

**IPAR**



**Public Assessment Report for a  
Medicinal Product for Human Use**

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Scientific Discussion

Mingocare 8 mg prolonged-release tablets  
Fesoterodine fumarate  
PA23232/001/002

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.

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## I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Mingocare 4 mg & 8 mg prolonged-release tablet, from Ceres Pharma on 6<sup>th</sup> January 2023 for treatment of the symptoms (increased urinary frequency and/or urgency and/or urgency incontinence that may occur with overactive bladder syndrome).

*This section should include information on the type of marketing authorisation application including reference to the legal basis of the application*

*For applications under Article 10c of Directive 2001/83/EC referred to as 'informed consent' applications, the following statement may be used:*

This application for a marketing authorisation was submitted in accordance with Article 10.1 of Directive 2001/83/EC and is referred to as an 'generic' application. This means that the Marketing Authorisation Holder for Toviaz (fesoterodine fumarate) 4 mg and 8 mg prolonged-release tablets, an authorised medicinal product in Europe, has permitted the applicant to refer to their dossier to obtain an authorisation for Fesoterodine fumarate. Fesoterodine fumarate has the same qualitative and quantitative composition in terms of actives substances and the same pharmaceutical form as Toviaz (fesoterodine fumarate) 4 mg and 8 mg prolonged-release tablets.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at [www.hpra.ie](http://www.hpra.ie)

Name of the product	Mingocare 8 mg prolonged-release tablets
Name(s) of the active substance(s) (INN)	Fesoterodine fumarate
Pharmacotherapeutic classification (ATC code)	B04BD11
Pharmaceutical form and strength(s)	8 mg prolonged-release tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA23232/001/002
Marketing Authorisation Holder	Ceres Pharma
MRP/DCP No.	IE/H/1187/002/DC
Reference Member State	IE
Concerned Member State	BE LU

## II. QUALITY ASPECTS

### II.1. Introduction

This application is for Mingocare 4 mg & 8 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

Each Mingocare 4 mg prolonged-release tablet is a blue elliptical, biconvex film-coated tablet approximately 6 mm diameter and debossed with "F4" on one side containing 4 mg fesoterodine fumarate corresponding to 3.1 mg of fesoterodine.

Each Mingocare 8 mg prolonged-release tablet is a dark blue elliptical, biconvex film-coated tablet approximately 6 mm diameter and debossed with "F8" on one side containing 8 mg fesoterodine fumarate corresponding to 6.2 mg of fesoterodine

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. 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 (BE) 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.

The manufacturing process has been validated according to European/ICH guidelines and the process is considered to be sufficiently validated.

### P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

The excipients used in the manufacture of Mingocare 4 mg & 8 mg tablet cores are standard excipients used in the 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 the Ph.Eur. pharmacopoeial monograph for tablets and the tests and control limits are considered appropriate for this type of product.

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 for a number of batches from the proposed production sites 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 Ph. Eur./EU legislation for use with foodstuffs requirements.

#### 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.

### II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Mingocare 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 or 8 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 substance, 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.2 Pharmacology

N/A

### III.3 Pharmacokinetics

N/A

### III.4 Toxicology

N/A

### 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 PEC<sub>sw</sub> is 0.04 µg/ml (utilising the default F<sub>pen</sub>) 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.

### 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 substance, 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 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 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 C<sub>max</sub> (ratio: 97.35), [86.63% - 103.06%] for AUC<sub>0-t</sub> (ratio: 94.48), and [87.14% - 104.31%] for AUC<sub>inf</sub> (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<sub>max</sub> (ratio: 101.43), [95.16% - 108.88%] for AUC<sub>0-t</sub> (ratio: 101.79), and [94.90% - 109.01%] for AUC<sub>inf</sub> (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 AUC<sub>0-t</sub> (90% confidence interval 95.72 – 104.44). The mean ratio of test over Toviaz for C<sub>max</sub> was 98.86 (90% confidence interval 91.33 – 107.01). The mean ratio of test over Toviaz for AUC<sub>0-inf</sub> 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)<sub>ss</sub> (90% confidence interval 88.89 – 99.96). The mean ratio of test over Toviaz for C<sub>max,ss</sub> was 94.30 (90% confidence interval 88.74 – 100.22). The mean ratio of test over Toviaz for C<sub>τ,ss</sub> was 94.16 (90% confidence interval 86.33 – 102.68). The generic product 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 generic product 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 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

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 C<sub>max</sub> 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), C<sub>max</sub> 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), C<sub>max</sub> and AUC are increased 2.0 and 2.3-fold, respectively.

### Hepatic impairment

In patients with moderate hepatic impairment (Child Pugh B), C<sub>max</sub> 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.

The MAH 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 fumarate.

#### Safety specification

<b>Summary of safety concerns</b>	
<b>Important identified risks</b>	<ul style="list-style-type: none"> <li>• None</li> </ul>
<b>Important potential risks</b>	<ul style="list-style-type: none"> <li>• QT Prolongation</li> <li>• Liver Enzyme Elevation</li> <li>• Urinary Retention</li> <li>• Cognitive Function Impairment</li> <li>• Angioedema</li> </ul>
<b>Missing information</b>	<ul style="list-style-type: none"> <li>• Elderly Male Patients</li> <li>• Paediatric Patients</li> <li>• Pregnant or Nursing Women</li> </ul>

#### Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed, which is endorsed.

#### Risk minimisation measures

Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed, which is endorsed.

#### Summary of the RMP

The submitted Risk Management Plan, version 2.0 signed 22<sup>nd</sup> October 2021 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

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 medicine's 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.

### Common renewal date

The proposed renewal date is five years after end of procedure.

## 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. The generic product 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 generic product 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

Mingocare 4 mg & 8 mg prolonged-release tablet are 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 Mingocare 4 mg & 8 mg prolonged-release tablet tablets demonstrated bioequivalence.

## VI. REVISION DATE

The proposed renewal date is five years after end of procedure.