

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fesoterodine Doc 8 mg Prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fesoterodine Doc 8 mg prolonged-release tablets

Each prolonged-release tablet contains 8 mg fesoterodine fumarate corresponding to 6.2 mg of fesoterodine.

Excipients with known effect

Fesoterodine Doc 8 mg prolonged-release tablets

Each contains 72 mg of fructose and 55 mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fesoterodine Doc 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.

4.2 Posology and method of administration

Posology

Adults (including elderly)

The recommended starting dose is 4 mg once daily. Based upon individual response, the dose may be increased to 8 mg once daily. The maximum daily dose is 8 mg.

Full treatment effect was observed between 2 and 8 weeks. Hence, it is recommended to re-evaluate the efficacy for the individual patient after 8 weeks of treatment.

In subjects with normal renal and hepatic function receiving concomitant administration of potent CYP3A4 inhibitors, the maximum daily dose of Fesoterodine Doc should be 4 mg once daily (see section 4.5).

Special population

Renal and hepatic impairment

The following table provides the daily dosing recommendations for subjects with renal or hepatic impairment in the absence and presence of moderate and potent CYP3A4 inhibitors (see sections 4.3, 4.4, 4.5 and 5.2).

| | | Moderate ⁽³⁾ or potent ⁽⁴⁾ CYP3A4 inhibitors | | |
|--|--|--|----------|--------|
| | | None | Moderate | Potent |

| | | | | |
|---|----------|-----------------------|-------------------|-------------------|
| Renal impairment ⁽¹⁾ | Mild | 4→8 mg ⁽²⁾ | 4 mg | Should be avoided |
| | Moderate | 4→8 mg ⁽²⁾ | 4 mg | Contraindicated |
| | Severe | 4 mg | Should be avoided | Contraindicated |
| Hepatic impairment | Mild | 4→8 mg ⁽²⁾ | 4 mg | Should be avoided |
| | Moderate | 4 mg | Should be avoided | Contraindicated |
| <ol style="list-style-type: none"> 1. Mild GFR = 50-80 ml/min; Moderate GFR = 30-50 ml/min; Severe GFR = <30 ml/min 2. Cautious dose increase. See sections 4.4, 4.5 and 5.2 3. Moderate CYP3A4 inhibitors. See section 4.5 4. Potent CYP3A4 inhibitors. See sections 4.3, 4.4 and 4.5 | | | | |

Fesoterodine Doc is contraindicated in subjects with severe hepatic impairment (see section 4.3).

Paediatric population

The safety and efficacy of Fesoterodine Doc in children aged less than 6 years have not been established. No data are available.

The safety and efficacy of Fesoterodine Doc in children aged 6 years to 17 years have not been established. Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Tablets are to be taken once daily with liquid and swallowed whole and must not be divided, crushed, dissolved, sucked or chewed.

Fesoterodine Doc can be administered with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Urinary retention
- Gastric retention
- Uncontrolled narrow angle glaucoma
- Myasthenia gravis
- Severe hepatic impairment (Child Pugh C)
- Concomitant use of potent CYP3A4 inhibitors in subjects with moderate to severe hepatic or renal impairment
- Severe ulcerative colitis
- Toxic megacolon.

4.4 Special warnings and precautions for use

Fesoterodine Doc should be used with caution in patients with:

- Clinically significant bladder outflow obstruction at risk of urinary retention (e.g. clinically significant prostate enlargement due to benign prostatic hyperplasia, see section 4.3)
- Gastrointestinal obstructive disorders (e.g. pyloric stenosis)
- Gastro-oesophageal reflux and/or who are concurrently taking medicinal products (such as oral bisphosphonates) that can cause or exacerbate oesophagitis
- Decreased gastrointestinal motility
- Autonomic neuropathy
- Controlled narrow-angle glaucoma

Caution should be exercised when prescribing or uptitrating fesoterodine to patients in whom an increased exposure to the active metabolite (see section 5.1) is expected:

- Hepatic impairment (see sections 4.2, 4.3 and 5.2)
- Renal impairment (see sections 4.2, 4.3 and 5.2)

- Concomitant administration of potent or moderate CYP3A4 inhibitors (see sections 4.2 and 4.5)
- Concomitant administration of a potent CYP2D6 inhibitor (see sections 4.5 and 5.2).

Dose increases

In patients with a combination of these factors, additional exposure increases are expected. Dose dependent antimuscarinic adverse reactions are likely to occur. In populations where the dose may be increased to 8 mg once daily, the dose increase should be preceded by an evaluation of the individual response and tolerability.

Organic causes must be excluded before any treatment with antimuscarinics is considered. Safety and efficacy have not yet been established in patients with a neurogenic cause for detrusor overactivity.

Other causes of frequent urination (treatment of heart failure or renal disease) should be assessed before treatment with fesoterodine. If urinary tract infection is present, an appropriate medical approach should be taken/antibacterial therapy should be started.

Angioedema

Angioedema has been reported with fesoterodine and has occurred after the first dose in some cases.

Some cases may be associated with upper airway swelling and may be life-threatening. If angioedema occurs, fesoterodine should be discontinued and appropriate therapy should be promptly provided.

Potent CYP3A4 inducers

The concomitant use of fesoterodine with a potent CYP3A4 inducer (i.e. carbamazepine, rifampicin, phenobarbital, phenytoin, St John's Wort) is not recommended (see section 4.5).

QT prolongation

Fesoterodine Doc should be used with caution in patients with risk for QT prolongation (e.g. hypokalaemia, bradycardia and concomitant administration of medicines known to prolong QT interval) and relevant pre-existing cardiac diseases (e.g. myocardial ischaemia, arrhythmia, congestive heart failure), (see section 4.8). This especially holds true when taking potent CYP3A4 inhibitors (see sections 4.2, 4.5 and 5.1).

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Fructose

This medicinal product contains fructose 72 mg per tablet. Fructose may damage teeth.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacological interactions

Caution should be exercised in coadministration of fesoterodine with other antimuscarinics and medicinal products with anticholinergic properties (e.g. amantadine, tri-cyclic antidepressants, certain neuroleptics) as this may lead to more pronounced therapeutic- and side-effects (e.g. constipation, dry mouth, drowsiness, urinary retention).

Fesoterodine may reduce the effect of medicinal products that stimulate the motility of the gastro-intestinal tract, such as metoclopramide.

Pharmacokinetic interactions

In vitro data demonstrate that the active metabolite of fesoterodine does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4, or induce CYP1A2, 2B6, 2C9, 2C19, or 3A4 at clinically relevant plasma concentrations. Thus fesoterodine is unlikely to alter the clearance of medicinal products that are metabolised by these enzymes.

CYP3A4 inhibitors

Potent CYP3A4 inhibitors

Following inhibition of CYP3A4 by co-administration of ketoconazole 200 mg twice daily, C_{max} and AUC of the active metabolite of fesoterodine increased 2.0 and 2.3-fold in CYP2D6 extensive metabolisers and 2.1 and 2.5-fold in CYP2D6 poor

metabolisers, respectively. Therefore, the maximum dose of fesoterodine should be restricted to 4 mg when used concomitantly with potent CYP3A4 inhibitors (e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir (and all ritonavir boosted PI-regimens), saquinavir and telithromycin (see sections 4.2 and 4.4)).

Moderate CYP3A4 inhibitors

Following blockade of CYP3A4 by coadministration of the moderate CYP3A4 inhibitor fluconazole 200 mg twice a day for 2 days, C_{max} and AUC of the active metabolite of fesoterodine increased approximately 19% and 27%, respectively. No dosing adjustments are recommended in the presence of moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole, diltiazem, verapamil and grapefruit juice).

Weak CYP3A4 inhibitors

The effect of weak CYP3A4 inhibitors (e.g. cimetidine), was not examined; it is not expected to be in excess of the effect of moderate inhibitor.

CYP3A4 inducers

Following induction of CYP3A4 by coadministration of rifampicin 600 mg once a day, C_{max} and AUC of the active metabolite of fesoterodine decreased by approximately 70% and 75%, respectively, after oral administration of fesoterodine 8 mg.

Induction of CYP3A4 may lead to subtherapeutic plasma levels. Concomitant use with CYP3A4 inducers (e.g. carbamazepine, rifampicin, phenobarbital, phenytoin, St John's Wort) is not recommended (see section 4.4).

CYP2D6 inhibitors

The interaction with CYP2D6 inhibitors was not tested clinically. Mean C_{max} and AUC of the active metabolite are 1.7 and 2-fold higher, respectively, in CYP2D6 poor metabolisers as compared to extensive metabolisers. Co-administration of a potent CYP2D6 inhibitor may result in increased exposure and adverse events. A dose reduction to 4 mg may be needed (see section 4.4).

Oral contraceptives

Fesoterodine does not impair the suppression of ovulation by oral hormonal contraception. In the presence of fesoterodine there are no changes in the plasma concentrations of combined oral contraceptives containing ethinylestradiol and levonorgestrel.

Warfarin

A clinical study in healthy volunteers has shown that fesoterodine 8 mg once daily has no significant effect on the pharmacokinetics or the anticoagulant activity of a single dose of warfarin.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of fesoterodine in pregnant women. Reproductive toxicity studies with fesoterodine in animals show minor embryotoxicity. In animal reproduction studies, oral administration of fesoterodine to pregnant mice and rabbits during organogenesis resulted in fetotoxicity at maternal exposures that were 6 and 3 times the maximum recommended human dose (MRHD), respectively, based on AUC (see section 5.3). The potential risk for humans is unknown. Fesoterodine Doc is not recommended during pregnancy.

Breast-feeding

It is unknown whether fesoterodine/metabolites are excreted into human milk; therefore, breast-feeding is not recommended during treatment with Fesoterodine Doc.

Fertility

No clinical trials have been conducted to assess the effect of fesoterodine on human fertility. Findings in mice at exposures approximately 5 to 19 times those at the MRHD show an effect on female fertility, however, the clinical implications of these animal findings are not known (see section 5.3). Women of child bearing potential should be made aware of the lack of human fertility data, and Fesoterodine Doc should only be given after consideration of individual risks and benefits.

4.7 Effects on ability to drive and use machines

Fesoterodine Doc has minor influence on the ability to drive and use machines.

Caution should be exercised when driving or using machines due to possible occurrence of side effects such as blurred vision, dizziness, and somnolence (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety of fesoterodine was evaluated in placebo-controlled clinical studies in a total of 2859 patients with overactive bladder, of which 780 received placebo.

Due to the pharmacological properties of fesoterodine, treatment may cause mild to moderate antimuscarinic effects like dry mouth, dry eye, dyspepsia and constipation. Urinary retention may occur uncommonly.

Dry mouth, the only very common adverse reactions, occurred with a frequency of 28.8% in the fesoterodine group compared to 8.5% in the placebo group. The majority of adverse reactions occurred during the first month of treatment with the exception of cases classified as urinary retention or post void residual urine greater than 200 ml, which could occur after long term treatment and was more common in male than female subjects.

Tabulated list of adverse reactions

The table below gives the frequency of treatment emergent adverse reactions from placebo- controlled clinical trials and from post-marketing experience. The adverse reactions are reported in this table with the following frequency convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| System organ class | Very common | Common | Uncommon | Rare |
|---|-------------|--|--|-----------------------|
| Infections and infestations | | | Urinary tract infection | |
| Psychiatric disorders | | Insomnia | | Confusional state |
| Nervous system disorders | | Dizziness; Headache | Dysgeusia; Somnolence | |
| Eye disorders | | Dry eye | Blurred vision | |
| Ear and labyrinth disorders | | | Vertigo | |
| Cardiac disorders | | | Tachycardia; Palpitations | |
| Respiratory, thoracic and mediastinal disorders | | Dry throat | Pharyngolaryngeal pain; Cough; Nasal dryness | |
| Gastrointestinal disorders | Dry mouth | Abdominal pain; Diarrhoea; Dyspepsia; Constipation; Nausea | Abdominal discomfort; Flatulence, Gastroesophageal reflux | Hypoaesthesia oral |
| Hepatobiliary disorders | | | ALT increased; GGT increased | |
| Skin and subcutaneous tissue disorders | | | Rash; Dry skin; Pruritus | Angioedema; Urticaria |
| Renal and | | Dysuria | Urinary | |

| | | | | |
|--|--|--|--|--|
| urinary disorders | | | retention (including feeling of residual urine; micturition disorder); Urinary hesitation | |
| General disorders and administration site conditions | | | Fatigue | |

Description of selected adverse reactions

In clinical trials of fesoterodine, cases of markedly elevated liver enzymes were reported with the occurrence frequency no different from the placebo group. The relation to fesoterodine treatment is unclear.

Electrocardiograms were obtained from 782 patients treated with 4 mg, 785 treated with 8 mg, 222 treated with 12 mg fesoterodine and 780 with placebo. The heart rate corrected QT interval in fesoterodine treated patients did not differ from that seen in placebo treated patients. The incidence rates of QTc ³500 ms post baseline or QTc increase of ³60 ms is 1.9%, 1.3%, 1.4% and 1.5%, for fesoterodine 4 mg, 8 mg, 12 mg and placebo, respectively. The clinical relevance of these findings will depend on individual patient risk factors and susceptibilities present (see section 4.4).

Post-marketing cases of urinary retention requiring catheterisation have been described, generally within the first week of treatment with fesoterodine. They have mainly involved elderly (≥ 65 years) male patients with a history consistent with benign prostatic hyperplasia (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

Overdose with antimuscarinics, including fesoterodine can result in severe anticholinergic effects. Treatment should be symptomatic and supportive. In the event of overdose, ECG monitoring is recommended; standard supportive measures for managing QT prolongation should be adopted. Fesoterodine has been safely administered in clinical studies at doses up to 28 mg/day.

In the event of fesoterodine overdose, treat with gastric lavage and give activated charcoal. Treat symptoms as follows:

- Severe central anticholinergic effects (e.g. hallucinations, severe excitation): treat with physostigmine
- Convulsions or pronounced excitation: treat with benzodiazepines
- Respiratory insufficiency: treat with artificial respiration
- Tachycardia: treat with beta-blockers
- Urinary retention: treat with catheterisation
- Mydriasis: treat with pilocarpine eye drops and/or place patient in darkroom.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, Urinary antispasmodics, ATC code: G04BD11.

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.

Clinical efficacy and safety

The efficacy of fixed doses of fesoterodine 4 mg and 8 mg was evaluated in two Phase 3 randomised, double-blind, placebo-controlled, 12-week studies. Female (79%) and male (21%) patients with a mean age of 58 years (range 19-91 years) were included. A total of 33% of patients were ≥65 years of age and 11% were ≥75 years of age.

Fesoterodine treated patients had statistically significant mean reductions in the number of micturitions per 24 hours and in the number of urge incontinence episodes per 24 hours at the end of treatment compared to placebo. Likewise, the response rate (% of patients reporting that their condition has been "greatly improved" or "improved" using a 4-point Treatment Benefit Scale) was significantly greater with fesoterodine compared to placebo. Furthermore, fesoterodine improved the mean change in the voided volume per micturition, and the mean change in the number of continent days per week (see Table 1 below).

Table1: Mean changes from Baseline to end of treatment for primary and selected secondary endpoints

| | Study 1 | | | | Study 2 | | |
|--|----------------|--------------------------|--------------------------|--------------------------|----------------|--------------------------|--------------------------|
| Parameter | Placebo | Fesoterodine 4 mg | Fesoterodine 8 mg | Active comparator | Placebo | Fesoterodine 4 mg | Fesoterodine 8 mg |
| Number of micturitions per 24 hours# | | | | | | | |
| | N=279 | N=265 | N=276 | N=283 | N=266 | N=267 | N=267 |
| Baseline | 12.0 | 11.6 | 11.9 | 11.5 | 12.2 | 12.9 | 12.0 |
| Change from baseline | -1.02 | -1.74 | -1.94 | -1.69 | -1.02 | -1.86 | -1.94 |
| p-value | | <0.001 | <0.001 | | | 0.032 | <0.001 |
| Responder rate (treatment response)# | | | | | | | |
| | N=279 | N=265 | N=276 | N=283 | N=266 | N=267 | N=267 |
| Responder rate | 53.4% | 74.7% | 79.0% | 72.4% | 45.1% | 63.7% | 74.2% |
| p-value | | <0.001 | <0.001 | | | <0.001 | <0.001 |
| Number of urge incontinence episodes per 24 hours | | | | | | | |
| | N=211 | N=199 | N=223 | N=223 | N=205 | N=228 | N=218 |
| Baseline | 3.7 | 3.8 | 3.7 | 3.8 | 3.7 | 3.9 | 3.9 |
| Change from baseline | -1.20 | -2.06 | -2.27 | -1.83 | -1.00 | -1.77 | -2.42 |
| p-value | | 0.001 | <0.001 | | | 0.003 | <0.001 |
| Number of continent days per week | | | | | | | |
| | N=211 | N=199 | N=223 | N=223 | N=205 | N=228 | N=218 |
| Baseline | 0.8 | 0.8 | 0.6 | 0.6 | 0.6 | 0.7 | 0.7 |
| Change from baseline | 2.1 | 2.8 | 3.4 | 2.5 | 1.4 | 2.4 | 2.8 |
| p-value | | 0.007 | <0.001 | | | <0.001 | <0.001 |
| Voided volume per micturition (ml) | | | | | | | |
| | N=279 | N=265 | N=276 | N=283 | N=266 | N=267 | N=267 |
| Baseline | 150 | 160 | 154 | 154 | 159 | 152 | 156 |
| Change from baseline | 10 | 27 | 33 | 24 | 8 | 17 | 33 |
| p-value | | <0.001 | <0.001 | | | 0.150 | <0.001 |

primary end points

Cardiac electrophysiology

The effect of fesoterodine 4 mg and 28 mg on the QT interval was thoroughly evaluated in a double-blind, randomised, placebo- and positive-controlled (moxifloxacin 400 mg) parallel group study with once-daily treatment over a period of 3 days in 261 male and female subjects aged 45 to 65 years. Change from baseline in QTc based on the Fridericia correction method did not show any differences between the active treatment and placebo group.

Paediatric population

Fesoterodine was evaluated in a randomised, open-label study consisting of a 12-week efficacy phase study followed by a 12-week safety extension phase in paediatric patients from 6 years to 17 years of age with neurogenic detrusor overactivity. Two cohorts were studied. In the Cohort 1, 124 patients weighing > 25 kg received a fixed dose of fesoterodine 4 mg or 8 mg

tablets once-daily or active comparator oxybutynin XL tablets. In the safety extension phase, patients randomised to active comparator tablets were switched to fesoterodine 4 mg or 8 mg tablets (allocated by the investigator). In the Cohort 2, 57 patients weighing ≤ 25 kg received a fixed dose of fesoterodine 2 mg or 4 mg investigational beads-in-capsule (BIC) formulation once daily. In the safety extension phase, patients continued on the dose of fesoterodine to which they had been randomised. For study inclusion, patients were required to have stable neurological disease and clinically or urodynamically-demonstrated neurogenic detrusor overactivity (see section 4.2).

The primary efficacy endpoint for both Cohorts was the mean change from baseline in maximum cystometric bladder capacity (MCBC) at Week 12. Treatment with fesoterodine 4 mg or 8 mg tablets resulted in improvements from baseline to Week 12 in the primary efficacy endpoint, MCBC, for paediatric patients in Cohort 1, with numerically higher changes from baseline for fesoterodine 8 mg tablets than for fesoterodine 4 mg tablets. Treatment with fesoterodine 2 mg and 4 mg BIC resulted in improvements from baseline to Week 12 in the primary efficacy endpoint, MCBC, for paediatric patients in Cohort 2, with numerically higher changes from baseline for fesoterodine 4 mg BIC than for fesoterodine 2 mg BIC.

Table 2: Mean baseline and change from baseline to week 12 maximum cystometric bladder capacity (mL)

| | Cohort 1 (body weight > 25 kg) | | | Cohort 2 (bodyweight ≤ 25kg) | |
|--|--|--------------------------|--------------------------|---|-------------------------|
| | Feso 4mg tablet | Feso 8mg tablet | Oxybutynin XL | Feso 2mg BIC | Feso 4mg BIC |
| | N = 41 | N = 41 | N = 38 | N = 25 | N = 28 |
| Baseline | 195.1 | 173.3 | 164.1 | 131.4 | 126.7 |
| Change from baseline (95% CI) ^a | 58.12 (28.84, 87.39) | 83.36 (54.22, 112.49) | 87.17 (56.82, 117.53) | 23.49 (3.03, 43.95) | 40.17 (20.84, 59.50) |
| p-value vs. baseline ^a | 0.0001 | <.0001 | <.0001 | -- ^b | -- ^b |

Abbreviations: BIC = beads-in-capsule; CI = confidence interval; Feso = fesoterodine, N = number of patients with a non-missing baseline measurement; vs. = versus.

Baseline is defined as the last available measurement prior to the start of treatment.

a. Based on an analysis of covariance model with terms for treatment group, baseline maximum cystometric bladder capacity and baseline weight. Last observation carried forward/baseline observation was used for imputing missing values.

b. No hypothesis testing was planned for Cohort 2; therefore, no p-values are presented.

Secondary endpoints

Treatment with fesoterodine 4 mg or 8 mg tablets resulted in statistically significant improvements in the urodynamic measure secondary endpoint bladder volume at first involuntary detrusor contraction.

The most commonly reported adverse reactions in the efficacy phase were diarrhoea, dry mouth, constipation, abdominal pain (including upper abdominal pain) and headache. These mild to moderate adverse reactions are consistent with the pharmacological, antimuscarinic properties of fesoterodine. Increases in heart rate were observed in patients who received fesoterodine which were not associated with clinical symptoms. Overall, the safety profile in paediatric patients with neurogenic detrusor overactivity was similar to that observed in adults with overactive bladder syndrome.

5.2 Pharmacokinetic properties

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. The steady-state exposures of 5-HMT in healthy adult subjects following fesoterodine 4 mg and 8 mg tablets once daily are summarised in Table 3.

Table 3: Summary of geometric mean [%CV] pharmacokinetic parameters for the active metabolite after steady-state dosing of fesoterodine in healthy adult subjects, 18 years to 50 years of age

| Dosage/Formulation | N | C_{max,ss}(ng/mL) | AUC_{tau,ss}(ng*h/mL) |
|---------------------------|----------|----------------------------------|--------------------------------------|
| 4 mg QD/tablet | 6 | 1.71 (74.9) | 16.39 (69.8) |

| | | | |
|----------------|---|-------------|--------------|
| 8 mg QD/tablet | 6 | 4.66 (43.3) | 46.51 (46.8) |
|----------------|---|-------------|--------------|

Abbreviations: AUC_{tau,ss} = steady-state area under the concentration time curve over the 24 hour dosing interval; C_{max,ss} = steady-state maximum plasma concentration; CV = coefficient of variation; N = number of patients with PK data; QD = once daily.

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_{max} 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

In paediatric patients, from 6 years to 17 years of age with neurogenic detrusor overactivity weighing 35 kg with CYP2D6 extensive metaboliser status receiving fesoterodine tablets, the mean values of apparent oral clearance, volume of distribution and absorption rate constant of 5-HMT are estimated to be approximately 72 L/h, 68 L and 0.09 h⁻¹, respectively. The T_{max} and half-life of 5-HMT are estimated to be approximately 2.55 h and 7.73 h, respectively. Like adults, the 5-HMT exposure in CYP2D6 poor metabolisers was estimated to be approximately 2-fold higher compared with extensive metabolisers.

The post-hoc estimates of steady-state exposures of 5-HMT in paediatric patients following fesoterodine 4 mg and 8 mg tablets once daily are summarised in Table 4.

Table 4: Summary of geometric mean [%CV] pharmacokinetic parameters for the active metabolite after steady-state dosing of fesoterodine in paediatric patients with NDO or OAB, weighing >25 kg

| Age | Dosage/Formulation | N | C _{max,ss} (ng/mL) | AUC _{tau,ss} (ng*h/mL) |
|--|-----------------------------|----|-----------------------------|------------------------------------|
| 6 to 17 years (patients with NDO) | 4 mg QD/tablet | 32 | 4.88 (48.2) | 59.1 (51.7) |
| | 8 mg QD/tablet | 39 | 8.47 (41.6) | 103 (46.2) |
| 8 to 17 years (patients with NDO or OAB) | 8 mg QD/tablet ¹ | 21 | 7.15 (39.5) | 86.4 (44.0) |

¹ dosing was initiated at 4 mg QD for 4 weeks and escalated to 8 mg QD for the next 4 weeks.

Abbreviations: AUC_{tau,ss} = steady-state area under the concentration time curve over the 24 hour dosing interval; C_{max,ss} = steady-state maximum plasma concentration; CV = coefficient of variation; N = number of patients with PK data; QD = once daily.

Renal impairment

In patients with mild or moderate renal impairment (GFR 30 – 80 ml/min), C_{max} 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_{max} and AUC are increased 2.0 and 2.3- fold, respectively.

Hepatic impairment

In patients with moderate hepatic impairment (Child Pugh B), C_{max} 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.

5.3 Preclinical safety data

In non-clinical safety pharmacology, general toxicity, genotoxicity and carcinogenicity studies no clinically relevant effects have been observed, except those related to the pharmacological effect of the active substance.

Reproduction studies have shown minor embryotoxicity at doses close to maternally toxic ones (increased number of resorptions, pre-implantation and post-implantation losses).

Supratherapeutic concentrations of the active metabolite of fesoterodine, have been shown to inhibit K⁺ current in cloned human ether-à-go-go-related gene (hERG) channels and prolong action potential duration (70% and 90% repolarisation) in canine isolated Purkinje fibres. However in conscious dogs, the active metabolite had no effect on the QT interval and QTc interval at plasma exposures at least 33-fold higher than mean peak free plasma concentration in human subjects who are extensive metabolisers and 21-fold higher than measured in subjects who are poor CYP2D6 metabolisers after fesoterodine 8 mg once daily.

In a study of fertility and early embryonic development in mice, fesoterodine had no effect on male reproductive function or fertility at doses up to 45 mg/kg/day. At 45 mg/kg/day, a lower number of corpora lutea, implantation sites and viable foetuses was observed in female mice administered fesoterodine for 2 weeks prior to mating and continuing through day 7 of gestation. The maternal No- Observed-Effect Level (NOEL) and the NOEL for effects on reproduction and early embryonic development were both 15 mg/kg/day. Based on AUC, the systemic exposure was 0.6 to 1.5 times higher in mice than in humans at the MRHD, whereas based on peak plasma concentrations, the exposure in mice was 5 to 9 times higher.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Fructose
Lactose monohydrate
Microcrystalline cellulose
Hypromellose
Glycerol dibehenate
Talc

Film-coating

Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol
Talc
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original blister package in order to protect from moisture.

6.5 Nature and contents of container

Fesoterodine Doc 4 mg and 8 mg tablets are packed in aluminium-aluminium blisters in cartons containing 14 or 28 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

DOC Generici S.r.l.
Via Turati 40
Milano
20121
Italy

8 MARKETING AUTHORISATION NUMBER

PA2244/002/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date for First Authorisation: 12th August 2022

10 DATE OF REVISION OF THE TEXT

March 2024