COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fexofenadine HCL Amarox 120 mg and 180 mg, film-coated tablets (fexofenadine hydrochloride)

NL/H/5214/001-002/DC

Date: 15 December 2021

This module reflects the scientific discussion for the approval of Fexofenadine HCL Amarox 120 mg and 180 mg, film-coated tablets. The procedure was finalised on 3 November 2021. 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 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 Fexofenadine HCL Amarox 120 mg and 180 mg, film-coated tablets, from Amarox Pharma B.V.

The products are indicated in adults and children 12 years and older for the relief of symptoms associated with chronic idiopathic urticaria.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Telfast 120 mg and 180 mg film-coated tablets, first authorised in the United Kingdom on 4 December 1996. In the Netherlands, the 120 mg reference product is Allegra Fexotabs 120 mg film-coated tablets (RVG 21624), which was authorised on 27 October 1997 by Sanofi-Aventis Netherlands B.V. by a national procedure. The current marketing authorisation holder (MAH) is Opella Healthcare France. The 180 mg reference product in the Netherlands is Telfast 180 mg film-coated tablets (RVG 21625), which was registered by Sanofi-Aventis Netherlands B.V. on 27 October 1997. The current MAH is Opella Healthcare France.

The concerned member state (CMS) involved in this procedure was Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Fexofenadine Amarox 120 mg and 180 mg are peach coloured, capsule shaped film-coated tablets, debossed with '120' or '180' on one side, respectively, and 'FX' on the other side.

The 120 mg and 180 mg film-coated tablets contain as active substance 120 mg and 180 mg of fexofenadine hydrochloride, respectively.

The film-coated tablets are packed in Alu-PVC/PVdC blisters and Alu/PVC/PE/ACLAR blisters.

The excipients are:
Tablet core - lactose monohydrate, LS-hydroxypropyl cellulose (E463), pregelatinised starch colloidal anhydrous silica (E551), microcrystalline cellulose (E460), croscarmellose sodium (E468) and magnesium stearate (E470b).

Film-coating - hypromellose (E464), povidone (E1201), titanium dioxide, iron oxide Red (E172), iron oxide Yellow (E172), colloidal anhydrous silica (E551) and macrogol.

The different strengths are fully dose proportional.

II.2 Drug Substance

The active substance is fexofenadine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white powder, slightly soluble in water and exists in different polymorphic forms. It is manufactured as polymorphic form I. Fexofenadine hydrochloride is a racemic mixture.

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 CEP with additional requirements for polymorphism and particle size. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scale batches. Data on four batches showed absence of microbial growth, therefore, the microbiological testing is excluded from the release specification.

Stability of drug substance
The active substance is stable for 60 months when stored in double polyethylene bags (outer black) placed in a polyethylene drum. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Products

Pharmaceutical development
The products are established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. The choices of packaging and manufacturing

process are adequately justified based on the dosage form. The optimal composition and manufacturing process parameters have been adequately investigated.

To support bioequivalence and the biowaiver of strengths, comparative dissolution studies at three pHs have been performed. The dissolution is faster for the test product batch in comparison to the reference product in two media. The potential clinical relevance of these differences in dissolution have been adequately discussed.

Manufacturing process

The manufacturing process is a wet granulation process which consists of mixing, granulation, lubrication, compression and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three batches on the lowest production scale. In addition, data for the process validation for full scaled batches have been provided.

Control of excipients

The excipients comply with Ph.Eur. and in-house requirements. These specifications are acceptable.

Quality control of drug products

The finished products specifications are adequate to control the relevant parameters for the dosage form. The products specifications includes tests for description, identification, average mass, uniformity of mass, disintegration time, dissolution, uniformity of dosage units, related substances, assay, microbial enumeration tests, loss on drying and residual solvents. Release and shelf life requirements are all identical, except for related substances and loss on drying. 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 the proposed production site have been provided on more than ten minimum scale batches per strength, demonstrating compliance with the release specification.

An acceptable risk evaluation on the presence of nitrosamine impurities in the drug products has been provided. No risk mitigation is deemed necessary.

Stability of drug product

Stability data on the products have been provided for three minimum scale batches per strength stored at 25°C/60% RH (24 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Alu/PVC/PVDC blister pack and Alu/PVC/PE/ACLAR blister pack. Photostability studies were performed in accordance with ICH recommendations and showed that the products are stable when exposed to light.

On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are “This medicinal product does not require any special storage conditions”.

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 Fexofenadine Amarox have 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 Fexofenadine Amarox are 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

These products are generic formulations of Telfast which are 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

Fexofenadine 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.

For this generic application, the MAH has performed one bioequivalence study with the highest product strength, and requested a biowaiver of strengths for the lower product strength. Both the study and biowaiver are discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Fexofenadine HCL Amarox 180 mg, film-coated tablets (Medreich Ltd, India) is compared with the pharmacokinetic profile of the reference product Telfast 180 mg film-coated tablets (Sanofi-Aventis, the United Kingdom).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of different strengths and batches of the reference and test product. Since the study was completed in 2017, before the Brexit transition period, the use of a UK reference product was considered acceptable by the RMS. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The requirements for a waiver for an additional strength are met since the proposed products are manufactured by the same manufacturing process and manufacturer, and are qualitatively the same and quantitatively dose-proportional. Furthermore, pharmacokinetics of fexofenadine can be considered dose-linear over the 120-180 mg dose range and comparative *in vitro* dissolution data confirm the dissolution similarity between the two strengths of the proposed product. Consequently, the biowaiver for the 120 mg film-coated tablets has been granted.

Bioequivalence studies

Design

An open label, balanced, single-dose, randomised, two treatment, two sequence (TRTR/RTRT), four period, crossover, fully replicated bioequivalence study was carried out under fasted conditions in 45 healthy male subjects, aged 20-43 years. Each subject received a single dose (180 mg) of one of the two fexofenadine hydrochloride formulations. The tablet was orally administered after an overnight fasting period of ten hours. There were four dosing periods, separated by a washout period of seven days.

Blood samples were collected within one hour before dosing and at 0.333, 0.667, 1.000, 1.333, 1.667, 2.000, 2.333, 2.667, 3.000, 3.333, 3.667, 4.000, 5.000, 6.000, 8.000, 10.000, 12.000, 16.000, 24.000, 36.000 and 48.000 hours after administration of the products in each period.

The design of the study is acceptable.

Fexofenadine hydrochloride may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of fexofenadine

hydrochloride. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with the *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
The numbers of dosed subjects were 44, 37, 35 and 35 for periods I, II, III and IV respectively. During period I – IV, five subjects were withdrawn and six subjects dropped out. The data from 36 subjects were included for statistical analysis and assessment of bioequivalence. Out of these subjects, 33 subjects completed all four periods, and three subjects completed at least one period for the test product and one period for the reference product according to the protocol.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of fexofenadine hydrochloride under fasted conditions.

Treatment **N(T1): 35** **N(T2): 34** **N(R1): 36** **N(R2): 35**	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	4.528 ± 1.308	4.596 ± 1.324	0.682 ± 0.246	2.33 (0.67 – 6.00)
Reference	4.586 ± 1.447	4.648 ± 1.461	0.679 ± 0.297	2.00 (0.67 – 6.00)
***Ratio** **(90% CI)**	1.00 (0.93-1.07)	1.00 (0.93-1.07)	1.04 (0.95-1.14)	-
$AUC_{0-\infty}$ 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 t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration				

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range (AUC_{0-t}: 0.80-1.25 and C_{max}: 0.7539 – 1.3264). Based on the submitted bioequivalence study, Fexofenadine Amarox 180 mg is considered bioequivalent with Telfast 180 mg.

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 Fexofenadine Amarox.

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 to identify, characterise and prevent the related risks.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Telfast. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of Fexofenadine Amarox 180 mg is similar to the pharmacokinetic profile of the respective reference product strength. A biowaiver has been granted for the lower 120 mg product strength. Risk management is adequately addressed. The generic medicinal products can be used instead of the reference products.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Fexofenadine Cipla 120 mg and 180 mg film-coated tablets (SE/H/1163/001-002/DC) for writing style and text content, and to Levetiracetam Hetero 750 mg film-coated tablets (PT/H/0515/001-004/DC) for layout and design. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fexofenadine HCL Amarox 120 mg and 180 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Telfast 120 mg and 180 mg film-coated tablets. Telfast are well-known medicinal products with established favourable efficacy and safety profiles. Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 Fexofenadine Amarox with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 November 2021.

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