

ENABLEX[®]

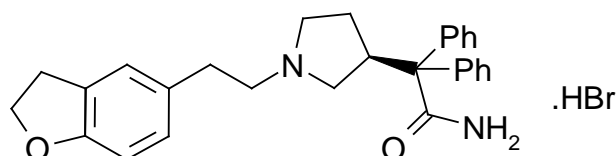
(darifenacin hydrobromide)

NAME OF DRUG

The active ingredient of Enablex is darifenacin hydrobromide.

Chemical name: (*S*)-2-{1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide hydrobromide

Chemical structure:



Molecular formula: C₂₈H₃₀N₂O₂.HBr

Molecular weight: 507.5

CAS registry no. 133099-07-7

DESCRIPTION

Darifenacin hydrobromide is a white to almost white monomorphic crystalline solid. The solubility of darifenacin hydrobromide in water is 6.03 mg/mL at 37°C, with a resulting pH of 5.5.

Enablex prolonged-release tablets are available in strengths of 7.5 mg and 15 mg darifenacin hydrobromide.

Excipients:

Enablex prolonged-release tablets 7.5 mg: calcium hydrogen phosphate anhydrous, hypromellose, magnesium stearate, Opadry White (00F18296).

Enablex prolonged-release tablets 15 mg: calcium hydrogen phosphate anhydrous, hypromellose, magnesium stearate, Opadry Yellow (00F12951), Opadry Red (00F15613).

PHARMACOLOGY

Pharmacodynamics

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

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 after darifenacin treatment. These findings are consistent with the clinical observations of reduced frequency of incontinence, reduced frequency of micturition, reduced frequency of urgency and increased functional bladder capacity.

Consistent with its 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.

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, randomised, 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 dose of Enablex was chosen because this achieves exposure similar to that observed in CYP2D6 poor metabolisers 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 steady state, while moxifloxacin treatment resulted in a mean increase from baseline QTcF of about 7.0 msec when compared to placebo.

Table 1 Change from baseline of QT/QTcF at PK Tmax

Interval (msec)	Active Treatment vs Placebo		
	Darifenacin 15 mg (95% CI)	Darifenacin 75 mg (95% CI)	Moxifloxacin 400 mg (95% CI)
QT	-4.9 (-10.6, -1.9)	-8.2 (-16.2, -0.2)	20.5* (13.2, 27.8)
QTcF	-0.4 (-4.8, 4.0)	-2.2 (-7.5, 3.0)	11.6* (6.9, 16.3)

Note: * p< 0.01

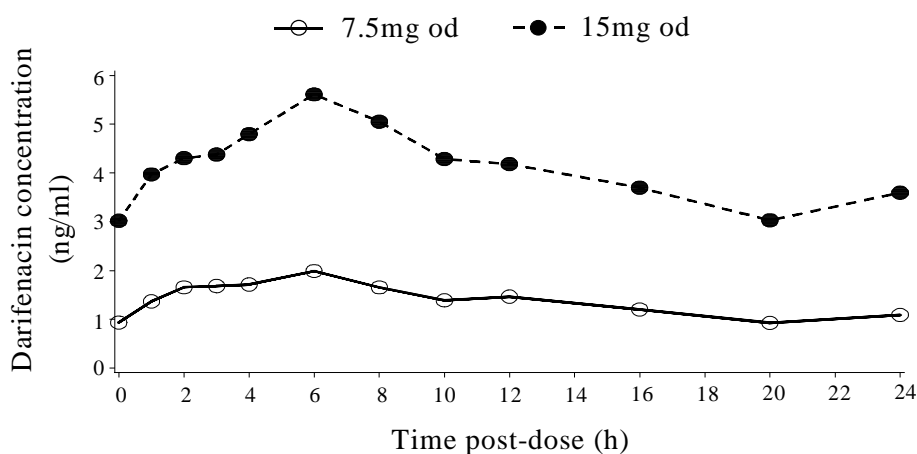
In this study, darifenacin 15 mg and 75 mg doses demonstrated a mean heart rate change of 3.1 and 1.3 bpm, respectively, when compared to placebo. However, in the phase II/III clinical studies, the change in median heart rate following treatment with Enablex was no different from placebo.

Pharmacokinetics

Absorption:

Darifenacin is rapidly and completely (>98%) absorbed after oral administration, although oral bioavailability is limited by first-pass metabolism (see “Metabolism”). The estimated mean oral bioavailability of darifenacin in extensive metabolisers at steady state is 15% and 19% for 7.5 and 15 mg prolonged-release tablets, respectively. 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 dosing. At steady state, peak-to-trough fluctuations in darifenacin concentrations are small, thereby maintaining therapeutic plasma levels over the 24 hour dosing interval (Figure 1).

Figure 1: Steady state darifenacin plasma concentration profile from once daily dosing with prolonged-release tablets in healthy subjects



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.

Based on free drug levels in animal cerebrospinal fluid and plasma, darifenacin shows negligible penetration of the blood-brain barrier.

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) are poor metabolisers of substrate for CYP2D6. 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.

Population pharmacokinetic analyses of Phase III 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 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 L/h for extensive metabolisers and 32 L/h for poor metabolisers. The estimated half-life for darifenacin following chronic dosing is 12.8 to 18.7 hrs.

The effect of food on pharmacokinetics:

Food had no effect on darifenacin pharmacokinetics during multiple-dose administration of prolonged-release tablets.

Gender influence on pharmacokinetics:

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.

Pharmacokinetics in elderly patients:

There are no special dosage requirements for the elderly. A Phase III population pharmacokinetic analysis of patient data (patients aged 60-89 years) indicated a trend for clearance to decrease with age by 19% per decade. The safety and efficacy profiles were not affected by age.

Pharmacokinetics in paediatric patients:

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

Pharmacokinetics in patients with impaired renal function:

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.

Pharmacokinetics in patients with impaired hepatic function:

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. The fraction of unbound darifenacin increased from 1.7% in subject with normal hepatic function to 4.5% in subject with 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 in subjects with normal hepatic function.

CLINICAL TRIALS

Enablex prolonged-release tablets were evaluated for the treatment of patients with overactive bladder whose signs and symptoms included urgency, urge urinary incontinence, increased frequency, nocturia and reduced functional bladder capacity in 4 randomised, placebo-controlled, multicentre, double-blind, 12-week studies. The majority of patients were white (94%) and female (84%), with a mean age of 58 years, range 19 to 93 years. 33% of patients were ≥ 65 years of age. These characteristics were well balanced across treatment groups. 60% of patients had never received prior pharmacotherapy for overactive bladder and the intentional randomisation of subjects known to be responsive to, or tolerant of, anticholinergic therapy was avoided.

The three fixed-dose studies included 1059 patients. Of this total, 337 and 334 patients were treated with Enablex prolonged-release tablets 7.5 mg daily and 15 mg daily, respectively. In addition, a dose-titration study included 395 patients, of whom 268 initially received Enablex prolonged-release tablets 7.5 mg daily with the option to increase to 15 mg daily after 2 weeks.

Tables 2 and 3 show the efficacy data from the placebo-controlled studies of patients treated with 7.5 and 15 mg once daily Enablex for 12 weeks. A significant decrease in symptoms of urge urinary incontinence was observed.

Table 2: Difference between Enablex (7.5mg and 15 mg) and placebo for the week 12 change from baseline (studies 1041, 1002 and 1001)

	Study 1041			Study 1002			Study 1001	
	Enablex 7.5mg	Enablex 15mg	Placebo	Enablex 7.5mg	Enablex 15mg	Placebo	Enablex 15mg	Placebo
No. of Patients	229	115	164	108	107	109	112	115
Incontinence Episodes Per Week								
Weekly episodes before treatment (median)	16.3	17.0	16.6	14.0	17.3	16.1	16.2	15.5
Weekly episodes after treatment (median)	5.0	5.0	8.0	4.0	3.9	7.7	3.2	4.5
Median absolute change from baseline	-9.0	-10.4	-7.6	-8.1	-10.4	-5.9	-11.4	-9.0
Percentage reduction in weekly episodes (median)	-68%	-73%	-56%	-69%	-77%	-46%	-83%	-71%
Difference between Enablex and Placebo (median) (95% C.I.)	-1.5 * (-3.0,-0.4)	-2.1 * (-3.5,-0.3)	-	-2.8 * (-4.8,-0.8)	-4.3 * (-6.7,-2.2)	-	-2.4* (-4.8,-0.01)	-
Micturitions Per Day [voluntary passing of urine]								
Daily micturitions before treatment (median)	10.1	10.1	10.1	10.3	11.0	10.1	10.5	10.4
Daily micturitions after treatment (median)	8.7	8.9	9.3	8.4	8.8	9.0	8.6	9.4
Median absolute change from baseline	-1.6	-1.7	-0.8	-1.7	-1.9	-1.1	-1.9	-1.2
Percentage reduction in daily micturitions (median)	-16%	-15%	-8%	-17%	-18%	-10%	-19%	-13%
Difference between Enablex and Placebo (median) (95% C.I.)	-0.8 * (-1.2,-0.4)	-0.9 * (-1.4,-0.4)	-	-0.5 (-1.1,0.0)	-0.7 * (-1.4,-0.1)	-	-0.5 (-1.02, 0.05)	-
Episodes Of Urgency Per Day								
Weekly episodes before treatment (median)	7.7	8.0	8.3	8.5	8.6	8.1	8.6	8.5
Weekly episodes after treatment (median)	5.5	6.0	7.0	5.9	5.2	6.5	6.2	6.6
Median absolute change from baseline	-2.0	-2.0	-0.9	-1.8	-2.3	-1.2	-2.6	-1.9
Percentage reduction in weekly episodes (median)	-29%	-29%	-13%	-29%	-27%	-16%	-33%	-25%
Difference between Enablex and Placebo (median) (95% C.I.)	-0.9 * (-1.5,-0.4)	-0.9 * (-1.5,-0.3)	-	-0.5 (-1.3,0.3)	-1.1 * (-1.9,-0.2)	-	-0.7 (-1.5,0.03)	-
Volume Of Urine Passed Per Void (mL)								
Volume before treatment (median)	160.2	151.8	162.4	161.7	157.3	162.2	155	147.1
Volume after treatment (median)	183.8	188.5	178.6	183.8	183.2	168.1	193	163.8
Median absolute change from baseline	14.9	30.9	7.6	16.8	23.6	7.1	26.7	4.6
Percentage increase in volume (median)	9%	20%	5%	10%	16%	4%	18%	3%
Difference between Enablex and Placebo (median) (95% C.I.)	9.1 * (0.4,17.8)	20.7 * (9.6,32.6)	-	9.2 (-1.1,18.9)	16.6 * (6.8,26.7)	-	20.1* (7.6,32.6)	-

*Indicates statistical significance difference against placebo (p<0.05, Wilcoxon rank-sum test)

Table 3: Difference between Enablex (7.5/15 mg) and placebo for the week 12 change from baseline (Study 1047)

	Study 1047	
	Enablex 7.5/15 mg	Placebo
No. of Patients	268	127
Incontinence Episodes Per Week		
Weekly episodes before treatment (median)	16.0	14.0
Weekly episodes after treatment (median)	7.0	7.0
Median absolute change from baseline	-8.2	-6.0
Percentage reduction in weekly episodes (median)	-63%	-48%
Difference between Enablex and Placebo (median) (95% C.I.)	-1.4* (2.9,-0.0)	
Micturitions Per Day [voluntary passing of urine]		
Daily micturitions before treatment (median)	9.9	10.4
Daily micturitions after treatment (median)	8.2	9.2
Median absolute change from baseline	-1.9	-1.0
Percentage reduction in daily micturitions (median)	-19%	-10%
Difference between Enablex and Placebo (median) (95% C.I.)	-0.8 * (-1.3,-0.3)	
Episodes Of Urgency Per Day		
Daily episodes before treatment (median)	8.3	8.0
Daily episodes after treatment (median)	6.2	6.7
Median absolute change from baseline	-2.3	-0.9
Percentage reduction in daily episodes (median)	-28%	-11%
Difference between Enablex and Placebo (median) (95% C.I.)	-1.2 * (-1.9,-0.6)	
Volume Of Urine Passed Per Void (mL)		
Volume before treatment (median)	173.7	177.2
Volume after treatment (median)	211.5	173.1
Median absolute change from baseline	18.8	6.6
Percentage increase in volume (median)	11%	5%
Difference between Enablex and Placebo (median) (95% C.I.)	13.3* (1.0,26.3)	

*Indicates statistical significance difference against placebo (p<0.05, Wilcoxon rank-sum test)

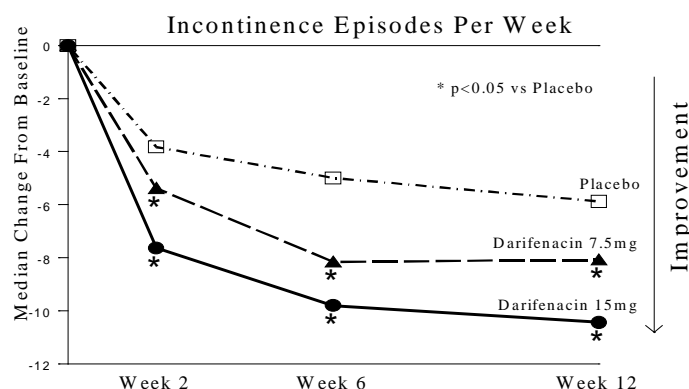
Incontinence responders (Table 4) were defined as patients who achieved a 50% or greater reduction from baseline in the number of incontinence episodes per week. Frequency responders (Table 4) were defined as the proportion of patients with ≥ 8 micturitions per day at baseline who achieved a normalisation of micturition, defined as a frequency of micturition of <8 micturitions per day.

Table 4: Incontinence & Frequency responders for Enablex (7.5 mg and 15 mg) and placebo at 12 weeks (studies 1041, 1002, 1001 and 1047)

	Study 1041			Study 1002			Study 1001		Study 1047	
	Enablex 7.5mg	Enablex 15mg	Placebo	Enablex 7.5mg	Enablex 15mg	Placebo	Enablex 15mg	Placebo	Enablex 7.5/15 mg	Placebo
No. of Patients	229	115	164	108	107	109	112	115	268	127
Incontinence responders**	65%	65%	54%	67%*	72%*	49%	73%	66%	62%*	49%
Frequency responders***	33%	31%	24%	36%	39%	31%	35%	31%	39%*	23%

As seen in Figure 2, significant improvement in the number of incontinence episodes per week was observed within the first 2 weeks in patients treated with Enablex 7.5 mg and 15 mg once daily compared to placebo. Further, these effects were sustained throughout the 12 week treatment period.

Figure 2: Median change from baseline to weeks 2, 6, 12 for number of incontinence episodes per week (Study 1002)



In a pooled analysis, significant improvements from baseline were also observed for key secondary efficacy endpoints, including the number of micturitions per day, the number and severity of urgency episodes, the average volume of urine passed per void and the number of incontinence episodes requiring a change of clothing or pads.

In a clinical study of 12 months duration at doses ranging from 7.5 to 30 mg, sustained improvements from baseline were observed in the number of incontinence episodes per week and in other key secondary efficacy endpoints including number of micturitions per day, episodes of urgency and 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 limitation 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.

INDICATIONS

Enablex prolonged-release tablets are indicated for the treatment of overactive bladder, with the symptoms of urgency, urge urinary incontinence or frequency of micturition.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients. Enablex is contraindicated in patients with urinary retention, gastric retention or uncontrolled narrow-angle glaucoma.

PRECAUTIONS

Concomitant conditions:

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

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 and seek immediate medical attention if they experience edema of the tongue or larynx, or difficulty breathing (see "ADVERSE EFFECTS").

Enablex should be used with caution in patients with risk of decreased gastrointestinal motility (see "CONTRAINDICATIONS"), gastro-oesophageal reflux and/or who are concurrently taking medicinal products (such as oral bisphosphonates) that can cause or exacerbate oesophagitis.

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

Use in hepatic impairment:

There is a risk of increased exposure in this population (see "Pharmacokinetics"). No dose adjustment is required in patients with mild hepatic impairment (Child Pugh A). For patients with moderate hepatic impairment (Child Pugh B) or when co-administered with potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, miconazole, nefazodone and ritonavir), the daily dose of Enablex should not exceed 7.5 mg. Enablex is not recommended for use in

patients with severe hepatic impairment (Child Pugh C) (see “DOSAGE AND ADMINISTRATION”).

Carcinogenicity, mutagenicity and impairment of fertility:

Two year carcinogenicity studies with dietary administration of darifenacin were conducted in mice and rats. No evidence of drug related carcinogenicity was revealed in mice (up to 100 mg/kg/day) or rats (up to 15 mg/kg/day). These doses correspond to unbound darifenacin exposure levels approximately 32 times (mice) and 10 times (rats) human exposure at the maximum recommended human dose (MRHD: 15 mg).

Darifenacin was neither mutagenic (bacterial and mammalian cell mutation assays) nor clastogenic (human lymphocyte assay) when tested *in vitro* in the presence and absence of metabolic activation. No chromosomal aberrations were observed in an *in vivo* mouse bone cytogenetics assay following systemic exposure to darifenacin at levels >32 times human exposures at the MRHD.

No significant effects on fertility were observed in male or female rats treated with darifenacin (2 weeks [female] or 9 weeks [male] prior to, and throughout mating) at oral doses up to 50 mg/kg/day, corresponding to approximately 55 times the human AUC at the MRHD.

Use in Pregnancy (Category B3)

Darifenacin and/or its metabolites cross the placenta in rats and rabbits. There was no evidence of teratogenicity in rats or rabbits following oral administration of darifenacin during the period of organogenesis and foetogenesis at doses up to 50 and 30 mg/kg/day, respectively (59 and 28 times the MRHD, based on unbound AUC).

At these maternotoxic doses, darifenacin caused delayed ossification of sacral and caudal vertebrae in rats and increased postimplantation loss/decreased foetal viability in rabbits.

When oral treatment of rats at this dose was extended throughout organogenesis and foetogenesis, gestation and lactation, additional findings included increased gestation length, dystocia, reductions in birth weight, postnatal survival and growth of offspring and altered indices of offspring behaviour.

At the NOEL for pup developmental effects (10 mg/kg/day), the relative systemic exposure to darifenacin was approximately 9 times that anticipated at the MRHD (based on AUC). Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy and embryofoetal development. The safety of darifenacin in human pregnancy has not been established and, because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the benefit to the mother outweighs the potential risk to the foetus.

Use in Lactation

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.

Use in Children

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

Interactions with Other Drugs

Effects of other medicinal products on darifenacin:

Darifenacin metabolism is primarily mediated by the cytochrome P450 enzymes CYP2D6 and CYP3A4. Therefore, drugs which inhibit these enzymes may alter darifenacin pharmacokinetics when they are co-administered (see “Pharmacokinetics”).

CYP2D6 inhibitors:

No special dosing requirements are necessary in the presence of CYP2D6 inhibitors, although the risk of adverse events may be increased following concomitant treatment of darifenacin with CYP2D6 inhibitors such as paroxetine, cimetidine and fluoxetine and caution should be exercised.

CYP3A4 inhibitors:

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

Ketoconazole

In a drug interaction study, when a 7.5 mg once-daily dose of Enablex was given to steady state, and co-administered with the potent CYP3A4 inhibitor ketoconazole 400 mg, mean darifenacin C_{max} increased to 11.2 ng/mL in EM (n=10) and 55.4 ng/mL in one PM subject (n=1). Mean AUC increased to 143 and 939 ng.h/mL in EM and in one PM subject respectively. When a 15 mg daily dose of Enablex was given with ketoconazole, mean darifenacin C_{max} increased to 67.6 ng/mL and 58.9 ng/mL in EM (n=3) and in one PM subject (n=1) respectively. Mean AUC increased to 1110 and 931 ng.h/mL in EMs and in one PM subject respectively.

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.

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

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.

Antimuscarinic agents:

The concomitant use of darifenacin with other antimuscarinic agents may increase the frequency and/or severity of antimuscarinic pharmacological effects such as dry mouth, constipation and blurred vision. The potentiation of anticholinergic effects with anti-parkinson agents and tricyclic antidepressants may also occur if antimuscarinic agents are used concurrently with such medicinal products. However, no studies involving the interaction with anti-parkinson agents and tricyclic antidepressants have been performed.

Effects on ability to drive and use machinery:

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

During the clinical development of Enablex, a total of 7271 patients and volunteers have been exposed to phase I-III clinical trials for up to one year duration of therapy for overactive bladder and other indications.

The Phase II and III overactive bladder clinical trial program for Enablex included 2678 patients who were treated with Enablex prolonged-release tablets 3.75 mg to 45 mg once daily for up to 12 months.

Of this total, 1059 patients participated in three, twelve-week, Phase III, fixed-dose efficacy and safety studies. Of this total, 337 and 334 patients were treated with Enablex prolonged-release tablets, 7.5 mg daily and 15 mg daily, respectively.

Adverse Events in Clinical Trials

Table 5 lists the adverse events reported (regardless of causality) in 1% or more patients treated with 7.5 or 15 mg Enablex prolonged-release tablets in fixed-dose, placebo-controlled Phase III studies. Adverse events were reported by 54.0% and 65.6% of patients receiving 7.5 and 15 mg once daily Enablex prolonged-release tablets, respectively, and by 48.7% of patients receiving placebo.

The majority of adverse events in Enablex treated subjects were mild or moderate and mostly occurred during the first two weeks of treatment. The incidence of serious adverse events was similar for 7.5 mg, 15 mg and placebo. The profile of adverse events remained consistent across all populations and doses studied.

The most frequently reported adverse events were dry mouth, and constipation. However, the patient discontinuation rates due to these events were low.

Consistent with M₃ muscarinic receptor selectivity, 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% at all doses and did not increase with dose.

In clinical trials of volunteers and patients (n=964 treated, n=261 placebo), clinically significant changes in QT interval were not observed with Enablex up to and including 60 mg once daily, the highest dose studied.

Table 5: Incidence of adverse events regardless of causality reported in $\geq 1\%$ of patients treated with Enablex prolonged-release tablets in fixed-dose, placebo-controlled phase III studies (1001, 1002, 1041)

Body System	Adverse Event	Percentage of subjects with adverse event (%)		
		Darifenacin 7.5mg N = 337	Darifenacin 15mg N = 334	Placebo N = 388
Body as a whole	Abdominal pain	2.4	3.9	0.5
	Asthenia	1.5	2.7	1.3
	Flu syndrome	2.1	2.1	2.6
	Headache	4.5	5.1	5.4
	Pain	1.2	0.6	0.8
Digestive	Constipation	14.8	21.3	6.2
	Diarrhoea	2.1	0.9	1.8
	Dry mouth	20.2	35.3	8.2
	Dyspepsia	2.7	8.4	2.6
	Nausea	2.7	1.5	1.5
	Vomiting	0.3	1.5	0.5
	Respiratory	Bronchitis	1.2	1.2
Respiratory tract infection		2.7	5.1	6.7
Rhinitis		0.6	1.8	1.3
Sinusitis		0.9	1.2	1.3
Urogenital	Urinary tract infection	4.7	4.5	2.6
	Urinary tract disorder	0.0	1.8	0.5
	Vaginitis	0.3	1.5	0.5
Miscellaneous	Accidental injury	1.2	1.2	0.5
	Abnormal vision	0.6	1.5	0.3
	Arthralgia	0.6	1.2	0.8
	Back pain	2.4	1.5	3.1
	Dizziness	0.9	2.1	1.3
	Dry eyes	1.5	2.1	0.5
	Dry skin	0.0	1.8	0.5
	Hypertension*	1.5	1.5	0.8
	Pharyngitis	2.7	1.2	2.3
	Peripheral oedema	1.2	1.5	0.3
	Pruritus	0.6	1.2	0.8
	Rash	1.2	0.0	1.3
	Weight gain	0.3	1.2	0.0

*subsequent clinical studies report this as an adverse reaction with suspected relationship to product

Discontinuations due to any adverse events occurred in 1.2% and 4.5% of 7.5 mg and 15 mg Enablex patients treated in fixed-dose placebo controlled trials, respectively and in 1.3% of placebo subjects. There were no discontinuations due to laboratory test abnormalities.

Long-term safety was evaluated in 410 patients for 6 months and 106 patients for 1 year. The long term safety profile of darifenacin was similar to that observed in the short-term pivotal studies.

Adverse reactions with suspected relationship to product:

The following adverse drug reactions, listed in Table 6, have been reported in clinical studies following treatment with Enablex and 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.

Table 6 Adverse drug reactions reported in clinical studies

Psychiatric disorders	
Uncommon:	Insomnia, thinking abnormal
Nervous system disorders	
Uncommon:	Dysgeusia, somnolence
Eye disorders	
Uncommon:	Visual disturbance, including vision blurred
Respiratory, thoracic and mediastinal disorders	
Common:	Nasal dryness
Uncommon:	Dyspnoea, cough
Gastrointestinal disorders	
Uncommon:	Flatulence, mouth ulceration
Skin and subcutaneous tissue disorders	
Uncommon:	Hyperhidrosis
Not known:	Angioedema
Renal and urinary disorders	
Uncommon:	Urinary retention, bladder pain
Reproductive system and breast disorders	
Uncommon:	erectile dysfunction
General disorders and administration site conditions	
Uncommon:	face oedema, oedema
Investigations	
Uncommon:	aspartate aminotransferase increased, alanine aminotransferase increased
Injury, poisoning, and procedural complications	
Uncommon:	injury

Post-marketing experience:

The following events have been reported in association with darifenacin use in worldwide post-marketing experience:

- Generalized hypersensitivity reactions including angioedema, with or without airway obstruction (see also “PRECAUTIONS”) have been reported
- Urinary retention,
- Palpitations.

Because these spontaneously reported events are from the worldwide post-marketing experience, the frequency of events and the role of darifenacin in their causation cannot be reliably determined.

DOSAGE AND ADMINISTRATION

The recommended starting dose of Enablex prolonged-release tablets is 7.5 mg once 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.

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.

Use in patients with hepatic or renal impairment:

For patients with moderate hepatic impairment (Child Pugh B) or when co-administered with potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, miconazole, nefazodone and ritonavir), the daily dose of Enablex should not exceed 7.5 mg. Enablex is not recommended for use in patients with severe hepatic impairment (Child Pugh C) (see “PRECAUTIONS”).

There are no special dosage requirements for patients with renal impairment.

OVERDOSAGE

Overdosage with antimuscarinic agents, including Enablex, can result in severe antimuscarinic effects. Treatment should be symptomatic and supportive. In the event of overdosage, ECG monitoring is recommended. Enablex has been administered in clinical trials at doses up to 75 mg (five times the maximum therapeutic dose) and signs of overdose were limited to abnormal vision.

Contact Poison Information Centre on 131 126 for advice on management.

PRESENTATION

Enablex 7.5 mg prolonged-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 prolonged-release tablets are round, shallow, convex, light peach-coloured tablets and are identified with “DF” on one side and “15” on the reverse.

Both strengths of Enablex tablets are available in blister packs containing 7, 14, 28, 56 or 98 tablets. Not all pack sizes or container types may be marketed.

Storage: Store below 25°C. Protect from light.

SPONSOR

Novartis Pharmaceuticals Australia Pty Ltd

ABN 18 004 244 160

54 Waterloo Road

North Ryde NSW 2113

® = Registered Trademark

Approved by the Therapeutic Goods Administration: 9 August 2010

Date of most recent amendment: 30 May 2011
