

NEW ZEALAND DATA SHEET

ENABLEX®

Darifenacin (as hydrobromide). 7.5 mg and 15 mg Modified-Release Tablets

Description and Composition

Pharmaceutical form

Modified-release tablets.

Enablex 7.5 mg modified-release tablets are round, shallow, convex white tablets and are identified with 'DF' on one side and '7.5' on the reverse.

Enablex 15 mg modified-release tablets are round, shallow, convex light-peach-coloured tablets and are identified with 'DF' on one side and '15' on the reverse.

Active substance

Darifenacin hydrobromide; (S)-2-{1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide hydrobromide

Therapeutic indications

Enablex is indicated for the treatment of overactive bladder. Symptoms of overactive bladder include urgency, urge urinary incontinence and frequency.

Dosage and administration

Dosage

General target population

Adults

The recommended starting dose is 7.5 mg daily. For those patients requiring greater symptom relief, the dose may be increased to 15 mg daily as early as two weeks after starting therapy, based on individual response.

Special populations

Geriatric patients

No dose adjustment is required in elderly patients (see Clinical pharmacology).

Paediatric patients No studies have been performed in children. Therefore, until more information is available, Enablex is not recommended for use in children.

Renal impairment

No dose adjustment is required in patients with impaired renal function (see Clinical pharmacology).

Hepatic impairment

There is a risk of increased exposure in this population (see Clinical pharmacology), however, no dose adjustment is required in patients with mild hepatic impairment (Child Pugh A). The daily dose of Enablex should not exceed 7.5 mg in patients with moderate hepatic impairment (Child Pugh B). Enablex is not recommended for use in patients with severe hepatic impairment (Child Pugh C).

Contraindications

Enablex is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients.
- Urinary retention.
- Gastric retention.
- Uncontrolled narrow-angle glaucoma.

Warnings and precautions

Enablex should be administered with caution to patients with clinically significant bladder outflow obstruction, risk for urinary retention, severe constipation (defined as two or less bowel movements per week), gastrointestinal obstructive disorders, such as pyloric stenosis (see Contraindications) or risk of decreased gastrointestinal motility.

Enablex should be used with caution in patients being treated for narrow-angle glaucoma (see Contraindications).

As with other antimuscarinics, patients should be instructed to discontinue Enablex/Emselex and seek immediate medical attention if they experience edema of the tongue or larynx, or difficulty breathing. (see Adverse effects)

Interactions

Effects of other medicinal products on darifenacin

Darifenacin metabolism is primarily mediated by the cytochrome P450 enzymes CYP2D6 and CYP3A4. Therefore, inhibitors of these enzymes may alter darifenacin pharmacokinetics (see also Pharmacokinetic properties).

CYP2D6 inhibitors

No special dosing requirements are necessary in the presence of CYP2D6 inhibitors. Darifenacin exposure following 30 mg once daily (two times greater than the recommended daily dose) at steady state was 33% higher in the presence of potent CYP2D6 inhibitor, paroxetine 20 mg.

CYP3A4 inhibitors

No special dosing requirements are necessary in the presence of moderate CYP3A4 inhibitors (e.g. fluconazole and erythromycin). The daily dose of darifenacin should not exceed 7.5 mg when co-administered with potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, miconazole, troleandomycin, nefazadone and ritonavir).

CYP450 mixed inhibitor

The mean C_{max} and AUC of darifenacin following 30 mg once daily at steady state were 42% and 34% higher, respectively, in the presence of cimetidine, a mixed CYP450 enzyme inhibitor.

P-glycoprotein inhibitors

Darifenacin is a substrate of the drug efflux transporter P-glycoproteins. The in vivo effect of P-glycoproteins inhibition on darifenacin exposure has not been studied.

Effects of darifenacin on other medicinal products

CYP2D6 substrates

Caution should be exercised when darifenacin is used concomitantly with medications that are predominantly metabolised by CYP2D6 and which have a narrow therapeutic window, such as flecainide, thioridazine, or tricyclic antidepressants such as imipramine.

CYP3A4 substrates

Darifenacin had no clinically relevant effect on the exposure of the CYP3A4 substrate midazolam and had no effect on the pharmacokinetics of the oral contraceptives levonorgestrel or ethinylestradiol.

Other medicinal products

Warfarin

Standard therapeutic prothrombin time monitoring for warfarin should be continued. The effect of warfarin on prothrombin time was not altered when co-administered with darifenacin.

Digoxin

Standard therapeutic drug monitoring for digoxin should be continued. Darifenacin 30 mg once daily (two times greater than the recommended daily dose) co-administered with digoxin at steady state resulted in a small increase in digoxin exposure.

Therapeutic drug monitoring for digoxin should be performed when initiating and ending darifenacin treatment as well as changing the darifenacin dose.

Antimuscarinic agents

The concomitant use of Enablex with other antimuscarinic agents may increase the frequency and/or severity of antimuscarinic pharmacological effects such as dry mouth, constipation and blurred vision.

Pregnancy and breast-feeding

Pregnancy

There are no studies of darifenacin in pregnant women. Enablex should be used during pregnancy only if the benefit to the mother outweighs the potential risk to the foetus.

Breast-feeding

Darifenacin is excreted into the milk of rats. It is not known whether darifenacin is excreted into human milk and therefore caution should be exercised before Enablex is administered to a breast-feeding woman.

Driving and using machines

No studies of the effects of Enablex on the ability to drive and use machines have been performed. However, antimuscarinics such as Enablex may produce dizziness or blurred vision. Patients should not drive vehicles, use machines or perform other tasks which require alertness if they experience these adverse events. **Adverse effects**

Consistent with the pharmacological profile, the most common adverse drug reactions (ADRs) in three Phase III studies (n=1069) were dry mouth (20.2% and 35.0% for the 7.5 mg and 15 mg dose, respectively vs. 8.0% placebo) and constipation (14.8% and 21.0% for the 7.5 mg and 15 mg dose, respectively vs. 5.4% placebo). However, the patient discontinuation rates due to these adverse drug reactions were low (dry mouth: 0% and 0.9% for the 7.5 mg and 15 mg dose, respectively, constipation: 0.6% and 1.2% for the 7.5 mg and 15 mg dose, respectively).

Adverse drug reactions from pivotal clinical trials (Table 1) with doses of 7.5 mg and 15 mg darifenacin, are listed according to system organ classes in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$) very rare ($< 1/10,000$), including isolated reports.

Most ADRs were mild or moderate and did not result in discontinuation in the majority of the patients. The incidence of serious adverse events with 7.5 mg and 15 mg darifenacin once daily was similar to placebo.

Table 1 Adverse drug reactions observed in Clinical trials

Infections and infestations	
Uncommon	Urinary tract infection
Psychiatric disorders	
Uncommon	Insomnia, thinking abnormal
Nervous system disorders	
Common	Headache
Uncommon	Dizziness, dysgeusia, somnolence
Eye disorders	
Common	Dry eye
Uncommon	Visual impairment
Vascular disorders	
Uncommon	Hypertension
Respiratory, thoracic and mediastinal disorders	
common	Nasal dryness
Uncommon	Dyspnoea, cough, rhinitis
Gastrointestinal disorders	
Very common	Constipation, dry mouth
Common	Abdominal pain, nausea, dyspepsia
Uncommon	Flatulence, diarrhoea, mouth ulceration
Skin and subcutaneous tissue disorders	
Uncommon	Rash, dry skin, pruritus, hyperhidrosis
Renal and urinary disorders	
Uncommon	Urinary retention, urinary tract disorder, bladder pain
Reproductive system and breast disorders	
Uncommon	Erectile dysfunction, vaginitis
General disorders and administration site conditions	
Uncommon	Oedema peripheral, asthenia, face oedema, oedema
Investigations	
Uncommon	Aspartate aminotransferase (SGOT) increased, alanine aminotransferase (SGPT) increased
Injury, poisoning, and procedural complications	
Uncommon	Accidental injury

In one flexible dose titration study (n=395) evaluating the dosing regimen approved for marketing, the overall ADR profile was comparable to that observed in the pooled analysis of three pivotal fixed-dose studies, with the most relevant difference in the very common ADRs. Dry mouth was reported in 18.7% of patients treated with darifenacin and in 8.7% of those treated with placebo. Constipation was reported in 20.9% and 7.9% of patients treated with darifenacin and placebo, respectively. The discontinuation rates due to these ADRs in patients treated with darifenacin were low (dry mouth: 0.7%; constipation: 2.2%).

The incidence of adverse events with the doses of Enablex 7.5 mg and 15 mg decreased during the treatment period up to 6 months. A similar trend is also seen for the discontinuation rates.

Adverse drug reaction from post-marketing experience

The following adverse drug reactions have been identified based on post-marketing spontaneous reports:

- Generalized Hypersensitivity reactions.
- Angioedema with or without airway obstruction (see also section 6 Warnings and precautions) have been reported.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency (frequency unknown).

Overdosage

Overdosage with darifenacin can potentially lead to severe antimuscarinic effects and should be treated accordingly. Therapy should be aimed at reversing the antimuscarinic symptoms under careful medical supervision. The use of agents such as physostigmine can assist in reversing such symptoms.

Clinical pharmacology

ATC Code Pharmacotherapeutic group: Urinary antispasmodic, ATC code: G04B D10.

Mechanism of action

Darifenacin is a potent muscarinic M3 selective receptor antagonist that exhibits 9 to 59 fold selectivity for the human M3 receptor over human M1, M2, M4 and M5 receptors. The M3 receptor is the major subtype that controls the detrusor muscle contraction in the bladder.

Pharmacodynamic properties

In cystometric studies performed with darifenacin in patients with involuntary bladder contractions increased bladder capacity as demonstrated by an increased volume threshold for unstable contractions and diminished frequency of unstable detrusor contractions after darifenacin treatment was shown. These findings are consistent with the clinical observations that darifenacin increases bladder capacity and decreases urinary urgency and the frequency of both incontinence and micturitions.

Consistent with the selectivity profile, the incidence of central nervous system adverse events at all doses was similar to placebo. The incidence of cardiovascular adverse events such as tachycardia was less than 1% for all doses and did not increase with dose. As expected from

this class of drugs, prolonged colonic transit and reduced salivary flow were observed in a dose-dependent manner.

The results of pooled analysis from three phase III clinical studies are described in the Clinical studies section.

Preclinical studies provide evidence that at concentrations equivalent to therapeutic concentrations, darifenacin has no effect at cardiac ion channels. However, at supra-therapeutic concentrations, darifenacin has a profile consistent with a mixed ion channel blocker. In a study performed in anaesthetized dogs, changes in the duration of action potential were observed with free plasma levels of 25 nM which corresponds to approximately 83 times the C_{max} at MRHD

Pharmacokinetic properties

Absorption

The mean oral bioavailability of darifenacin at steady state is estimated to be 15% and 19% for 7.5 and 15 mg tablets, respectively. Darifenacin is completely (> 98%) absorbed after oral administration, although oral bioavailability is limited by first-pass metabolism (see Metabolism). Maximum plasma levels are reached approximately 7 hours after administration of the modified-release tablets and steady-state plasma levels are achieved by the sixth day of administration. At steady state, peak-to-trough fluctuations in darifenacin concentrations are small (peak to trough fluctuations: 0.87 for 7.5 mg and 0.76 for 15 mg), thereby maintaining therapeutic plasma levels over the dosing interval. Food had no effect on darifenacin pharmacokinetics during multiple-dose administration of modified-release tablets.

Distribution

Darifenacin is a lipophilic base and is 98% bound to plasma proteins (primarily to alpha-1-acid-glycoprotein). The steady-state volume of distribution (V_{ss}) is estimated to be 163 litres.

Biotransformation/Metabolism

Darifenacin is extensively metabolised by the liver following oral administration.

Metabolism is mediated by cytochrome P450 enzymes CYP2D6 and CYP3A4. The three main metabolic routes are as follows:

1. monohydroxylation in the dihydrobenzofuran ring;
2. dihydrobenzofuran ring opening;
3. N-dealkylation of the pyrrolidine nitrogen.

The initial products of the hydroxylation and N-dealkylation pathways are major circulating metabolites but none contributes significantly to the overall clinical effect of darifenacin.

Variability in metabolism: A subset of individuals (approximately 7% of the Caucasian population) are devoid of CYP2D6 enzyme activity. Therefore, the metabolism of darifenacin in these poor metabolisers will be principally mediated via CYP3A4. Individuals with full CYP2D6 activity are referred to as extensive metabolisers. The darifenacin ratios (poor metabolisers: extensive metabolisers) for C_{max} and AUC following darifenacin 15 mg once-daily at steady state were 1.9 and 1.7, respectively.

Population pharmacokinetic analyses of Phase 3 data indicated that on average steady-state exposure is 66% higher in poor metabolisers than in extensive metabolisers. However, there is considerable overlap between the ranges of exposures seen in these two populations (see

Dosage and administration) and clinical experience confirms that there are no special dosing requirements for poor metabolisers.

Elimination

Following administration of an oral dose of ¹⁴C-darifenacin solution to healthy volunteers, approximately 60% of the radioactivity was recovered in the urine and 40% in the faeces. Only a small percentage of the excreted dose was unchanged darifenacin (3%). Estimated darifenacin clearance is 40 litres/hour for extensive metabolisers and 32 litres/hour for poor metabolisers. The elimination half-life of darifenacin following chronic dosing is approximately 13-19 hours.

Special population

Gender

No special dosage requirements are necessary based on gender. A population pharmacokinetic analysis of patient data indicated that darifenacin exposure was 23% lower in males than females.

In clinical studies, the safety and efficacy profiles were not affected by gender.

Geriatric patients

There are no special dosage requirements for the elderly.

A population pharmacokinetic analysis of patient data indicated a trend for clearance to decrease with age (19% per decade based on Phase III population pharmacokinetic analysis of patients aged 60-89 years). The safety and efficacy profiles were not affected by age.

Paediatric patients

The pharmacokinetics of darifenacin have not been studied in the paediatric population.

Renal insufficiency

There are no special dosage requirements for patients with renal impairment. A small study of subjects (n=24) with varying degrees of renal impairment (creatinine clearance between 10 and 136 ml/min) given darifenacin 15 mg once daily to steady state demonstrated no relationship between renal function and darifenacin clearance.

Hepatic insufficiency

Darifenacin pharmacokinetics were investigated in subjects with mild (Child Pugh A) or moderate (Child Pugh B) impairment of hepatic function given darifenacin 15 mg once daily to steady state. Mild hepatic impairment had no effect on the pharmacokinetics of darifenacin. However, protein binding of darifenacin was affected by moderate hepatic impairment. After adjusting for plasma protein binding, unbound darifenacin exposure was estimated to be 4.7-fold higher in subjects with moderate hepatic impairment than subjects with normal hepatic function.

Clinical studies

The table 1 shows the primary and secondary pooled efficacy results after 12 weeks for the 7.5 and 15 mg darifenacin once-daily fixed doses.

Table 2 Pooled analysis of results from three phase III clinical studies assessing fixed doses of 7.5 and 15 mg Enablex

	N	Median base-line	Median change from baseline	Median difference from placebo	95% CI	P value
No of incontinence episodes per week						
Placebo (1002 & 1041)	271	16.6	-7.0	--	--	--
Darifenacin 7.5 mg <i>od</i>	335	16.0	-8.8	-2.0*	(-3.6, -0.7)	0.004
Placebo (1002, 1001 & 1041)	384	16.6	-7.5	--	--	--
Darifenacin 15 mg <i>od</i>	330	16.9	-10.6	-3.2*	(-4.5, -2.0)	< 0.001
No of episodes of urgency per day						
Placebo (1002 & 1041)	271	8.2	-1.0	--	--	--
Darifenacin 7.5 mg <i>od</i>	335	8.0	-2.0	-0.8*	(-1.3, -0.4)	< 0.001
Placebo (1002, 1001 & 1041)	384	8.4	-1.2	--	--	--
Darifenacin 15 mg <i>od</i>	330	8.4	-2.3	-0.9*	(-1.3, -0.5)	< 0.001
No of micturitions per day						
Placebo (1002 & 1041)	271	10.1	-0.9	--	--	--
Darifenacin 7.5 mg <i>od</i>	335	10.2	-1.6	0.8*	(-1.1, -0.4)	< 0.001
Placebo (1002, 1001 & 1041)	385	10.2	-1.0	--	--	--
Darifenacin 15 mg <i>od</i>	330	10.6	-1.9	0.8*	(-1.1, -0.4)	< 0.001
Volume of urine passed per void (mL)						
Placebo (1002 & 1041)	255	162	8	--	--	--
Darifenacin 7.5 mg <i>od</i>	322	161	15	10*	(3, 17)	0.007
Placebo (1002, 1001 & 1041)	366	157	6	--	--	--
Darifenacin 15 mg <i>od</i>	320	155	27	20*	(14, 27)	<0.001

No of incontinence episodes per week resulting in a change of clothing or pad						
Placebo (1002 & 1041)	270	7.4	-2.0	--	--	--
Darifenacin 7.5 mg <i>od</i>	333	8.1	-4.0	-1.8*	(-2.8, -0.9)	< 0.001
Placebo (1002, 1001 & 1041)	378	7.2	-2.7	--	--	--
Darifenacin 15 mg <i>od</i>	324	8.0	-4.8	-2.0*	(-3.0, -1.1)	< 0.001

od once daily

* The difference between darifenacin and placebo was statistically significant ($p < 0.05$, stratified Wilcoxon test)

Effective treatment can be expected within two weeks.

At two weeks, darifenacin 7.5 mg and 15 mg both produced statistically significant greater improvements in the number of incontinence episodes per week compared to placebo and these were maintained through the course of treatment.

In a clinical study of 12 months duration, the improvements from baseline for the number of incontinence episodes per week were sustained. Improvements from baseline were also sustained over 12 months for the key secondary efficacy endpoints of the number of micturitions per day, the episodes of urgency per day and the average volume of urine passed per void.

On quality of life measures darifenacin 7.5 mg and 15 mg were associated with statistically and clinically meaningful improvements over placebo in the incontinence impact, role limitations, social limitations and severity measures domains as defined by the King's Health Questionnaire (KHQ). Darifenacin 15 mg was also associated with improvements on the emotions domain of the KHQ.

Electrophysiology

The effect of six-day treatment with 15 mg and 75 mg Enablex on QT/QTc interval was evaluated in a multiple-dose, double-blind, randomized, placebo- and active-controlled (moxifloxacin 400 mg) parallel-arm design study in 179 healthy adults (44% male, 56% female) aged 18 to 65. Subjects included 18% poor metabolisers and 82% extensive metabolisers. The QT interval was measured over a 24-hour period both pre-dosing and at steady state.

The 75 mg Enablex dose was chosen because this achieves exposure similar to that observed in CYP2D6 poor metabolizers administered the highest recommended dose (15 mg) of darifenacin in the presence of a potent CYP3A4 inhibitor. At the doses studied, Enablex did not result in QT/QTc interval prolongation at any time during the steady state, while moxifloxacin treatment resulted in a mean increase from baseline QTcF of about 7.0 msec when compared to placebo.

In this study, darifenacin 15 mg and 75 mg doses demonstrated a mean heart rate change of 3.1 and 1.3 bpm, respectively, when compared to placebo. However, in the phase II/III clinical studies, the change in median heart rate following treatment with Enablex was no different from placebo.

Non-clinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies , repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

Carcinogenicity studies with darifenacin were conducted in mice and rats. No evidence of drug related carcinogenicity was revealed in a 24-month study in mice at dietary doses up to 100 mg/kg/day or approximately 32 times the estimated human free AUC_{0-24h} (Area under the Curve) reached with 15 mg, the maximum recommended human dose (AUC at MRHD) and in a 24-month study in rats at doses up to 15 mg/kg/day or up to approximately 12 times the AUC at MRHD in female rats and approximately 8 times the AUC at MRHD in male rats.

Darifenacin was not mutagenic in the bacterial mutation assays (Ames test) and the Chinese hamster ovary assay, and not clastogenic in the human lymphocyte assay, and the *in vivo* mouse bone marrow cytogenetics assay.

There was no evidence for effects on fertility in male or female rats treated at oral doses up to 50 mg/kg/day. Exposures in this study correspond to approximately 78 times the AUC at MRHD.

Darifenacin was not teratogenic in rats and rabbits at doses up to 50 and 30 mg/kg/day respectively. At the dose of 50 mg/kg in rats, there was a delay in the ossification of the sacral and caudal vertebrae which was not observed at the lower doses of 3 and 10 mg/kg. Exposure in this study at 50 mg/kg corresponds to approximately 59 times the AUC at MRHD. At the dose of 30 mg/kg in rabbits, darifenacin was shown to increase post-implantation loss but not at the lower doses tested (3 and 10 mg/kg). Exposure to unbound drug at 30 mg/kg in this study corresponds to approximately 28 times the AUC at MRHD. In perinatal and postnatal studies in rats, dystocia, increased fetal deaths in utero and toxicity to post-natal development (pup body weight and development land marks) were observed at systemic exposure levels up to 11 times the AUC_{0-24h} of free plasma concentration at MRHD

Pharmaceutical information

List of excipients

7.5 mg modified-release tablets

Tablet core: calcium hydrogen phosphate (anhydrous), hypromellose, magnesium stearate.

Tablet coating: hypromellose, titanium dioxide (E171), polyethylene glycol, talc.

15 mg modified-release tablets

Tablet core: calcium hydrogen phosphate (anhydrous), hypromellose, magnesium stearate.

Tablet coating: hypromellose, polyethylene glycol, talc, titanium dioxide (E171), red iron oxide (E172), yellow iron oxide (E172).

Incompatibilities

Not applicable.

Shelf-life

Three years.

Special precautions for storage

Do not store above 30° Enablex must be kept out of the reach and sight of children.

Special precautions for disposal

No special requirements.

Medicine classification

Prescription Medicine

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