PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

FENRI 175 µg/3 ml Inhalation solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each FENRI vial contains 175 µg of revefenacin in 3 ml of aqueous solution.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Inhalation solution.

FENRI inhalation solution is supplied as a sterile, clear, colourless, aqueous solution for nebulisation in low-density polyethylene unit-dose vials.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

FENRI inhalation solution is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

4.2 Posology and method of administration

Posology:

The recommended dose of FENRI inhalation solution is one 175 µg unit-dose vial administered once daily by nebuliser using a mouthpiece.

FENRI should be administered by the orally inhaled route via a standard jet nebuliser connected to an air compressor (See Patient Information).

The safety and efficacy of FENRI have been established in clinical trials when administered using the PARI LC Sprint nebulizer with a mouthpiece and the PARI Trek S compressor. The safety and efficacy of FENRI delivered from non-compressor based nebuliser systems have not been established.

The FENRI unit-dose vial should only be removed from the foil pouch and opened IMMEDIATELY BEFORE USE. The vial and any residual content should be discarded after use.

No dosage adjustment is required for elderly patients, or patients with renal impairment (see section 4.4).

The compatibility (physical and chemical), efficacy, and safety of FENRI when mixed with other medicines in a nebuliser have not been established.

4.3 Contraindications

- FENRI is contraindicated in patients with known hypersensitivity revefenacin or any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

Deterioration of Disease and Acute Episodes

FENRI should not be initiated in patients during acutely deteriorating or potentially life-threatening episodes of COPD. FENRI has not been studied in subjects with acutely deteriorating COPD. The initiation of FENRI in this setting is not appropriate.

FENRI is intended as a once-daily maintenance treatment for COPD and should not be used for relief of acute symptoms, i.e. as rescue therapy for the treatment of acute episodes of bronchospasm, and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta-agonist.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If FENRI no longer controls symptoms of bronchoconstriction, the patient's inhaled, short-acting beta-agonist becomes less effective, or the patient needs more inhalations of a short-acting beta-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of FENRI beyond the recommended dose is not appropriate in this situation.

Paradoxical Bronchospasm

FENRI can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs following dosing with FENRI, it should be treated immediately with an inhaled, short-acting bronchodilator; FENRI should be discontinued immediately and alternative therapy should be instituted.

Worsening of Narrow-Angle Glaucoma

FENRI should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g. eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema). Instruct patients to consult a medical practitioner immediately if any of these signs or symptoms develops.

Worsening of Urinary Retention

FENRI should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g. difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of FENRI. If such a reaction occurs, therapy with FENRI should be stopped at once and alternative treatments should be considered.

Special Populations

Paediatric Use

FENRI is not indicated for use in children. The safety and efficacy in paediatric patients have not been established.

Elderly Use

Based on available data, no adjustment of the dosage of FENRI in elderly patients is necessary.

Clinical trials of FENRI included 441 subjects aged 65 years and older, and of those, 101 subjects were aged 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment

The systemic exposure of revefenacin is unchanged while that of its active metabolite is increased in subjects with moderate hepatic impairment.

The safety of FENRI has not been evaluated in COPD patients with mild-to-severe hepatic impairment. FENRI is not recommended in patients with any degree of hepatic impairment (*see section 5.2*).

Renal Impairment

No dosage adjustment is required in patients with renal impairment. Monitor for systemic antimuscarinic side effects in COPD patients with severe renal impairment (*see section 5.2*).

4.5 Interaction with other medicines and other forms of interaction

Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of FENRI with other anticholinergic-containing medicines as this may lead to an increase in anticholinergic adverse effects (*see section 4.4*).

Transporter-Related Interactions

OATP1B1 and OATP1B3 inhibitors (e.g. rifampicin, ciclosporin, etc.) could lead to an increase in systemic exposure of the active metabolite.

Therefore, coadministration with FENRI is not recommended (*see section 5.2*).

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary

There are no adequate and well-controlled studies with FENRI in pregnant women. Women should be advised to contact their medical practitioner if they become pregnant while using FENRI. In animal reproduction studies, subcutaneous administration of revefenacin to pregnant rats and rabbits during the period of organogenesis produced no evidence of foetal harm at respective exposures approximately 209 times the exposure at the maximum recommended human dose (MRHD) (on an area under the curve [AUC] basis) (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

In an embryo-foetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6 to 17, revefenacin was not teratogenic and did not affect foetal survival at exposures up to 209 times the MRHD (based upon summed AUCs for revefenacin and its active metabolite at maternal subcutaneous doses up to 500 mcg/kg/day).

In an embryo-foetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 7 to 19, revefenacin was not teratogenic and did not affect foetal survival at exposures up to 694 times the MRHD (based upon summed AUCs for revefenacin and its active metabolite at maternal subcutaneous doses up to 500 mcg/kg/day).

Placental transfer of revefenacin and its active metabolite was observed in pregnant rabbits.

In a pre- and postnatal development (PPND) study in pregnant rats dosed during the periods of organogenesis and lactation from gestation day 6 to lactation day 20, revefenacin had no adverse developmental effects on pups at exposures up to 196 times the MRHD (based upon summed AUCs for revefenacin and its active metabolite at maternal subcutaneous doses up to 500 mcg/kg/day).

Lactation

Risk Summary

There is no information regarding the presence of revefenacin in human milk, the effects on the breastfed infant, or the effects on milk production. However, revefenacin was present in the milk of lactating rats following dosing during pregnancy and lactation (see Data).

Mothers taking FENRI are advised not to breastfeed their infants

The mother's clinical need for FENRI should be considered and any potential adverse effects on the breastfed infant from FENRI or from the underlying maternal condition.

Data

Animal Data

In a PPND study revefenacin and its active metabolite were present in milk of lactating rats on lactation day 22. Milk-to-plasma concentration ratios were up to 10 for revefenacin and its active metabolite.

4.7 Effects on ability to drive and use machines

FENRI has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

a. Summary of the safety profile

The following serious adverse reactions are discussed in section 4.4 Special warnings and precautions for use:

- Paradoxical bronchospasm
- Worsening of narrow-angle glaucoma
- Worsening of urinary retention
- Immediate hypersensitivity reactions

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a medicine may not reflect the rates observed in practice.

The revefenacin safety database included 2,285 subjects with COPD in two 12-week efficacy studies and one 52-week long-term safety study. A total of 730 subjects received treatment

with revefenacin 175 mcg once daily. The safety data described below are based on the two 12-week trials and the one 52-week trial.

12-Week Trials

Revefenacin was studied in two 12-week replicate placebo-controlled trials in patients with moderate to very severe COPD (Trials 1 and 2). In these trials, 395 patients were treated with revefenacin at the recommended dose of 175 µg once daily.

The population had a mean age of 64 years (range from 41 to 88 years), with 50 % males, 90 % Caucasian, and had COPD with a mean postbronchodilator forced expiratory volume in one second (FEV) percent predicted of 55 %. Of subjects enrolled in the two 12-week trials, 37 % were taking concurrent long-acting beta-agonist (LABA) or inhaled corticosteroid (ICS) /LABA therapy. Patients with unstable cardiac disease, narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials.

Table 1 shows the most common adverse reactions that occurred with a frequency of greater than or equal to 2 % in the revefenacin group and higher than placebo in the two 12-week placebo-controlled trials.

The proportion of subjects who discontinued treatment due to adverse reactions was 13 % for the revefenacin-treated subjects and 19 % for placebo-treated subjects.

b. Tabulated summary of adverse reactions

Table 1: Adverse Events with Revefenacin ≥ 2 % Incidence and Higher than Placebo

	Placebo (N = 418)	**Revefenacin 175 µg (N = 395)**
Respiratory, Thoracic and Mediastinal Disorders		
Cough	17 (4 %)	17 (4 %)

Infections and Infestations		
Nasopharyngitis	9 (2 %)	15 (4 %)
Upper respiratory tract infection	9 (2 %)	11 (3 %)
Nervous System Disorders		
Headache	11 (3 %)	16 (4 %)
Musculoskeletal and Connective Tissue Disorders		
Back pain	3 (1 %)	9 (2 %)

Other adverse reactions defined as events with an incidence of ≥ 1,0 %, less than 2,0 %, and more common than with placebo included the following: hypertension, dizziness, oropharyngeal pain, and bronchitis.

52-Week Trial

Revefenacin was studied in one 52-week, open-label, active-control (tiotropium 18 µg once daily) trial in 1,055 patients with COPD. In this trial, 335 patients were treated with revefenacin 175 µg once daily and 356 patients with tiotropium. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled 12-week studies described, with the exception that concurrent LABA or LABA/ICS therapy was used in 50 % of patients. The adverse reactions reported in the long-term safety trial for revefenacin were consistent with those observed in the placebo-controlled studies of 12-weeks.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug**

Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

An overdose of FENRI may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, light-headedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances, or reddening of the eye), constipation or difficulties in voiding. In COPD patients, orally inhaled administration of FENRI at a once-daily dose of up to 700 µg (4 times the maximum recommended daily dose) for 7 days was well tolerated.

Treatment of overdosage consists of discontinuation of FENRI along with institution of appropriate symptomatic and/or supportive therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for obstructive airways diseases, Inhalants, ATC code: R03BB08

Mechanism of Action

Revefenacin is a long-acting muscarinic antagonist, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* models, prevention of methacholine- and acetylcholine-induced bronchoconstrictive effects was dose-dependent and lasted longer than 24 hours. The clinical relevance of these findings is unknown. The bronchodilation following inhalation of revefenacin is predominantly a site-specific effect.

Pharmacodynamics

Cardiac Electrophysiology

QTc interval prolongation was studied in a randomized, double-blind, placebo- and positive-controlled, single dose, crossover trial in 48 healthy subjects. Following a single dose of revefenacin 700 mcg (4 times the recommended dosage), no effects on prolongation of QTc interval were observed.

5.2 Pharmacokinetic properties

Revefenacin pharmacokinetic parameters are presented as the mean [standard deviation (SD)] unless otherwise specified. Following repeat dosing of inhaled revefenacin, steady-state was achieved within 7 days with < 1,6-fold accumulation. Revefenacin exposure (C_{max} and AUC) in COPD patients is approximately 60 % lower as compared to healthy subjects. Exposure (C_{max} and AUC) of the active metabolite in COPD patients is approximately 2-fold higher as compared to healthy subjects. Revefenacin C_{max} was 0,16 ng/ml (0,11) and AUC was 0,22 ng·hr/ml (0,20) at steady-state after inhaled revefenacin 175 µg dose in COPD patients. C_{max} of the active metabolite was 0,20 ng/ml (0,13) and AUC was 0,69 ng·hr/ml (0,53) at steady-state after inhaled revefenacin 175 µg dose in COPD patients.

Revefenacin and its active metabolite exposure increased in a slightly greater than dose proportional manner with increasing revefenacin dose.

After single or multiple once-daily dosing of revefenacin, both AUC and C_{max} of revefenacin and its active metabolite increased by approximately 11-fold over the 88 to 700 µg (8-fold) dose range.

Absorption

Following inhaled administration of revefenacin in healthy subjects or COPD patients, C_{max} of revefenacin and its active metabolite occurred at the first post-dose sampling time which

ranged from 14 to 41 minutes after start of nebulization. The absolute bioavailability following an oral dose of revefenacin is low (< 3 %).

Distribution

Following intravenous administration to healthy subjects, the mean steady-state volume of distribution of revefenacin was 218 L suggesting extensive distribution to tissues. *In vitro* protein binding of revefenacin and its active metabolite in human plasma was on average 71 % and 42 %, respectively.

Elimination

The terminal half-life of revefenacin and its active metabolite after once-daily dosing of revefenacin in COPD patients is 22 to 70 hours.

Metabolism

In vitro and *in vivo* data showed that revefenacin is primarily metabolized via hydrolysis of the primary amide to a carboxylic acid forming its major active metabolite. Following inhaled administration of revefenacin in COPD patients, conversion to its active metabolite occurred rapidly, and plasma exposures of the active metabolite exceeded those of revefenacin by approximately 4- to 6-fold (based on AUC). The active metabolite is formed by hepatic metabolism and possesses activity at target muscarinic receptors that is lower (approximately one-third to one-tenth) than that of revefenacin. It could potentially contribute to systemic antimuscarinic effects at therapeutic doses.

Excretion

Following administration of a single intravenous dose of radio-labeled revefenacin to healthy male subjects, approximately 54 % of total radioactivity was recovered in the faeces and 27 % was excreted in the urine. Approximately 19 % of the administered radioactive dose was

recovered in the faeces as the active metabolite. Following administration of a single radio-labeled oral dose of revefenacin, 88 % of total radioactivity was recovered in the faeces and < 5 % was present in urine, suggesting low oral absorption. There was minimal renal excretion (< 1 %) of revefenacin and its active metabolite following inhaled administration of revefenacin in COPD patients.

Specific Populations

Population pharmacokinetic analysis showed no evidence of a clinically significant effect of age (44 to 79 years), gender (59 % male), smoking status (42 % current smoker), or weight (46 to 155 kg) on systemic exposure of revefenacin and its active metabolite.

Patients with Hepatic Impairment

The pharmacokinetics of revefenacin was evaluated in subjects with moderate hepatic impairment (Child-Pugh score of 7-9). There was no increase in C_{max} of revefenacin and 1,5-fold increase in C_{max} of the active metabolite. There was 1,2-fold increase in AUC of revefenacin and up to 4,7-fold increase in AUC of the active metabolite. Revefenacin has not been evaluated in subjects with severe hepatic impairment.

Patients with Renal Impairment

The pharmacokinetics of revefenacin was evaluated in subjects with severe renal impairment (CrCl <30 ml/min). There was 1,5-fold increase in C_{max} of revefenacin and up to 2-fold increase in C_{max} of the active metabolite. There was up to 2,3-fold increase in AUC_{inf} of revefenacin; the active metabolite exposure (AUC_{inf}) was increased by up to 2,5-fold. Revefenacin has not been evaluated in subjects with end-stage renal disease.

Medicine Interaction Studies

Revefenacin and Cytochrome P450

Neither revefenacin nor its active metabolite inhibits the following cytochrome P450 isoforms: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. Neither revefenacin nor its active metabolite induces CYP1A2, CYP2B6, and CYP3A4/5.

Revefenacin and Efflux Transporters

Revefenacin is a substrate of P-gp and BCRP. Neither revefenacin nor its active metabolite is an inhibitor of these efflux transporters.

Revefenacin and Uptake Transporters

The active metabolite of revefenacin is a substrate of OATP1B1 and OATP1B3. Neither revefenacin nor its active metabolite is an inhibitor of the uptake transporters OATP1B1, OATP1B3, OAT1, OAT3, or OCT2.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year inhalation studies in Sprague-Dawley rats and CD1 mice were conducted to assess the carcinogenic potential of revefenacin. No evidence of tumorigenicity was observed in male and female rats at inhaled doses up to 338 mcg/kg/day (approximately 35 times the MRHD based upon summed AUCs for revefenacin and its active metabolite). No evidence of tumorigenicity was observed in male and female mice at inhaled doses up to 326 µg/kg/day (approximately 40 times the MRHD based on summed AUCs for revefenacin and its active metabolite).

Revefenacin and its active metabolite were negative for mutagenicity in the Ames test for bacterial gene mutation. Revefenacin was negative for genotoxicity in the *in vitro* mouse lymphoma assay and *in vivo* rat bone marrow micronucleus assay.

There were no effects on male or female fertility and reproductive performance in rats at subcutaneous revefenacin doses up to 500 µg/kg/day (approximately 30 times the MRHD on an mg/m^2 basis for revefenacin).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid

Sodium chloride

Sodium citrate

Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store FENRI in the protective foil pouch.

Store at or below 25 °C. Protect from direct sunlight and excessive heat.

The FENRI solution unit-dose vial should only be removed from the foil pouch and opened IMMEDIATELY BEFORE USE. The vial and any residual content should be discarded after use.

Discard any solution that is not clear and colourless.

In-use period of 14 days.

FENRI should only be administered via a standard jet nebuliser connected to an air compressor with an adequate airflow and equipped with a mouthpiece.

Do not swallow or inject FENRI.

6.5 Nature and contents of container

FENRI is supplied as 3 ml of revefenacin solution packaged in a unit-dose low-density polyethylene vial overwrapped in a foil pouch. Each vial contains 175 µg of revefenacin in 3

ml of an isotonic, sterile aqueous solution containing sodium chloride, citric acid, sodium citrate, and water for injection at pH 5,0.

Pack size:

Each vial is overwrapped in a foil pouch and supplied in cartons containing either 30 individually pouched unit-dose vials or 7 individually pouched unit-dose vials.

6.6 Special precautions for disposal and other handling

No special precautions are required.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Mylan (Pty) Ltd

4 Brewery Street

Isando

1609

8 REGISTRATION NUMBERS

55/5.4/0036

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 February 2023

10 DATE OF REVISION OF THE TEXT