COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fenogal 160 mg hard capsules (fenofibrate)

NL License RVG: 127290

Date: 28 November 2022

This module reflects the scientific discussion for the approval of Fenogal 160 mg hard capsules. The marketing authorisation was granted on 28 July 2022. 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
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of medicinal Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Fenogal 160 mg hard capsules, from Interdos Pharma BV.

The product is indicated as an adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the following:

- Treatment of severe hypertriglyceridemia with or without low HDL cholesterol;
- Mixed hyperlipidaemia when a statin is contraindicated or not tolerated;
- Mixed hyperlipidaemia in patients at high cardiovascular risk in addition to a statin when triglycerides and HDL cholesterol are not adequately controlled.

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

This national procedure concerns a generic application claiming essential similarity with the innovator product Lipidil-Ter 160 mg, film-coated tablets, registered since 1 July 2000 by Fournier Pharma GmbH (DE/H/0235/001). Lipidil-Ter has not been registered in the Netherlands.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Fenogal is a green (cap) and orange (body) hard capsule and contains as active substance 160 mg of fenofibrate.

The capsules are packed in transparent PVC/aluminium blisters.

The excipients are:
Capsule filling – lauryl macrogol glycerides, macrogol (20,000), hydroxypropyl cellulose and sodium carboxymethyl starch (type A);
Capsule shell (size N° 0) – gelatine, red iron oxide (E172) yellow iron oxide (E172), black iron oxide (E172), titanium dioxide (E171) and indigotin I (E132).

Capsule size N° 0 is a large but usual capsule size for oral administration. The excipients and packaging are usual for this type of dosage form.

II.2 Drug Substance

The active substance is fenofibrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a is a white to off-white crystalline powder which is practically insoluble in water. One manufacturer is used.

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 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 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 three batches. An acceptable re-test period is applied in line with the information on the CEP.

As the active substance is melted and as hot melt cooled to a homogeneous mixture with excipients, initial particle size distribution and morphological form are not relevant for the quality of the drug product.

Stability of drug substance
The retest period of the active substance is 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 excipients is justified and their functions explained. Fenofibrate is normally hydrophobic and not soluble in water. The MAH has produced a pharmaceutical form of fenofibrate with an enhanced solubility in water, by using an excipient with both hydrophobic and hydrophilic components (called amphiphilic). This combination (by process of solubilising) of the active substance in the amphiphilic excipient enhances its bioavailability, meaning it can be absorbed more easily after oral intake.

The MAH used an improved dissolution method, which was accepted. It was shown that this dissolution method is capable to control the formation of crystalline active substance over manufacture and storage of the drug product, which is considered to be the important stability indicating parameter for this formulation. An appropriate dissolution specification has been set.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines, followed by six baches after the introduction of a new capsule filling machine. The process involves melting, mixing, filling and packaging. The MAH proved the process is adequate to ensure the homogeneity over the capsule filling process and the absence of crystallinity of the active substance.

Control of excipients

For all excipients, except the colourants (indigotin and iron oxides), reference is made to the Ph Eur. For the colourants, reference is made to EU Directive 95/45/EC. Additionally, a specification from the French Pharmacopeia has been provided for the hard gelatine capsule. Specifications for functionality-related characteristics as described in the Ph.Eur. mono-graphs have been applied where possible. 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, average mass, uniformity of mass, identification and assay of fenofibrate, related substances, dissolution, identification of colourants, and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Stability has been demonstrated by the high-performance liquid chromatography method for assay and related substances. Potential degradation impurities have adequately been discussed. Results of batch analyses have been provided of three batches (from 2001), five full scale batches (from 2013), and three full scale batches (from 2018). The dissolution of the last three batches has been tested with the new method. The results demonstrate compliance with the approved release specification. An appropriate risk evaluation for the presence of nitrosamine impurities has been provided.

Stability of drug product

Stability data on the product have been provided of three full scale batches up to 36 months storage at 25°C/60% RH, 12 months storage at 30°C/65% RH, and 6 months storage at 40°C/75% RH. In these batches, dissolution was tested with the old dissolution method. Stability results have also been provided of three recent batches, 36 months storage at 25°C/60% RH, where dissolution has been tested with the improved method. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed blister packaging. The tested parameters are appropriate. The only trend observed was a slight increase in average mass (slightly more pronounced at intermediate and accelerated storage conditions) possibly due to the uptake of water. All

results comply and are consistent between batch sizes. Photostability studies with the unpacked product showed that it was not sensitive for light. The proposed shelf-life and storage conditions are acceptable: 3 years, Do not store above 25°C. Store in the original blister packaging to protect from moisture.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
For gelatine, certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Fenogal 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 Fenogal is intended for generic 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 generic formulation of Lipidil-Ter, 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

Fenofibrate 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, besides the bioequivalence study which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Fenogal 160 mg hard capsules (Interdos Pharma BV, the Netherlands) is compared with the pharmacokinetic profile of the reference product Lipidil-Ter 160 mg, film-coated tablets (Fournier Pharma GmbH, Germany).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, two-treatment, two-sequence, two-period, randomised, crossover oral bioequivalence study was carried out under fed conditions in 18 healthy subjects (9 male/ 9 female), aged 20-46 years. Each subject received a single dose (160 mg) of one of the two fenofibrate formulations. The tablet or capsule was orally administered with 180 mL water after a breakfast, followed by 1 hour without drinking water and 5 hours (after administration) without food, followed by an standardised lunch. There were two dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 7, 9, 12, 24, 36, 48, 60, and 72 hours after administration of the products.

The design of the study is acceptable. Since it is stated in the package leaflet (PL) to take this product with food, the fed conditions of the study are appropriate.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The bioequivalence study and analysis were performed before the requirement to perform incurred sample reanalysis (ISR) was introduced (EMA Guideline on bioanalytical method validation came into force in February 2012). The MAH provided justification for the lack of ISR according to the points listed in the document Q&A: Positions on specific questions addressed to the pharmacokinetic working party (EMA/618604/2008 Rev.13, published 19 November 2015). The justification is accepted.

The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All 18 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of fenofibrate 160 mg under fed conditions.

Treatment N=18	AUC_{0-t} (µg.h/ml)	$AUC_{0-\infty}$ (µg.h/ml)	C_{max} (µg/ml)	t_{max} (h)
Test	160.4 ± 70.5	172.4 ± 85.8	9.12 ± 2.10	4.5 (3.0 – 6.0)
Reference	161.2 ± 74.3	173.3 ± 90.8	9.54 ± 1.97	4.2 (2.0 – 7.0)
***Ratio (90% CI)**	0.94 – 1.05	0.94 – 1.05	0.88 – 1.03	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
* ln-transformed values

Conclusion on the bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Fenogal 160 mg hard capsules is considered bioequivalent with Lipidil-Ter 160 mg, film-coated tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Fenogal.

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

Important identified risks	• Myopathy/Rhabdomyolysis • Abnormal liver function
Important potential risks	None
Missing information	• Use during pregnancy and lactation • Use in the paediatric population

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 Lipidil-Ter. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study 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 Dutch. The test consisted of a pilot test with four participants, followed by two rounds with ten 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

Fenogal 160 mg hard capsules has a proven chemical-pharmaceutical quality and is a generic form of Lipidil-Ter 160 mg, film-coated tablets. Lipidil-Ter is a well-known medicinal product with an established favourable efficacy and safety profile.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Fenogal with the reference product, and have therefore granted a marketing authorisation. Fenogal was authorised in the Netherlands on 28 July 2022.

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
IA - C.I.8.a	Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use; Introduction of a summary of pharmaco-vigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	No	27-9-2022	Approved	N/A