COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Gelisia 1 mg/g, eye gel in single dose container (timolol maleate)

NL/H/5357/001/DC

Date: 23 September 2024

This module reflects the scientific discussion for the approval of Gelisia 1 mg/g, eye gel in single dose container. The procedure was finalised on 20 March 2023. 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
MAH	Marketing Authorisation Holder
LDPE	Low Density Polyethylene
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 Gelisia 1 mg/g, eye gel in single dose container, from Sifi S.p.A.

The product is indicated for: reduction of the elevated intraocular pressure in patients with:

- ocular 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 claiming similarity with the innovator product. The MAH provided results which confirm the comparability of the products, whereby bioequivalence studies were not required.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Timogel 1 mg/g eye gel (NL RVG 33801) which has been registered in France by Laboratoires Théa since 2006 (original product). In the Netherlands, Timogel has been registered since 2009 by the procedure number FR/H/0288/001.

The concerned member states (CMS) involved in this procedure were France, Germany, Italy, Romania and Spain.

A CHMP referral procedure was conducted on 22 October 2022.Three main issues were raised in the CHMP referral procedure, which pertained to 1) *In vitro* equivalence between the applied product and the reference product for the parameter viscosity was not shown with an adequate statistical methodology referring to the Reflection paper on the statistical methodology for the comparative assessment of quality attributes in drug development; 2) concern about the representativeness of the batches used to evaluate the parameter viscosity; 3) unacceptability of post-hoc justifications of the clinical irrelevance of viscosity. The CHMP concluded that the extended pharmaceutical equivalence has been demonstrated, including vis-à-vis viscosity, and in turn, the therapeutic equivalence of Gelisia and associated names to the reference medicinal product is established. Therefore, CHMP considers the benefit-risk balance of Gelisia and associated names favourable.

II. QUALITY ASPECTS

II.1 Introduction

Gelisia is an opalescent, colourless to slightly yellow gel. It has a pH of 6.5 – 7.5 and an osmolality of 0.290 – 0.340 Osmol/kg.

1 g Gelisia contains as active substance 1 mg of timolol as timolol maleate.

The excipients are: sorbitol (E 420), polyvinyl alcohol, carbomer 974 P, sodium acetate trihydrate, L-Lysine monohydrate and purified water.

The eye gel is packed in low density polyethylene (LDPE) single-dose containers, each filled with 0.4 g gel. The single-dose containers are moulded in 5 sealed units strip, which in turn are wrapped in a polyester/aluminium/polyethylene sachet and packaged inside a carton box.

II.2 Drug Substance

The active substance is timolol maleate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder and is soluble in water. The active substance is chiral. Polymorphism is not relevant as the drug substance is dissolved in the drug product.

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 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. with additional tests for microbial control. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for five 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, choice of excipients and their function are adequately described in accordance with the relevant European guidelines.

The qualitative composition is based on reverse engineering analysis of the reference product. During the initial development of the product different excipients were tested. One of the final excipients chosen differed from the reference product. Technical data of the two

excipients are provided, showing that they have similar physico-chemical characteristics. However, during the procedure this excipient was replaced with the same as the reference product. The MAH has provided batch analytical results of one batch of drug product manufactured with the final excipient and drug substance from the current supplier, also results of an in-use stability study with this batch are provided. The results confirm the comparability of the products.
A pharmaceutical equivalence study has been performed on three batches of both the reference and test product. The parameters tested are appearance, colour, opalescence, particle size, mean fill weight, pH, osmolality, dynamic viscosity, surface tension, identification, assay, related substances, density and droplet volume.
Viscosity was tested at different shear rates to reflect the non-Newtonian fluid properties. During the CHMP referral procedure, an additional statistical comparison on viscosity was conducted by combining the available stability data on the dynamic viscosity of the test product with the viscosity data of test and reference product submitted for the justification of the biowaiver, in order to increase the sample size and to obtain samples from batches with similar age. Overall, the pharmaceutical equivalence of test and reference products is considered adequately demonstrated.
The manufacturing development has been described in sufficient detail. An acceptable justification is provided for the selected sterilisation method, including heat sterilization of one component and sterile filtration of others.
The usability of the containers has been acceptably discussed based on the experience of the applicant with similar products.

Manufacturing process

The drug product is manufactured in several steps including preparation of start solutions, sterilization and mixing. The final bulk solution is packed using a blow/fill/seal process.

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scaled batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. and in-house requirements. The apparent viscosity of carbomer is stated in the excipient's specification. The in-house methods for L-Lysine, including microbiological methods, have been adequately validated. These specifications are acceptable.

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, colour, opalescence, particle size, pH, mean fill weight, osmolality, dynamic viscosity (in two ranges of shear rate), identification, assay, uniformity of dosage units, related substances, packaging and sterility. The release and shelf life limits are identical, except for mean fill weight, uniformity of dosage units and packaging, not included in the shelf life specification, and dynamic viscosity, with a lower limit at end of shelf life. 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 from three full scaled 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 three full scaled batches (manufactured with drug substance from a different supplier and the initially chosen different excipient) stored at 25°C/40% RH (24 months for one batch, 18 months for two batches), 30°C/NMT 65% RH (12 months) and 40°C/NMT 25% RH (6 months) in accordance with applicable European guidelines. Photostability studies were not performed, which is considered acceptable in view of the Ph.Eur. monograph for Timolol maleate and the reference product, from which it is known that Timolol is sensitive to light and the product should be stored protected from light. Water loss at the end of shelf life is tested and the results are acceptable. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are 'store below 25°C'. The medicinal product does not contain preservatives.

In-use stability data demonstrated that the product remains stable for 28 days following first opening of the sachet, when stored in the sachet in the carton box to protect from light. After opening of the single-dose container: use immediately and discard the single-dose container after use even if only partially used

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 Gelisia 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 Gelisia is intended for generic 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 generic formulation of Timogel 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

Timolol maleate is a well-known active substance with established efficacy and tolerability. A waiver of the need to provide therapeutic equivalence data is claimed. A pharmaceutical equivalence study has been performed on three batches of both the reference and test product. Manufacturability and physico-chemical characterization of one drug product batch has been provided, confirming the comparability of the products. No clinical pharmacokinetic studies or additional clinical studies for efficacy and safety were performed, as the MAH claims therapeutic equivalence based upon *in vitro* data.

IV.2 Pharmacokinetics

During the CHMP referral additional statistical comparison on viscosity was conducted by combining the available stability data on the dynamic viscosity of the test product with the viscosity data of test and reference product. Considering the data available and the additional calculations performed, the CHMP concluded that the similarity of viscosity of the test and reference products was established and that extended pharmaceutical equivalence was shown. Taking into account all data provided from the pharmaceutical equivalence study and additional calculations during the CHMP referral, according to the draft EMA Guideline on quality and equivalence of topical products (CHMP/QWP/708282/2018), demonstration of equivalence with respect to quality, i.e. extended pharmaceutical equivalence, is considered to be sufficient. Therefore, a waiver of the need to provide therapeutic equivalence data is acceptable.

No bioequivalence study was performed as the MAH claims therapeutic equivalence based

upon *in vitro* data comparing Gelisia with the reference product Timogel. Taking into account all data provided from the pharmaceutical equivalence study and additional calculations during the CHMP referral, according to the draft EMA Guideline on quality and equivalence of topical products (CHMP/QWP/708282/2018), demonstration of equivalence with respect to quality, i.e. extended pharmaceutical equivalence, is considered to be sufficient. Therefore, a waiver of the need to provide therapeutic equivalence data is acceptable.

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 Gelisia.

Table 1. 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.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Timogel. No new clinical studies were conducted. The MAH demonstrated through a biowaiver that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic 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 language used for the purpose of user testing the PL was Spanish.
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

Gelisia 1mg/g, eye gel in single dose container has a proven chemical-pharmaceutical quality and is a generic form of Timogel 1 mg/g eye gel. Timogel 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 *in vitro* studies on the relevant quality attributes. A waiver of the need to provide therapeutic equivalence data is granted.

In the Board meeting of 30 June 2022, the following was discussed:

- The final product was reformulated. However, tests were missing. The MAH indicated in a commitment that these test will be formed before the completion of the procedure.
- The filter process is not in-line with the 'EMA guideline on sterility (EMA/CHMP/CVMP/QWP/850374/201) guidelines. The sterility of the final product cannot be guaranteed.
- According to the data provided the proposed shelf life of 24 months is not acceptable.

The Board meeting concluded that the points should be resolved before authorisation of the product. The MAH resolved the points and the product was approved.

The procedure was discussed in the CMD(h) meeting on 22 October 2022 and referred to CHMP. On 15 December 2022, based on the evidence presented, it was agreed by the member states that the Benefit/Risk for Gelisia was positive.

The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Gelisia with the reference product, and have therefore granted a marketing authorisation The decentralised procedure was finalised with a positive outcome on 20 March 2023.

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/5357/001/IA/001	***Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State*** • *Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State* • *Excipient/active substance starting material*	No	27-02-2024	Approved	N/A