Enablex ® (Darifenacin)

PRESENTATIONS

Enablex® 7.5mg Prolonged-release Tablets are round, shallow, convex, white tablets and are identified with “DF” on one side and “7.5” on the other. Each tablet contains 7.5mg of darifenacin (as hydrobromide).

Enablex® 15mg Prolonged-release Tablets are round, shallow, convex, light-peach-coloured tablets and are identified with “DF” on one side and “15” on the reverse. Each tablet contains 15mg of darifenacin (as 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

Adults

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

Geriatric patients

No dose adjustment is required in elderly patients (*see section 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 section 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).

Method of Administration

Enablex prolonged-release tablets should be taken once daily with liquid. They may be taken with or without food, and should be swallowed whole and not chewed, divided or crushed.

Contra-indications

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
- Myasthenia gravis
- Severe hepatic impairment (Child Pugh C)
- Severe ulcerative colitis
- Toxic megacolon
- Concomitant treatment with potent CYP3A4 inhibitors (*see INTERACTIONS*)

WARNINGS AND PRECAUTIONS FOR USE

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

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

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

Enablex should be used with caution in patients with risk of decreased gastrointestinal motility, gastroesophageal reflux and/or who are concurrently taking medicinal products (such as oral bisphosphonates) that can cause or exacerbate esophagitis.

Safety and efficacy have not yet been established in patients with a neurogenic cause for detrusor overactivity.

Caution should be used when prescribing antimuscarinics to patients with pre-existing cardiac diseases.

As with other antimuscarinics, patients should be instructed to discontinue Enablex and seek immediate medical attention if they experience edema of the tongue or laropharynx, or difficulty breathing (*see section ADVERSE DRUG REACTIONS*).

Driving and using machines

No studies of the effects of Enablex on the ability to drive and use machines have been performed. However, 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.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS

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 section CLINICAL PHARMACOLOGY*).

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

Darifenacin should not be used together with potent CYP3A4 inhibitors (*see section 4.3*) such as protease inhibitors (e.g. ritonavir), ketoconazole and itraconazole. Potent P-glycoprotein inhibitors such as ciclosporin and verapamil should also be avoided. Co-administration of darifenacin 7.5 mg with the potent CYP3A4 inhibitor ketoconazole 400mg resulted in a 5-fold increase in steady-state darifenacin AUC. In subjects who are poor metabolisers, darifenacin exposure increased approximately 10-fold. Due to a greater contribution of CYP3A4 after higher darifenacin doses, the magnitude of the effect is expected to be even more pronounced when combining ketoconazole with darifenacin 15 mg.

When co-administered with moderate CYP3A4 inhibitors such as erythromycin, clarithromycin, telithromycin, fluconazole and grapefruit juice, the recommended starting dose of darifenacin should be 7.5 mg daily. The dose may be titrated to 15 mg daily to obtain an improved clinical response provided the dose is well tolerated. Darifenacin AUC24 and Cmax from 30 mg once daily dosing in subjects who are extensive metabolisers were 95% and 128% higher when erythromycin (moderate CYP3A4 inhibitor) was co-administered with darifenacin than when darifenacin was taken alone.

Enzyme inducers
Substances that are inducers of CYP3A4, such as rifampicin, carbamazepine, barbiturates and St John´s wort (Hypericum perforatum) are likely to decrease the plasma concentrations of darifenacin.

CYP450 mixed inhibitor
The mean Cmax 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 treatment resulted in a modest increase in the exposure of the CYP3A4 substrate midazolam. The interaction with midazolam lacks clinical relevance but is indicative of a slight CYP3A4 inhibition by darifenacin.

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
Therapeutic drug monitoring for digoxin should be performed when initiating and ending darifenacin treatment as well as changing the darifenacin dose. 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 (AUC: 16% and Cmax: 20%). The increase in digoxin exposure could be caused by competition between darifenacin and digoxin for P-glycoprotein. Other transporter-related interactions cannot be excluded.

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 LACTATION

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 nursing woman.

UNDESIRABLE EFFECTS

Consistent with the pharmacological profile, the most commonly reported adverse drug reactions (ADRs) in three Phase III studies (n=1069) were dry mouth (20.2% and 35% for the 7.5 mg and 15 mg dose, respectively, 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% - 1.2% for 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 (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥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 Uncommon	Dry eye Visual impairment
Vascular disorders	
Uncommon	Hypertension
Respiratory, thoracic and mediastinal disorders	
Common Uncommon	Nasal dryness Dyspnoea, cough, rhinitis
Gastrointestinal disorders	
Very common Common Uncommon	Constipation, dry mouth Abdominal pain, nausea, dyspepsia 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 15mg decreased during the treatment period up to 6 months. A similar trend is also seen for the discontinuation rates.

Adverse drug reactions 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 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).

SYMPTOMS AND TREATMENT OF OVERDOSE

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

Pharmacodynamic

Pharmacotherapeutic group: Urinary antispasmodic, ATC code: G04B D10

Darifenacin is a selective muscarinic M3 receptor antagonist (M3 SRA) *in vitro*. The M3 receptor is the major subtype that controls urinary bladder muscle contraction. It is not known whether this selectivity for the M3 receptor translates into any clinical advantage when treating symptoms of overactive bladder syndrome.

Cystometric studies performed with darifenacin in patients with involuntary bladder contractions showed increased bladder capacity, increased volume threshold for unstable contractions and diminished frequency of unstable detrusor contractions.

Treatment with Enablex administered at dosages of 7.5 mg and 15 mg daily has been investigated in four double-blind, Phase III, randomised, controlled clinical studies in male and female patients with symptoms of overactive bladder. As seen in Table 2 below, a pooled analysis of 3 of the studies for the treatment with both Enablex 7.5 mg and 15 mg provided a statistically significant improvement in the primary endpoint, reduction in incontinence episodes, versus placebo.

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

Dose	N	Incontinences episodes per week				95% CI	P value[2]
		Baseline (median)	Week 12 (median)	Change from baseline (median)	Difference from placebo[1] (median)		
Placebo	271	16.6	7.9	-7.0 (-54%)	--	--	--
Darifenacin 7.5 mg *od*	335	16.0	4.9	-8.8 (-68%)	-2.0	(-3.6, -0.7)	0.004
Placebo	384	16.6	6.4	-7.5 (-58%)	--	--	--
Darifenacin 15 mg *od*	330	16.9	4.1	-10.6 (-77%)	-3.2	(-4.5, -2.0)	<0.001

[1] Hodges Lehmann estimate: median difference from placebo in change from baseline
[2] Stratified Wilcoxon test for difference from placebo.

Enablex 7.5 mg and 15 mg doses significantly reduced both the severity and number of urinary urgency episodes and the number of micturitions, while significantly increasing the mean volume voided from baseline.

Enablex 7.5 mg and 15 mg were associated with statistically significant improvements over placebo in some aspects of quality of life as measured by the Kings Health Questionnaire including incontinence impact, role limitations, social limitations and severity measures.

For both doses of 7.5 mg and 15 mg, the percentage median reduction from baseline in the number of incontinence episodes per week was similar between males and females. The observed differences from placebo for males in terms of percentage and absolute reductions in incontinence episodes was lower than for females.

The effect of treatment with 15 mg and 75mg of darifenacin on QT/QTc interval was evaluated in a study in 179 healthy adults (44% male: 56% females) aged 18 to 65 for 6 days (to steady state). Therapeutic and supra-therapeutic doses of darifenacin resulted in no increase in QT/ QTc interval prolongation from baseline compared to placebo at maximum darifenacin exposure.

Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, 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} 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.

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 Biotransformation/Metabolism below). Maximum plasma levels are reached approximately 7 hours after administration of the prolonged-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 prolonged-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 (Vss) 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:

I monohydroxylation in the dihydrobenzofuran ring;
II dihydrobenzofuran ring opening;
III 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) is 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 Cmax 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 section 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.

PHARMACEUTICAL PARTICULARS

Shelf-life

3 years.

Special Precautions for Storage

Do not store above 30°C.

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

Nature and Contents of Container

Enablex® 7.5mg Prolonged-release Tablets are packed in blister packs containing 28 tablets.

Enablex® 15mg Prolonged-release Tablets are packed in blister packs containing 28 tablets.

Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

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

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Made by
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