COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Arteoptic LA Preservative Free 20 mg/ml eye drops, prolonged-release solution (carteolol hydrochloride)

NL/H/5580/001/DC

Date: 8 July 2025

This module reflects the scientific discussion for the approval of Arteoptic LA Preservative Free 20 mg/ml eye drops prolonged-release solution. The procedure was finalised on 16 February 2024. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
IOP	Intraocular Pressure
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Arteoptic LA Preservative Free 20 mg/ml eye drops prolonged-release solution, from Bausch + Lomb Ireland Limited.

The product is indicated for: adult patients for the symptomatic treatment of:

- Intraocular hypertension
- Chronic open-angle glaucoma

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, which concerns a hybrid application. The legal basis is considered appropriate for two reasons: it concerns a locally applied locally acting (Long Acting) product and there is a difference in pharmaceutical form from the reference product.

In this decentralised procedure, therapeutical equivalence is proven between the new product and a European Reference Product (ERP), Carteol 2%, collyre en solution, Eye drops, solution, which has been registered in France via national procedure in France since 20 February 1985.

As mentioned previously, this applicant is a hybrid application due to the differences between the medicinal product and reference product. Compared to the reference product there are three differences:

1. the current product under application contains alginic acid (mucoadhesive agent) in contrast to the reference product,
2. while the reference product contains benzalkonium chloride (BAK) and the current product does not.
3. In addition, because Carteolol LP 2% is a prolonged release formulation, the administration is 1 instead of 2 times a day.

In the past (2004) the Netherlands and other Member States approved the registration of a prolonged release formulation containing alginic acid with the same reference product (FR/H/0244/002/MR). The differences in pharmaceutical form and composition for this product were substantiated with PK, PD, efficacy and safety data. This was withdrawn in the Netherlands (post authorisation) but is still authorised in a few other Member States. The difference between the reference product and the product currently applied for consists, next to the absence of BAK, the need for a slightly higher amount of sodium hydroxide as neutralising agent. The PK and (non-)clinical package submitted for the current application is largely identical to the data which formed the basis of the approval of the reference (BAK containing) product. Not all of the non-clinical package has been assessed since the data are not always considered to be relevant (e.g. the tox studies are not deemed necessary/relevant since alginic acid is not considered to be a novel excipient anymore). Where relevant, the non-clinical data have been assessed in relation to the clinical data provided.

The concerned member states (CMS) involved in this procedure were Belgium, France, Croatia, Italy, Luxembourg, Poland, Portugal, Slovenia and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Arteoptic LA Preservative Free 20 mg/ml is a clear and slightly brown yellow solution. The pH is between 6.3 – 7.0, compatible with the pH of the tears, and the osmolality is between 270 - 315 mosmol/kg. Every 1 ml of solution contains as active substance 20 mg of carteolol hydrochloride. Every 1 drop of the solution contains as active substance 756 µg of carteolol hydrochloride.

The excipients are: alginic acid (E 400), sodium dihydrogen phosphate dihydrate (E 339), disodium phosphate dodecahydrate (E 339), sodium chloride, sodium hydroxide (for pH adjustment), and purified water.

The eye drops are packed in a preservative-free multidose container closure system developed for ophthalmic solutions consisting of a 10 ml translucent bottle (low-density polyethylene) with an ophthalmic squeeze dispenser system (high-density polyethylene, polypropylene, elastomer) and a cap with safety ring (low-density polyethylene). Each container is filled with 8 ml of ophthalmic solution, which correspond to approximate 211 drops.

II.2 Drug Substance

The active substance is carteolol hydrochloride, an established active substance described in the European, British and United States Pharmacopoeia (Ph.Eur., BP and USP). The active substance is a crystalline powder. No polymorphism is known. It is provided as the racemate. The substance is soluble in water, sparingly soluble in methanol, slightly soluble in alcohol, practically insoluble in dichloromethane.

The Active Substance Master File (ASMF) procedure is used for the active substance at site I. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

The CEP procedure is used for the active substance at site II. 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

Site I: The synthesis starts with one starting material and consists of six steps. No class 1 solvents are used in the synthesis. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Site II: A CEP has been submitted; therefore no details 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. and CEP. Batch analytical data demonstrating compliance with this specification have been provided for three batches from each site.

Stability of drug substance

Site I: stability data on the active substance have been provided for six commercial batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 5 years. Based on the data submitted, a retest period could be granted of 5 years when stored under the stated conditions.

Site II: the active substance is stable for 5 years when stored under the stated conditions. Based on the data submitted, a retest period could be granted of 5 years. 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 excipients is justified and their functions explained. The test and reference product are not pharmaceutically equivalent. However, the test and reference product are considered therapeutically equivalent according to the clinical assessment. For the assessment of the therapeutic equivalence reference is made to the clinical assessment report. The formulation development has been discussed. The selection of sterilisation is sufficiently justified. Microbial challenge testing is performed by means of dynamic integrity testing and Closure and Ventilation Integrity Test (CVIT, aerosol chamber test). The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process includes the following steps: compounding of bulk solution, filtration of solution, filling and closing of bottles. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for two full-scaled batches and one pilot batch in accordance with the relevant European guidelines. Process validation for at least one commercial scale batch with the maximum bottles volume that can be filled will be performed post authorisation.

Control of excipients

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

Microbiological attributes

For sterile products, the integrity of the container closure system to prevent microbial contamination was addressed. Microbial challenge testing was performed by means of a dynamic integrity testing and Closure and Ventilation Integrity Test (CVIT, aerosol chamber test) and the formation of biofilm has been sufficiently investigated. The results of the dynamic integrity testing demonstrate that removing the residual drop is critical and if not done correctly there is a risk for contamination. The available data confirm that, if the residual drop is adequately removed, the microbial quality of the product is sufficiently ensured.

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 degree of coloration, clarity and degree of opalescence, visible particles, pH, osmolality, identification, assay, related substances and sterility. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data on two full scaled and one pilot batch from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for two full scaled and one pilot stored at 25°C/60% RH (24 months), 30°C/65% RH (24 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. Photostability studies were performed in accordance with ICH recommendations and showed an increase in total impurities when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are “Keep the bottle in the outer carton in order to protect from light.”

In-use stability data have been provided : “Shelf-life after first opening of the container: 2 months”.

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 Arteoptic LA Preservative Free 20 mg/ml has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- Process validation for at least one commercial scale batch with the maximum bottles that can be filled will be performed post authorisation.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Arteoptic LA Preservative Free 20 mg/ml is intended for substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Carteol 20 mg/ml which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 MAH provided a pharmacokinetics (PK) study (LCM-1037-02-01) and conducted clinical studies (LCM 1037-98-01 and LCM-1037-98-02).

IV.2 Pharmacokinetics

The MAH provided a PK study (LCM-1037-02-01) designed to test whether the new formulation reduces the systemic delivery of carteolol. The point estimates (90% CIs) for the steady-state Cmax and residual level ratios for the test and reference product comparison (T/R) are clearly below 100% and were 59.0 (47.0-69.8) and 32.3 (24.1-43.3), respectively. The data provided by the MAH refers to a study conducted in 2002/2003, which does not fully comply with the current guidelines (i.e. Guideline on the investigation of bioequivalence, Guideline on bioanalytical method validation and ICH M10) due to the difference between the test product used in the study and the test product for which marketing approval is sought. Therefore, this study is considered supportive data which indicates that systemic test exposure might be lower than reference exposure.

IV.3 Pharmacodynamics

Reference is made to the review by Chrisp (1992) to describe the pharmacodynamics (PD) of 1% and 2% carteolol. This review concerns the immediate release formulation of carteolol with twice daily administration. In addition, PD-study LCM 1037-98-01 is shortly described. This study was conducted to justify the PD of, at that time new, prolonged release formulation Carteol LP, 2%, eye drops with the conventional Carteol, 2%, eye drops. This study is however of limited support for the current product, as there are differences between the eye drops with respect to the absence of BAK in the current formulation.

IV.4 Clinical efficacy

In an effort to provide a once daily dosing regimen, carteolol was formulated with 1% alginic acid. The MAH conducted a clinical study (LCM 1037-98-01) in which the effect on intraocular pressure of Carteolol 2% long-acting formulation (with alginic acid) was compared with that of Carteolol 2% regular formulation (without alginic acid). Twenty-eight healthy volunteers were included in a trial to compare the tolerability and the hypotensive effect of abovementioned formulations. It was a randomised, double-blinded and cross-over study. The baseline intraocular pressure (IOP) values ranged between 10 and 14 mmHg. Subjects received 1 drop of each treatment in one and the same eye, separated by a wash-out period of 11 days. The ocular hypotensive activiy of carteolol 2% LA was more pronounced 8 hours after the drug instillation, and remained noticeable after 24 and 30 hours, contrary to regular carteolol 2% (See table 1).

Table 1: Percentage pf (PreserFlo) reduction of IOP (Intraocular Pressure) since baseline.

	Time after instillation			
	3h	8h	24h	30h
IOP decrease (LA)	8.3%	15.4%	3.6%	7.7%
IOP decrease (regular)	8.7%	8.3%	0.0%	0.0%

These results indicate the long-lasting effect of carteolol LA in human after 1 single drop instillation. The assessment of the safety, using clinical score (signs and symptoms from 0 up

to 24), fluorescein test, far visual acuity, local tolerance upon instillation, blood pressure and heart rate, showed no clinically relevant changes in these parameters with both formulations.

To further support the application the MAH carried out study LCM-1037-98-02. The objective of this study was to evaluate the efficacy and safety of 2% carteolol alginate solution in comparison with standard 2% carteolol solution. This was a double masked, parallel group, multicentre study. Patients with ocular hypertension or open angle glaucoma (n = 235) were randomly assigned to receive either carteolol alginate once a day or standard carteolol solution, twice daily. The masking was maintained through the use of a vehicle in the evening for the alginate group. Patients were evaluated at baseline, 15, 60, and 120 days. At 09:00 (presumed trough) on day 60, mean reductions in intraocular pressure (IOP) from baseline were 6.09 (SD 2.97) and 6.09 (3.18) mmHg for the standard carteolol and alginate, respectively. At 11:00 (presumed peak), mean reductions were 6.51 (2.53) and 6.47 (2.76) mmHg, respectively. Results were similar at other times (day 15 and day 120). The most common side effect was transient stinging on instillation of drops, which did not differ significantly between groups. There were no differences of note in other ocular or systemic signs or symptoms. The alginate-based formulation of carteolol 2% given once daily was as effective as standard carteolol 2% given twice daily with no meaningful differences regarding safety.

However, this study was conducted to investigated the efficacy and safety of the, at that time new, prolonged release formulation Carteol LP, 2%, eye drops with the conventional Carteol, 2%, eye drops. At the time of assessment it was concluded that the B/R was similar for the immediate and prolonged release formulations. Daily administration was considered an advantage as it is expected to improve patient compliance. However, this study is of limited support for the current product, as there are differences between eye drops with respect to the absence of BAK in Carteolol LP 2% PFMD.

IV.5 Clinical safety

No clinical studies with the current product are conducted. The proposed SmPC is similar to the SmPC of the reference product. The clinical studies that were conducted with Carteol LP, 2%, eye drops (containing BAK) are submitted in support of the safety.

In the clinical studies conducted with other carteolol eyedrops adverse events like irritation and worsening of dry eye were reported. The non-ophthalmic adverse event's (AE) known as possible B-blocker side effects are not specified. In PK study LCM 1037-02-01, systemic adverse events were reported.

In the VigiAccess database, maintained by the Uppsala Monitoring Centre, the most common reported AE's are bradycardia, dry eye, eye pain, dizziness, dyspnoea, headache, eye irritation an pruritus.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan (version 1.2 with DLP 24 November 2023, date of final sign off 4 December 2023), 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 Arteoptic LA Preservative 20 mg/ml.

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

Important identified risks	None
Important potential risks	None
Missing information	None

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

IV.7 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Carteol 2%. Since there are differences in in terms of composition: BAK and alginic acid equal absorption cannot be assumed on quality grounds. Alginic acid is added as long acting excipient for the prolonged release. The MAH submitted clinical study 1037-98-02 to justify the efficacy and safety of the current product. This study was conducted to investigate the efficacy and safety of the, at that time new, prolonged release formulation Carteol LP, 2%, eye drops containing BAK with the conventional alginic acid containing Carteol, 2%, eye drops. While there is no direct confirmation provided that a combination of the differences in (non-)presence of BAK and alginic acid still leads to a similarly acting product when compared to the reference product, based on the evidence presented, it is unlikely that a different conclusion could be reached. This uncertainty is therefore not further pursued and the B/R is considered to be positive from a clinical point of view. Risk management is adequately addressed. This medicinal product can be used as hybrid substitution 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 3 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

Arteoptic LA Preservative Free 20 mg/ml eye drops prolonged-release solution has a proven chemical-pharmaceutical quality and is a form of Carteol 2% collyre en solution, Eye drops, solution. Carteol 2% is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of studies on the relevant quality attributes.

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 Arteoptic LA Preservative Free 20 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised recognition procedure was finalised with a positive outcome on 16 February 2024.

LITERATURE REFERENCES

Chrisp, P., & Sorkin, E. M. (1992). Ocular carteolol: a review of its pharmacological properties, and therapeutic use in glaucoma and ocular hypertension. *Drugs & aging, 2*, 58-77.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5580/001 /E/001	Repeat-Use Procedure: CK and SK	No	08-11-2024	Approved	N.A.