COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fesoterodine Accord 4 mg prolonged release tablets
(fesoterodine fumarate)

NL/H/5107/002/DC

Date: 5 January 2023

This module reflects the scientific discussion for the approval of Fesoterodine Accord 4 mg prolonged release tablets. The procedure was finalised at 21 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

5-HMT	5-hydroxymethyl tolterodine
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 4 mg prolonged release tablets, from Accord Healthcare BV.

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 4 mg, prolonged release tablets (EU/1/07/386) which has been registered in the EEA by Pfizer Europe MA EEIG since 20th April 2007 via the centralised procedure (EMEA/H/C/000723).

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

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

II. QUALITY ASPECTS

II.1 Introduction

Fesoterodine Accord is a yellow coloured, oval shaped, film-coated tablet, debossed with "F l" on one side and plain on the other side. Each prolonged-release tablet contains 4 mg fesoterodine fumarate corresponding to 3.1 mg of fesoterodine.

The tablets are packed in aluminium-aluminium blisters in cartons or in HDPE bottles with a polypropylene child-resistant closure.

The excipients are:
Tablet core – microcrystalline cellulose (E460), hypromellose (E464), anhydrous lactose, colloidal anhydrous silica (E551) and magnesium stearate (E572).
Film-coating – titanium dioxide (E171), partially hydrolysed polyvinyl alcohol (E1203), talc (E553b), soy lecithin (E322), xanthan gum (E415) and yellow iron oxide (E172).

II.2 Drug Substance

The active substance is fesoterodine fumarate, an established active substance not described in any pharmacopoeia. The drug substance is a white to off-white powder and is

freely soluble in methanol and practically insoluble in heptane. 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 of fesoterodine fumarate is divided into two parts covering six stages of synthesis – Part I consists of a two-stage synthesis of an intermediate and Part II is the four-stage synthesis of the final active substance. The final step in the synthesis is the purification of fesoterodine fumarate. The starting material is acceptable. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. The drug substance specification includes tests and limits for description, solubility, identification, loss on drying, sulphated ash, fumaric acid 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. Batch analytical data demonstrating compliance with the specifications have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three commercial scale batches in accordance with applicable European guidelines, demonstrating the stability of the active substance at 5°C for 48 months and at 25°C/60% RH for 6 months. Based on the data submitted, a retest period could be granted of 4 years when stored in a well-closed container at 2-8 °C protected from light and moisture.

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. Compared to the reference product, different excipients are used; the choice is justified and the excipients' functions have been explained. Main development studies were performed 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. Compared to the already approved 8 mg strength Fesoterodine Accord product, the amount of hypromellose was reduced and the amount of microcrystalline cellulose was increased, keeping the total weight of the tablets constant.

From the final formulation, three batches of commercial scale were produced of which one was used in three bioequivalence studies. The batch used in the studies was acceptable and comparable dissolution was observed between this batch and the reference product at three pH's.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines and consists of granulation (blending followed by lubrication), compression, coating, and packaging. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

Control of excipients

All excipients used in manufacturing the drug product are widely used in pharmaceutical formulations and are compliant with the European Pharmacopoeia except for two ingredients. Colloidal anhydrous silica (silicon dioxide) complies with the current edition of United States National Formulary and yellow iron oxide (Opadry Amb Yellow) complies with an in-house specification. 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 (HPLC and TLC), water content, dissolution, uniformity of dosage units, related substances, assay, and microbial examination. The release and shelf-life specifications are identical except for water content and one impurity. Impurity limits are in line with the ICH Q3A guideline and the drug substance manufacturer specification. All tests and limits are acceptable.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided on three production scale batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Upward trends are seen for most impurities under all storage conditions, however, these stay within specification up to 18 months under long term conditions. 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. The proposed shelf-life of 24 months is acceptable. No special storage conditions are required for the product.

Stability data have been provided demonstrating that the product remains stable for 90 days following the first opening of the HDPE bottles when stored at room temperature. Although an in-use study was performed, an in-use shelf-life was not included in the SmPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

TSE/BSE statements have been provided for the drug substance and all excipients, including anhydrous lactose, which is the only excipient from animal origin. 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 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 performed 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 4 mg prolonged release tablets (Accord Healthcare BV, The Netherlands) is compared with the pharmacokinetic profile of the reference product Toviaz 4 mg, prolonged release tablets (Pfizer Europe MA EEIG, Belgium). The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing. Fesoterodine fumarate may be taken with or without food, according to the SmPC. Two fasted studies and one fed study were performed, this is considered sufficient for this application.

Bioequivalence studies

Study 1 – single dose, fasting, 4 mg

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 21-44 years. Each subject received a single dose (4 mg) of one of the two fesoterodine fumarate formulations. The tablet was orally administered with 240 ml water after a fasting period of at least 10 hours pre-dose and followed by 4 hours of fasting post-dose. There were two dosing periods, separated by a washout period of at least 5 days.

Blood samples were collected pre-dose and at 0.50, 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

Fesoterodine fumarate is considered a prodrug which can be found in plasma only at very low levels, plus it is highly variable in its pharmacokinetics. As stated in the SmPC, there was no analytical method sensitive enough to measure fesoterodine in plasma at the time of this study. Therefore, the active metabolite 5-hydroxymethyl tolterodine (5-HMT) was analysed and considered the pivotal substance for proving bioequivalence. 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 due to a mild adverse event in period I. This left 59 subjects 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 = 59	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	26.29 ± 9.69	27.07 ± 9.58	2.17 ± 0.89	5.0 (2.0 - 6.0)
Reference	26.87 ± 8.76	27.61 ± 8.53	2.30 ± 0.72	5.0 (2.0 - 9.0)
***Ratio (90% CI)**	0.96 (0.92 – 1.01)	0.97 (0.92 – 1.01)	0.92 (0.87 – 0.97)	--

$AUC_{0-\infty}$ 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

Study 2 – single dose, fed, 4 mg

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 60 healthy male subjects, aged 18-43 years. Each subject received a single dose (4 mg) of one of the two fesoterodine fumarate formulations. The tablet was orally administered with 240 ml water after a fasting period of at least 10 hours and 30 minutes after consumption of a high-fat, high-calorie vegetarian breakfast. There were two dosing periods, separated by a washout period of at least 5 days.

Blood samples were collected pre-dose and at 0.50, 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. As in study 1, the analysis of 5-HMT was used to prove bioequivalence instead of the analysis of fesoterodine fumarate because it provided better sensitivity. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Six subjects were withdrawn from the study: two were withdrawn on medical grounds, one subject was withdrawn because of non-compliance to the protocol and three subjects were withdrawn on their own accord. This left 54 subjects 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 = 54	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	25.84 ± 9.78	26.74 ± 9.77	2.51 ± 0.89	5.5 (1.5 - 6.5)
Reference	25.87 ± 9.81	26.73 ± 9.64	2.40 ± 0.80	5.5 (2.5 - 8.0)
***Ratio (90% CI)**	1.00 (0.96 – 1.03)	1.00 (0.96 – 1.03)	1.04 (1.00 – 1.08)	--

$AUC_{0-\infty}$	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

Study 3 – multiple dose, fasting, 4 mg

Design

A multiple-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 20-43 years. After an overnight fast of at least 10 hours, multiple oral doses (five times 4 mg) of one of the two fesoterodine fumarate formulations were administered to the subjects on Day 1 to Day 5 (at an interval of 24 hours with reference to the previous dose). The tablet was orally administered with 240 ml water. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose at day 1, 3, 4 and 5. On day 5 post-dose samples were withdrawn at 0.50, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 20 and 24 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. As in studies 1 and 2, the analysis of 5-HMT was used to prove bioequivalence instead of the analysis of fesoterodine fumarate because it provided better sensitivity. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Three subjects were withdrawn from the study on their own accord during period II (all three for the reference product). This left a total of 45 subjects eligible for pharmacokinetic analysis.

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

Treatment N = 45	AUC_{0-t} (ng.h/ml)	$C_{max,ss}$ (ng/ml)	$C_{\tau,ss}$ (ng/ml)	$t_{max,ss}$ (h)
Test	22.28 ± 6.76	2.12 ± 0.65	0.30 ± 0.17	5.00 (1.35 - 6.00)
Reference	23.45 ± 7.52	2.20 ± 0.66	0.29 ± 0.16	5.00 (2.67 - 8.00)
***Ratio (90% CI)**	0.95 (0.91 – 0.99)	0.96 (0.89 – 1.02)	1.04 (0.95 – 1.13)	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
$C_{max,ss}$	maximum plasma concentration at steady state
$C_{\tau,ss}$	concentration at the end of the dosing interval (24h) at steady state
$t_{max,ss}$	time for maximum concentration at steady state
*	ln-transformed values

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, $C_{max,ss}$ and $C_{\tau,ss}$ are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the performed bioequivalence studies Fesoterodine Accord 4 mg prolonged release tablets is considered bioequivalent with reference product Toviaz 4 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 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 Toviaz 4 mg, prolonged release tablets. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies 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 Toviaz 4 mg, prolonged release tablets (EU/1/07/386) for the content and Mycophenolic acid 180 mg and 360 mg gastro-resistant tablets (ES/H/0183/001-002/DC) for the layout. 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 4 mg prolonged release tablets has a proven chemical-pharmaceutical quality and is a generic form of Toviaz 4 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 21 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
N/A	N/A	N/A	N/A	N/A	N/A