COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fesoterodine Accord 8 mg prolonged release tablets
(fesoterodine fumarate)

NL/H/5107/001/DC

Date: 21 February 2022

This module reflects the scientific discussion for the approval of Fesoterodine Accord 8 mg prolonged release tablets. The procedure was finalised on 7 May 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 Fesoterodine Accord 8 mg prolonged release tablets, from Accord Healthcare B.V.

The product is indicated in adults for treatment of the symptoms (increased urinary frequency and/or urgency and/or urgency incontinence) that may occur with overactive bladder syndrome. 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 Toviaz 8 mg prolonged release tablets which has been registered in the EEA by Pfizer Europe MA EEIG since 20 April 2007 by a centralised procedure (EU/1/07/386).

The concerned member states (CMS) involved in this procedure were Cyprus, Czech Republic, Germany, Denmark, Finland, Hungary, Ireland, Norway, Sweden and the United Kingdom (Northern Ireland).

The marketing authorisation has been granted pursuant to Article 10(1).

II. QUALITY ASPECTS

II.1 Introduction

Fesoterodine Accord is a blue coloured, oval shaped, film coated tablet, debossed with “F ll” on one side and plain on the other side and contains as active substance 8 mg of fesoterodine fumarate corresponding to 6.2 mg of fesoterodine.

The prolonged-release tablets are packed in aluminium-aluminium blisters in cartons. In addition, the tablets are also packed in HDPE bottles with a child-resistant closure.

The excipients are:
Tablet core - cellulose microcrystalline (E460), hypromellose (E464), lactose anhydrous, silicon dioxide (E551) and magnesium stearate (E572).
Film-coating - titanium dioxide (E171), polyvinyl alcohol-part. hydrolyzed (E1203), talc (E553b), soya lecithin (E322), xanthan gum (E415) and indigo carmine aluminium lake (E132).

II.2 Drug Substance

The active substance is fesoterodine fumarate, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a white to off-white powder and is freely soluble in methanol and practically insoluble in heptane. The solubility in aqueous solutions is ~0.032 mg/ml across the gastrointestinal pH range of 1.2 to 7.4. The drug substance is chiral and exhibits polymorphism. The R-isomer is manufactured.

The Active Substance Master File (ASMF) procedure is used for the active substance. 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.

Manufacturing process

The manufacturing process is divided into two parts covering 6-stage synthesis. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The drug substance specification has been established in-house by the MAH. The drug substance specification includes tests and limits for description, solubility, identification, loss on drying, sulphated ash, content, enantiomeric purity, related substances, assay, residual solvents, specific optical rotation and melting range. Additional requirements have been adopted for particle size distribution and microbial purity. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three commercial scale batches stored at 5°C (48 months) and 25°C/60% RH (six months) in accordance with applicable European guidelines. In one of the batches an increase in one impurity at long term storage conditions after 48 months was observed.

Based on the data submitted, a retest period could be granted of four years when stored in a well closed container at 2-8 °C, and protected from light and moisture.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and the development of the product has been described, the choice of excipients is justified and their functions explained. The aim of

the product development was to formulate robust, essentially similar, stable and bioequivalent generic formulation of Toviaz (fesoterodine fumarate) 8 mg prolonged-release tablets. Compared to the reference product different excipients are used, main development studies were on the choice of the excipients and their ratio, to obtain a drug product that has a prolonged release profile comparable with the reference product.

The MAH conducted a bioequivalence study to compare the *in vivo* bioavailability of the test and reference product. To support the bioequivalence study, adequate *in vitro* dissolution studies were performed, which showed comparable dissolution at three pH's.

Manufacturing process

The manufacturing process consists of the following main steps: granulation, compression, coating, and packaging. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients are widely used in pharmaceutical formulations. The excipients comply with the current edition of the Ph.Eur., except for silicon dioxide which complies with the current edition of the United States National Formulary, and except for the film-coating, which complies with in-house specifications. 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 weight of tablets, identification, water content, dissolution, uniformity of dosage units, related substances, assay, and microbial examination. The release and shelf-life specifications are identical except for related substances. 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 three full scale 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 production scaled batches stored at 25°C/60%RH (12 months) and 40°C/75%RH (12 months) in accordance with the applicable ICH stability guideline. The batches were stored in alu-alu blisters or in HDPE bottles.

Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. Upward trends are seen for all impurities under all storage conditions, however, staying within specification up to 12 months storage under long term conditions, and it is expected that all batches will stay within specification up to 24 months.

On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage condition 'This medicinal product does not require any special storage condition' has been justified and is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or 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 member states consider that Fesoterodine Accord 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 Fesoterodine Accord 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 Toviaz 8 mg prolonged release tablets 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

Fesoterodine fumarate 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 three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Fesoterodine Accord 8 mg prolonged release tablets (Accord Healthcare B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Toviaz 8 mg prolonged release tablets (Pfizer Europe MA EEIG, Belgium).

The three bioequivalence studies performed were a single dose fasting study, a single dose study under fed conditions and a multiple dose fasting study. Since Fesoterodine Accord is a prolonged-release tablet, submission of these types of bioequivalence studies was considered adequate. According to the SmPC the tablets can be taken with or without food.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the test and reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence is based on the active metabolite 5-HMT, in accordance with the protocol, which is acceptable as fesoterodine fumarate is considered an inactive prodrug having very low plasma levels after administration with a very high variability. Moreover, fesoterodine could not be reliable measured in plasma.

Bioequivalence studies

Study I: single dose, fasting study

Design

A single-dose, randomised, two-period, two-treatment, crossover bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 19-42 years. Each subject received a single dose (8 mg) of one of the two fesoterodine fumarate formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of five days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 14, 16, 20, 24, 36 and 48 hours after administration of the products. The design of the study is acceptable.

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
One subject was withdrawn from the study on medical grounds in Period I. Another subject withdrew from the study on his own accord in Period II. 58 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 5-HMT under fasted conditions.

Treatment N=58	AUC_{0-t} (pg.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (pg/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	62840 ± 21594	63607 ± 21801	4950 ± 1729	5.27 (2.5 – 7.0))	6.0 ± 1.8
Reference	67252 ± 19396	68125 ± 19585	5194 ± 1869	5.5 (2.5 – 10.0)	6.3 ± 2.0
***Ratio (90% CI)**	0.92 (0.89-0.96)	0.94 (0.90-0.98)	0.87 (0.81-0.94)	0.92 (0.89-0.96)	0.95 (0.90-1.01)
CV (%)	12.2	14.9	22.9	12.3	18.7

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Study II: single dose, fed study
Design
A single-dose, randomised, two-period, two-treatment, crossover bioequivalence study was carried out under fed conditions in 60 healthy male subjects, aged 21-41 years. Each subject received a single dose (8 mg) of one of the two fesoterodine fumarate formulations. The tablet was orally administered with 240 ml water within 30 minutes after the start of a high fat, high caloric breakfast (540 kcal fat, 938 kcal total). There were two dosing periods, separated by a washout period of six days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 14, 16, 20, 24, 36 and 48 hours after administration of the products. The design of the study is acceptable.

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
One subject withdrew from the study on his own accord in Period II. 59 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 5-HMT under fed conditions.

Treatment N=59	AUC_{0-t} (pg.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (pg/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	81392 ± 26815	82106 ± 27644	6440 ± 1732	6.0 (2.0 – 9.0)	5.7 ± 1.0
Reference	80955 ± 22520	81526 ± 22709	6250 ± 1518	6.0 (3.0 – 9.0)	5.6 ± 0.9
***Ratio (90% CI)**	0.99 (0.96 – 1.03)	0.99 (0.96 – 1.03)	1.03 (0.98 – 1.07)	-	-
CV (%)	12.6	12.6	13.6	-	-

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Study III: multiple dose, fasting study
Design
A multiple dose, randomised, two-period, two-treatment, crossover bioequivalence study was carried out under fasting conditions in 60 healthy male subjects, aged 18-43 years. Each subject received a single dose (8 mg) of one of the two fesoterodine fumarate formulations. The tablet was orally administered once daily with 240 ml water after an overnight fast, for five consecutive days. There were two dosing periods, separated by a washout period of six days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 14, 16, 20, 24, 36 and 48 hours after administration of the products. The design of the study is acceptable.

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
Five subjects were withdrawn from the study in period I on medical grounds. Three subjects withdrew from the study on his own accord in period II. Two subjects were withdrawn in period II on medical grounds and one subject was withdrawn from the study due to misbehaviour in period II. 69 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 5-HMT under fasted conditions.

Treatment N=69	$AUC_{0\text{-}tau}$ (pg.h/ml)	C_{max} (pg.h/ml)	C_{tau} (pg/ml)	t_{max} (h)
Test	61504 ± 21891	5504 ± 2029	852 ± 472	5.0 (3.0 – 10.0)
Reference	64515 ± 24934	5820 ± 1976	850 ± 503	5.0 (3.33 – 7.0)
***Ratio (90% CI)**	0.96 (0.92 – 0.99)	0.93 (0.89 – 0.98)	1.00 (0.90 – 1.11)	-
CV (%)	12.9	17.5	37.3	-

$AUC_{0\text{-}tau}$	area under the plasma concentration-time curve during steady-state dosing interval
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for the active metabolite 5-HMT for $AUC_{0\text{-}t}$, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies, Fesoterodine Accord is considered bioequivalent with Toviaz 8 mg prolonged release 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 Fesoterodine Accord.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	• Urinary retention • Angioedema
Important potential risks	• QT prolongation • Liver enzyme elevations • Cognitive function impairment
Missing information	• Elderly male patients • Paediatric patients • Pregnant or nursing women

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 Toviaz. 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

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 Mycophenolic acid 180 mg and 360 mg gastro-resistant tablets (ES/H/0183/001-002/DC). 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

Fesoterodine Accord 8 mg prolonged release tablets have a proven chemical-pharmaceutical quality and are generic forms of Toviaz 8 mg prolonged release tablets. Toviaz 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 Fesoterodine Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 May 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