IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Fesoterodine Doc 4 mg Prolonged-release tablet
Fesoterodine fumarate
PA2244/002/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Fesoterodine Doc 4 mg & 8 mg Prolonged-release tablets with DOC Generici S.r.l. as MAH,on 12th August 2022 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.

This decentralised application concerns a generic version of fesoterodine. The applicant has submitted these decentralised Marketing Authorisation Applications for Fesoterodine 4 mg & 8 mg Prolonged Release tablets in accordance with Article 10(1) of Directive 2001/83/EC. Ireland is the Reference Member State. The active substance, fesoterodine fumarate, is not considered a new active substance.

The EU reference medicinal product is TOVIAZ 4 mg prolonged release tablets, of MAH Pfizer Europe MA EEIG, Belgium. The product has been registered since 20th April 2007. The applicant has demonstrated essential similarity to the reference product.

With IE as the Reference Member State in this Decentralized Procedure, DOC Generici S.r.l. is applying for the Marketing Authorisations for Fesoterodine Doc 4 mg & 8 mg Prolonged-release Tablets in IT.

Product subject to prescription which may not be renewed. The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at The Health Products Regulatory Authority (hpra.ie)

Name of the product	Fesoterodine Doc 4 mg Prolonged-release tablet
Name(s) of the active substance(s) (INN)	Fesoterodine fumarate
Pharmacotherapeutic classification (ATC Code)	G04BD11
Pharmaceutical form and strength(s)	4 mg Prolonged-release tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA2244/002/001
Marketing Authorisation Holder	DOC Generici S.r.l. Via Turati 40 Milano 20121 Italy
MRP/DCP No.	IE/H/1207/001/DC
Reference Member State	IE
Concerned Member State(s)	IT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Fesoterodine Doc 4 mg Prolonged-release tablets.

II.2 Drug substance

The active substance is fesoterodine fumarate, an established active substance not described in the European Pharmacopoeia.

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.

The active substance is fesoterodine fumarate is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The drug substance specification has been established in-house. The drug substance specification is considered adequate to control the quality in view of the route of synthesis and the various European guidelines.

Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition
Fesoterodine 4 mg Prolonged-release tablet are blue elliptical, biconvex film-coated tablets approximately 6 mm diameter and debossed with "F4" on one side.

Fesoterodine 8 mg Prolonged-release tablet are Dark Blue elliptical, biconvex film-coated tablets approximately 6 mm diameter and debossed with "F8" on one side.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
Compatibility between the active substance and the excipients is supported by stability studies. The packaging materials have shown to be suitable by acceptable stability studies.
The aim of the product development was to formulate essentially similar and bioequivalent generic formulation of Toviaz (fesoterodine fumarate) 4 mg and 8 mg prolonged-release tablets.
Bioequivalence studies were performed for demonstration of bioequivalence between the generic product and the EU reference product Toviaz. Comparative dissolution profiles between the generic Biobatch of each strength and the reference product used in BE studies are provided and demonstrate comparability for each dissolution medium proposed by the BE-Guideline. Based on the dissolution profiles of the Bio-batches an acceptable dissolution specification has been derived.

P.3 Manufacture of the Product
The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

Batch formulae have been provided for the manufacture of the product. In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation data on the product have been presented for three full-scale batches in accordance with the relevant European guidelines. The manufacturing process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)
The excipients used in the manufacture of Fesoterodine PR Tablet cores are standard excipients in manufacturing of prolonged release film-coated tablets and controlled and tested in compliance with the respective Ph. Eur. monograph. Detailed information on the qualitative and quantitative composition and specifications of the film coating agent, Opadry II White 85F18422, including reference to the quality standard of each component is provided. The colourant, Indigo Carmine lake, is specified in compliance with current foodstuff regulations and can therefore be accepted. An acceptable in-house specification is provided.

P.5 Control of Finished Product
The finished product specification is adequate to control the relevant parameters for the dosage form and they are and in line with ICH Q6A and Ph Eur requirements for tablets.

The tests and control limits in the specifications have been adequately justified and are considered appropriate for adequate quality control of the product. The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with relevant Ph. Eur requirements and EU legislation on plastic materials and articles intended to come into contact with food.

P.7 Stability of the Finished Product
Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by EDQM have been provided and compliance with the Note For Guidance on Minimising the Risk of f Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products has been satisfactorily demonstrated

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Based on the submitted dossier, the member states consider that satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Fesoterodine 4 mg & 8 mg Prolonged-release tablets

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Toviaz® 4 mg prolonged release tablets, (MAH Pfizer Europe), on the European market since 2007. No new preclinical data have been submitted.

The pharmacodynamic, pharmacokinetic and toxicological properties of fesoterodine are well known. As fesoterodine is a widely used, well-known active substances, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The overview provided based on literature review is thus appropriate.

III.5 Ecotoxicity/environmental risk assessment

Since fesoterodine 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. No new ERA studies have been performed by the applicant but a summary of data from the publically available literature is presented.
Log Pow is reported as 0 at pH 7. The calculated PECsw is 0.04 µg/ml (utilising the default Fpen) and is in excess of the action limit of 0.01µg/L and therefore a phase II risk assessment was triggered. Fesoterodine is not a PBT substance.

Considering the data, fesoterodine is unlikely to pose a risk to the environment. Fesoterodine should be used according to the precautions stated in the SmPC in order to minimise any potential risks to the environment.

III.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of fesoterodine are well known. As fesoterodine is a widely used, well-known active substances, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. Non-clinical findings are adequately represented in the appropriate sections of the SmPC. Fesoterodine is unlikely to pose a risk to the environment. Fesoterodine should be used according to the precautions stated in the SmPC in order to minimise any potential risks to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

Fesoterodine is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Toviaz 4 mg and 8 mg prolonged release tablets by Pfizer Ltd.

For this generic application, the applicant has submitted four bioequivalence studies in which the pharmacokinetic profile of the test product Fesoterodine Normon is compared with the pharmacokinetic profile of the reference product Toviaz (N-FES-18-239, N-FES-18-242, N-FES-18-243, N-FES-18-245).

Study N-FES-18-239:
Randomised, crossover bioequivalence clinical trial of fesoterodine 4 mg prolonged-release tablets, after a single oral dose administration to healthy volunteers under fasting conditions.

Bioequivalence criteria were met with respective 90% confidence intervals of [84.68% - 111.93%] for Cmax (ratio: 97.35), [86.63% - 103.06%] for AUC0-t (ratio: 94.48), and [87.14% - 104.31%] for AUCinf (ratio: 95.34), all within the acceptance range limits of 80.00% - 125.00%.

Study N-FES-18-242:
Randomised, crossover bioequivalence clinical trial of fesoterodine 8 mg prolonged-release tablets, after a single oral dose administration to healthy volunteers under fasting conditions.

Bioequivalence criteria were met with respective 90% confidence intervals of [90.87% - 113.22%] for C_{max} (ratio: 101.43), [95.16% - 108.88%] for AUC0-t ration: (101.79), and [94.90% - 109.01%] for AUCinf (ratio: 101.71).

Study N-FES-18-243:
Randomised, crossover bioequivalence clinical trial of fesoterodine 8 mg prolonged-release tablets, after a single oral dose administration to healthy volunteers under fed conditions.

Based on a model independent approach this mean ratio of test over Toviaz for was 99.98 for AUC0-t (90% confidence interval 95.72 – 104.44). The mean ratio of test over Toviaz for C_{max} was 98.86 (90% confidence interval 91.33 – 107.01). The mean ratio of test over Toviaz for AUC0-inf was 99.88 (90% confidence interval 95.73 – 104.22).

Study N-FES-18-245:
Randomized, crossover bioequivalence clinical trial of fesoterodine 8 mg prolonged-release tablets, after multiple oral dose administration to healthy volunteers under fasting conditions.

Based on a model independent approach this mean ratio of test over Toviaz for was 94.26 for AUC(0-τ)ss (90% confidence interval 88.89 – 99.96). The mean ratio of test over Toviaz for Cmax,ss was 94.30 (90% confidence interval 88.74 – 100.22). The mean ratio of test over Toviaz for Cτ,ss was 94.16 (90% confidence interval 86.33 – 102.68).

Fesoterodine Normon was demonstrated to be bioequivalent to Toviaz when administered in 4 bioequivalence studies, 3 comparing the higher strength (8 mg) in single dose fed and fasted studies and a multiple dose fasted study, and one comparing the lower strength (4 mg) in a single dose fasted study.

Fesoterodine Normon 4mg and 8mg prolonged-release tablets, Laboratorios Norman S.A., was compared to the reference product Toviaz 4mg and 8mg prolonged-release tablets, R-Pharm Germany GmbH. Based on the pharmacokinetic parameters of active substance, the reference tablet Toviaz 4mg and 8mg prolonged-release tablets marketed by Pfizer Ltd. and test tablet Fesoterodine Normon 4mg and 8mg prolonged-release tablets are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

A biowaiver for the fed and multiple dose study for the lower strength was accepted.

Risk Management Plan
The Applicant 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 4 mg & 8 mg Prolonged Release tablets. Routine risk minimisation and pharmacovigilance activities are considered sufficient. The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews

PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Toviaz 4mg and 8mg prolonged-release tablets marketed by Pfizer Ltd.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

No additional studies investigating the pharmacokinetic effects of Fesoterodine 4mg and 8mg prolonged-release tablets were conducted which is acceptable for this generic application.

Absorption
After oral administration, due to rapid and extensive hydrolysis by non-specific plasma esterases, fesoterodine was not detected in plasma.

Bioavailability of the active metabolite is 52%. After single or multiple-dose oral administration of fesoterodine in doses from 4 mg to 28 mg, plasma concentrations of the active metabolite are proportional to the dose. Maximum plasma levels are reached after approximately 5 hours.

Therapeutic plasma levels are achieved after the first administration of fesoterodine. No accumulation occurs after multiple-dose administration.

Distribution
Plasma protein binding of the active metabolite is low with approximately 50% bound to albumin and alpha-1-acid glycoprotein. The mean steady-state volume of distribution following intravenous infusion of the active metabolite is 169 l.

Biotransformation
After oral administration, fesoterodine is rapidly and extensively hydrolysed to its active metabolite. The active metabolite is further metabolised in the liver to its carboxy, carboxy-N-desisopropyl, and N-desisopropyl metabolite with involvement of CYP2D6 and CYP3A4. None of these metabolites contribute significantly to the antimuscarinic activity of fesoterodine. Mean Cmax and AUC of the active metabolite are 1.7 and 2-fold higher, respectively, in CYP2D6 poor metabolisers as compared to extensive metabolisers.

Elimination
Hepatic metabolism and renal excretion contribute significantly to the elimination of the active metabolite. After oral administration of fesoterodine, approximately 70% of the administered dose was recovered in urine as the active metabolite (16%), carboxy metabolite (34%), carboxy-N-desisopropyl metabolite (18%), or N-desisopropyl metabolite (1%), and a smaller amount (7%) was recovered in faeces. The terminal half-life of the active metabolite following oral administration is approximately 7 hours and is absorption rate-limited.

Age and gender
No dose adjustment is recommended in these subpopulations. The pharmacokinetics of fesoterodine are not significantly influenced by age and gender.

Paediatric population
The pharmacokinetics of fesoterodine have not been evaluated in paediatric patients.

Renal impairment
In patients with mild or moderate renal impairment (GFR 30 – 80 ml/min), Cmax and AUC of the active metabolite increased up to 1.5 and 1.8-fold, respectively, as compared to healthy subjects. In patients with severe renal impairment (GFR < 30 ml/min), Cmax and AUC are increased 2.0 and 2.3-fold, respectively.

Hepatic impairment
In patients with moderate hepatic impairment (Child Pugh B), Cmax and AUC of the active metabolite increased 1.4 and 2.1-fold, respectively, as compared to healthy subjects. Pharmacokinetics of fesoterodine in patients with severe hepatic impairment have not been studied.

IV.3 Pharmacodynamics

No additional studies investigating the pharmacodynamic effects of Fesoterodine 4mg and 8mg prolonged-release tablets were conducted which is acceptable for this generic application.

Mechanism of action
Fesoterodine is a competitive, specific muscarinic receptor antagonist. It is rapidly and extensively hydrolysed by non-specific plasma esterases to the 5-hydroxymethyl derivative, its primary active metabolite, which is the main active pharmacological principle of fesoterodine.

IV.4 Clinical Efficacy

No new Applicant-generated efficacy studies were submitted in this application. The bibliographical review on the clinical pharmacology, efficacy and safety was reflective of the known medicine.

IV.5 Clinical Safety

No new Applicant-generated safety studies or bibliographical safety signals were submitted in this application.

The reference product for this application, Toviaz 4 mg and 8 mg prolonged release tablets by Pfizer limited, registered since 20/4/07. Fesoterodine has an established clinical safety profile.

In the 4 submitted BE studies, no significant differences in terms of safety were apparent between the two formulations. Both incidence and intensity of adverse events reported during the study periods were consistent with fesoterodine product label and with results of other studies in healthy volunteers, and did not suggest differences between test and reference drugs.

Risk Management Plan
The Applicant 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 4 mg & 8 mg Prolonged Release tablets.
Summary of safety concerns

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

Routine pharmacovigilance activities and routine risk minimisation measures are considered sufficient to identify, characterise and minimise the risks of the product in the proposed indication.
An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines

web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

This decentralised application concerns a generic version of Fesoterodine. The legal basis of this application is Article 10.1 of European Directive 2001/83/EC, as amended.

The originator product is Toviaz® 4 mg and 8 mg prolonged release tablets by Pfizer limited, registered since 20/4/07.

To support the clinical application, four bioequivalence studies (N-FES-18-239, N-FES-18-242, N-FES-18-243, N-FES-18-245) are reported.

Fesoterodine Normon was demonstrated to be bioequivalent to Toviaz when administered in 4 bioequivalence studies, 3 comparing the higher strength (8 mg) in single dose fed and fasted studies and a multiple dose fasted study, and one comparing the lower strength (4 mg) in a single dose fasted study. The ratio between logarithmically transformed means of Fesoterodina Normon and reference product Toviaz are within the accepted ranges and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. The justification biowaiver can be accepted.

Fesoterodine is a well-known active substance with established efficacy and tolerability. The reference product for this application, Toviaz 4 mg and 8 mg prolonged release tablets by Pfizer Ltd, registered since 20/4/07. The safety results reported in the bioequivalence study were found to be consistent with the known safety profile of Fesoterodine and no other safety studies were submitted in support of this application which is acceptable.

V. OVERALL CONCLUSIONS

Fesoterodine Doc 4mg and 8mg prolonged-release tablets is a generic form of Toviaz 4mg and 8mg prolonged-release tablets. Toviaz 4mg and 8mg prolonged-release tablets are a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Fesoterodine Doc 4mg and 8mg prolonged-release tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

5 years from the finalisation of the procedure.