated for ocular hypertension and primary open-angle glaucoma.

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

This decentralised procedure concerns a hybrid application claiming essential similarity with the European reference product Carteol 2%, eye drops, solution which has been registered in Italy by SIFI S.p.A) since 27 March 2000. The innovator product is registered in several European countries under various trade names.

The concerned member states (CMS) involved in this procedure were Germany, Ireland and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application, as for locally acting medicinal products such as eye drops bioequivalence cannot be demonstrated through bioavailability studies.

II. QUALITY ASPECTS

II.1 Introduction

Carteolol hydrochloride Thea is a clear, colourless to slightly brown-yellow solution with pH 6.0-7.0 and the osmolality 270-340 mOsm/kg.

One ml of solution contains 20 milligrams of carteolol hydrochloride. One vial of 5 ml solution contains 100 mg of carteolol hydrochloride. One drop contains approximately 0.58 milligram of carteolol hydrochloride.

5 ml (at least 150 drops) of solution is packed in a 15 ml multidose bottle (PE) with a dropper applicator (PE) equipped with a 0.2 microns filtering membrane (polyethersulphone) and a PE cap.

The excipients are: sodium chloride, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate and water for injections.
II.2 Drug Substance

The active substance is carteolol hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The substance are white or almost white crystals or a crystalline powder. Carteol hydrochloride is soluble in water, sparingly soluble in methanol, slightly soluble in ethanol (96%) and practically insoluble in methylene chloride. Polymorphism and particle size are not relevant for the present product, as the product is a solution.

The CEP procedure is used for the active substance. 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 general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details, except for a short summary, on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for six batches.

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.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of the excipients in the product is justified and their functions explained. The excipients used are common for eye drops, solutions. The objective of the development studies was to manufacture a formulation with a composition as close as possible to that of the reference product Carteol.

No clinical study was performed. In accordance with the NfG on the Investigation of Bioequivalence, a waiver for the need to provide equivalence data can be considered if the test product is the same type of aqueous solution and contains the same active substance and same excipients as the medicinal product currently approved. Comparative data of
chemical physical characteristics are provided between the proposed product and the reference product. The characteristics are comparable.

The selected product sterilisation method (aseptic preparation with sterile filtration) is acceptable, in view of draft Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container. It has been adequately justified that final heat sterilisation of the product in its intended container closure system is not feasible, based on amongst others the stability studies provided. The container closure system is sufficiently described. Study results are provided regarding suitability of the multi-dose eye drop container for the intended (multi-dose) use of the product. Adequate results have been submitted, including regarding sterility & microbial aspects of the product packaged in the container up to the end of the in-use period.

Manufacturing process
The manufacturing process is a complex, non-standard process, considering the aseptic filling steps in the preparation of the product. The process steps, including the experimental process conditions in the different process steps are described (including process temperatures, mixing times). The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for five batches in accordance with the relevant European guidelines.

Control of excipients
All excipients comply with the requirements of the Ph. Eur. These specifications are acceptable.

Microbiological attributes
The drug product is routinely tested for sterility. This is in line with the requirements for eye drops solutions of the general Ph.Eur. eye preparations monograph.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, opalescence, colour, pH, density, osmolality, deliverable volume, identity, assay, degradation products, sterility and leak test. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from five batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for five production batches stored at 25°C/40% RH and 30°C/65% RH (up to 24 months for four batches and up to 3 months for the fifth batch) and 40°C/≤25% RH (up to 6 months for four batches and up to 3 months for the fifth batch). The batches were stored in accordance with applicable European guidelines. On basis of the data submitted, a shelf life was granted of 2 years. No specific storage conditions need to be included in the SmPC or on the label. Stability data have been
provided demonstrating that the product remains stable for 2 months following first opening of the container.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Carteolol hydrochloride Thea has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

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

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Carteolol 2%, eye drops, solution which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Carteolol hydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.
IV.2 Pharmacokinetics

No comparative bioavailability studies or therapeutic equivalence studies have been conducted to support the application. Essential similarity with the reference product is claimed based on comparative quality attributes of the products.

In line with the guideline on Investigation of Bioequivalence, a waiver of the need to provide equivalence data may be acceptable in the case of solutions, e.g. eye drops, nasal sprays or cutaneous solutions, if the test product is of the same type of solution (aqueous or oily), and contains the same concentration of the same active substance as the medicinal product currently approved.

Since the qualitative and quantitative composition of the product is similar to that of the reference product Carteolol 2%, eye drops, solution and the pharmaceutical properties (i.e. osmolarity, pH, relative density, surface tension and droplet volume) are comparable to that of the reference product as well, a biowaiver can be granted. Carteolol hydrochloride Thea may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product.

IV.3 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 Carteolol hydrochloride Thea.

Table 2. Summary table of safety concerns as approved in RMP

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>- Increased risk of anaphylaxis and inhibition of response to adrenaline in anaphylaxis</th>
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<tbody>
<tr>
<td></td>
<td>- Bronchospasm in bronchial asthma or COPD patients</td>
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<td></td>
<td>- Deterioration of cardiovascular diseases – Serious cardiac disorders (AV Block, CHF, Cardiac arrest)</td>
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<tr>
<td>Important potential risks</td>
<td>- Choroidal detachment after filtration procedures</td>
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<tr>
<td>Missing information</td>
<td>- Use during pregnancy and lactation</td>
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<tr>
<td></td>
<td>- Use in paediatric population</td>
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</tbody>
</table>

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Carteolol 2%, eye drops, solution. No new clinical studies were
conducted. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results show that the PL 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

Carteolol hydrochloride Thea 20 mg/ml eye drops, solution has a proven chemical-pharmaceutical quality and is a hybrid form of Carteolol 2%, eye drops, solution. Carteolol is a well-known medicinal product with an established favourable efficacy and safety profile.

Carteolol hydrochloride Thea is a product for ocular use (eye drops) intended to act without systemic absorption. Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of in vitro studies on the relevant quality attributes. A biowaiver has been granted.

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 Carteolol hydrochloride Thea with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 August 2018.
# STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Procedure number*</th>
<th>Scope</th>
<th>Product Information affected</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Summary/ Justification for refuse</th>
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