

Public Assessment Report
Scientific discussion

**Fexofenadine Sandoz 120 mg and 180 mg
film-coated tablets**
(fexofenadine hydrochloride)

NL/H/3619/001-002/DC

Date: 9 May 2017

This module reflects the scientific discussion for the approval of Fexofenadine Sandoz 120 mg and 180 mg film-coated tablets. The procedure was finalised on 26 October 2016. 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 Sandoz 120 mg and 180 mg film-coated tablets from Sandoz B.V.

Fexofenadine Sandoz 120 mg is indicated in adults and children 12 years and older for the relief of symptoms associated with seasonal allergic rhinitis.

Fexofenadine Sandoz 180 mg film-coated tablets 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 product Telfast 120 mg and 180 mg film-coated tablets, which has been registered by Sanofi-aventis in the United Kingdom since 4 December 1996. In the Netherlands Telfast 180 mg coated tablets (NL License RVG 21625) has been registered since 27 October 1997.

The concerned member states (CMS) involved in this procedure were Denmark and Finland.

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

II. QUALITY ASPECTS

II.1 Introduction

Fexofenadine Sandoz 120 mg is a peach coloured, oblong, biconvex film-coated tablet, plain on both sides. It contains 120 mg of fexofenadine hydrochloride, which is equivalent to 112 mg of fexofenadine.

Fexofenadine Sandoz 180 mg is a yellow coloured, oblong, biconvex film-coated tablet, plain on both side and a central breakline on the other side. It contains 180 mg of fexofenadine hydrochloride, which is equivalent to 168 mg of fexofenadine. The score line is not intended for breaking the tablet.

The film-coated tablets are packed in PVC/PVDC/Aluminium blisters.

The excipients are:

Tablet core - microcrystalline cellulose, maize starch, croscarmellose sodium, povidone, magnesium stearate

Coating - hypromellose, titanium dioxide, macrogol 400, macrogol 4000, iron oxide yellow, iron oxide red (only in the 120 mg strength).

The two strengths are 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 slightly soluble in water. The active substance exists in different polymorphic forms. The active substance manufacturers produce polymorphic form I. Fexofenadine has one asymmetric carbon atom. It is used as racemic mixture.

The CEP procedure is used for both manufacturers of 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

CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification of the MAH is in line with the Ph.Eur and the CEPs and contains additional requirements for particle size and polymorphic identity. The drug substance specification is acceptable. Batch analysis data demonstrating compliance with the drug substance specification were provided for three batches of each supplier.

Stability of drug substance

The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEPs and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The choice of excipients is justified and their functions explained. A bioequivalence study was carried out with the 180 mg strength. The provided comparative dissolution profiles of the biobatches in 0.01 N HCl, acetate buffer pH 4.5, and phosphate buffer pH 6.8 support bioequivalence.

A biowaiver has been granted for the 120 mg strength. Comparative dissolution profiles of the 180 mg strength and the 120 mg strength obtained at pH 1.2, pH 2, pH 4.5, and pH 6.8 support the biowaiver for the 120 mg strength.

Manufacturing process

The manufacturing process includes wet granulation, compression, and film-coating. It is considered a standard process. The manufacturing process was adequately described.

The manufacturing process was successfully validated with three batches of each batch size proposed for the two strengths. All predefined acceptance criteria were met.

Control of excipients

With the exception of the coating materials, excipients are tested according to the Ph.Eur. Acceptable specifications are provided for the coating materials.

Quality control of drug product

The product specification includes tests for description, identification of the drug substance and colourants, average weight, disintegration time, water content, uniformity of dosage units, related substances, dissolution, assay and microbial contamination. The release and shelf life specification differ with regard to water content and related substances. Different release and shelf life criteria for these parameters are justified based on the provided stability data. Analytical methods were adequately described and validated.

Batch analytical data from four batches of the smallest proposed commercial batch size of each strength were provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three batches of the smallest proposed commercial batch size of each strength stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months) and of two full scale batches of each strength stored at 25°C/60% RH (6 to 24 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVDC-aluminium blisters.

No significant changes were seen at any of the storage conditions. Photostability was tested under ICH conditions. The drug product was shown to be photostable.

On the basis of the provided stability data, the claimed shelf life of 24 months without specific storage conditions is justified.

Specific measures for 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 Sandoz 120 mg and 180 mg 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 Fexofenadine Sandoz 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 Telfast, 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

Fexofenadine 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 submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Fexofenadine Sandoz 180 mg (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Telfast 180 mg film-coated tablets (Sanofi-aventis, UK).

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.

Biowaiver

A biowaiver for a bioequivalence study for the additional 120 mg strength was applied for. The pharmacokinetics for fexofenadine is linear. Both strengths are manufactured by the same process and the composition of the different strengths is qualitatively the same. The proportional amount of excipients is contained in strengths, which is considered acceptable. Thus the composition of the strengths is dose proportional.

Comparative dissolution profiles of the biobatch and a batch of the 120 mg strength in 0.01 N HCl, acetate buffer pH 4.5, and phosphate buffer pH 6.8 support a biowaiver, however according the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), dissolution testing to justify a biowaiver should normally be performed at pH 1.2, 4.5 and 6.8 unless

otherwise justified. As the biobatch had expired, comparative dissolution data at these pH was provided on newer batches of both strengths. The data of the newer batches support a biowaiver.

Bioequivalence study

Design

A single-dose, randomised, two-treatment, four-period, two-sequence, single dose, crossover replicate bioequivalence study was carried out under fasted conditions in 48 health male subjects, aged 28±6 years. Each subject received a single dose (180 mg) of one of the 2 fexofenadine formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. Fasting was continued for 4 hours after dosing. There were 4 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 12, 18, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Taking into account the expected elimination half-life of fexofenadine in plasma (about 11-15 hours) the wash-out period of 8 days is considered to be adequate to avoid any carry-over. No pre-dose level was observed. The sample collection period of 72 hours should adequately cover the elimination of the drug.

The sampling scheme is considered appropriate, as the sampling is frequent around the expected t_{max} (1-3 hours). It is acceptable that the study is conducted under fasting conditions since literature indicates no problems with concomitant food intake and no recommendations are given in the SmPC for administration of the drug in relation to food.

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

A total of 45 subjects completed the clinical phase, and samples from 47 subjects were analysed and considered in the statistical analysis. One subject did not arrive from period II on the clinical site. Only the plasma samples from this subject were not analysed because this subject did not have data for a test and a reference product.

One subject did not arrive for period III due to personal reasons and another subject opted out from the study on his own will in period IV.

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

Treatment	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test (N=92)	4489.1±1922.8	4612.6±1943.6	710.7±351.9	2.0 (0.67-6.0)	--
Reference (N=93)	4649.38±2014.4	4770.7±2028.5	759.6±364.4	1.69 (0.67-6.0)	--
*Ratio (90% CI)	0.96 (0.89-1.04)	--	0.94 (0.87-1.03)	--	--
AUC_{0-∞} 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 t_{1/2} half-life CV coefficient of variation					

**In-transformed values*

Conclusion on bioequivalence study

T_{max} was not observed in the first sampling point. The elimination half-life for test and reference products was 5.6 ± 2.7 hours and 5.3 ± 2.6 hours, respectively. The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Fexofenadine Sandoz 180 mg is considered bioequivalent with Telfast 180 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 Fexofenadine Sandoz.

- Summary table of safety concerns as approved in RMP

Important identified risks	Hypersensitivity reactions Cardiovascular events (tachycardia and palpitations)
Important potential risks	-
Missing information	Pregnant and lactating women Children aged less than 12 years old Older people, renally or hepatically impaired patients

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 Telfast. 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) for Fexofenadine Sandoz 120 mg 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 results show that the package leaflet 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. The majority of the respondents described the leaflet as short, concise, well set-out, clear and easy to find the information. A bridging report was submitted for the 180 mg strength, which has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fexofenadine Sandoz 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 is a well-known medicinal product with an established favourable efficacy and safety profile.

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 Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 October 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location Change in the product name in NL.	NL/H/3619/001-002/IB/001/G	IB/G	21-2-2017	23-3-2017	Approval	N