1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

ENABLEX 7,5 mg (controlled-release tablet)

ENABLEX 15 mg (controlled-release tablet)

COMPOSITION

ENABLEX 7,5 mg:

Each film-coated controlled-release tablet of ENABLEX 7,5 mg contains 8,93 mg of darifenacin as a hydrobromide salt (equivalent to 7,5 mg of darifenacin free base).

Excipients:

Calcium hydrogen phosphate anhydrous, hypromellose, macrogol, magnesium stearate, talc, titanium dioxide (C.I. 77891)

Sugar free

ENABLEX 15 mg:

Each film-coated controlled-release tablet of ENABLEX 15 mg contains 17,85 mg of darifenacin as a hydrobromide salt (equivalent to 15 mg of darifenacin free base).

Excipients:

Calcium hydrogen phosphate anhydrous, hypromellose, iron oxide yellow (C.I. 77492), iron oxide red (C.I. 77491), macrogol, magnesium stearate, talc, titanium dioxide (C.I. 77891)

Sugar free

CATEGORY AND CLASS

A 5.4 Medicines affecting autonomic functions - Cholinolytics (Anticholinergics)

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Darifenacin is a muscarinic M3 selective receptor antagonist that *in-vitro* 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, colonic mobility and salivary flow.

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.

Pharmacokinetic properties

Absorption:

Darifenacin is almost 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 controlled-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. Food had no effect on darifenacin pharmacokinetics during multiple-dose administration of controlled-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. 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.

Variability in metabolism: The estimated mean oral bioavailability of darifenacin in extensive metabolisers at steady state is 15 % and 19 % for 7,5 and 15 mg controlled-release tablets, respectively.

Population pharmacokinetic analyses of Phase 3 data indicated that on average steady-state exposure is 66 % higher in poor metabolisers (deficient in cytochrome P450 enzyme CYP2D6) 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.

Excretion:

Following administration of an oral dose of ^{14}C-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.

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. No special dosage requirements are necessary based on gender.

Elderly patients:

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

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 study of

subjects 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. 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.

INDICATIONS

ENABLEX is indicated for the treatment of overactive bladder with symptoms of urinary urgency, frequency and /or urge incontinence.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Co-administration with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, miconazole, troleandomycin, nefazadone, ritonavir, nelfinavir and clarithromycin.

ENABLEX is contraindicated in patients with urinary retention, gastric retention or uncontrolled narrow-angle glaucoma.

Severe hepatic impairment.

Children under the age of 18 years: the safety and efficacy in children have not been established.

WARNINGS AND SPECIAL PRECAUTIONS

ENABLEX should be used with caution in patients with controlled narrow-angle glaucoma.

Special 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) or gastrointestinal obstructive disorders, such as pyloric stenosis (see CONTRAINDICATIONS).

Effects on ability to drive and use machines

Studies on the effects of ENABLEX on the ability to drive and use machines have not been performed. Nevertheless, caution should be exercised when driving or using machines.

INTERACTIONS

Effects of other medicinal products on ENABLEX:

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

No major safety issues were noted in any of the clinical studies and no treatment-related serious adverse events were observed.

CYP2D6 inhibitors:

No special dosing requirements are necessary in the presence of CYP2D6 inhibitors.

CYP3A4 inhibitors:

In patients receiving medicines that are moderate CYP3A4 inhibitors such as fluconazole and erythromycin, the recommended starting dose is 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. However, caution should be exercised.

Effects of ENABLEX on other medicinal products:

CYP2D6 substrates:

Caution should be exercised when ENABLEX 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. **Because there is a potential for increased exposure to these substrates, physicians may consider reducing the dose of concomitantly administered medicines that are CYP2D6 substrates.**

CYP3A4 substrates:

ENABLEX 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:

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

Standard therapeutic drug monitoring for digoxin should be continued. ENABLEX (30 mg once daily) co-administered with digoxin at steady state resulted in a small but potentially clinically significant increase in digoxin exposure (AUC: 16 %; C_{max}: 20 %).

HUMAN REPRODUCTION

Use in pregnancy:

There are no studies of ENABLEX in pregnant women. ENABLEX should not be used during pregnancy.

Use in lactation:

ENABLEX is excreted into the milk of rats. ENABLEX should not be used in breastfeeding women.

DOSAGE AND DIRECTIONS FOR USE

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 and tolerability.

ENABLEX controlled-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.

Elderly patients:

Dose adjustment is not required in elderly patients (see *Pharmacokinetic properties*).

Use in renal impairment:

Dose adjustment is not required in patients with impaired renal function (see *Pharmacokinetic properties*).

Use in hepatic impairment

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).

SIDE EFFECTS

Very common adverse drug reactions (ADRs) were dry mouth and constipation. 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).

In the pivotal clinical trials with doses of 7,5 mg and 15 mg ENABLEX, ADRs were reported

as presented in the table below. Most 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 ENABLEX once daily was similar to placebo.

Frequency estimate: common (≥ 1 % to < 10 %), uncommon (> 0,1 % to < 1 %), occurred once only (0,1 %)

Body system	**Incidence of adverse events by dose**		
	7,5 mg	**15 mg**	**7,5/15***
Body as a whole			
Abdominal pain	> 0,1 % to < 1 %	> 1 % to < 10 %	> 1 % to < 10 %
Accidental injury	0,1 %	-	0,1 %
Asthenia	0,1 %	> 0,1 % to < 1 %	> 1 % to < 10 %
Back pain, chest pain, halitosis	0,1 %	-	-
Facial oedema	-	> 0,1 % to < 1 %	-
Headache	> 1 % to < 10 %	> 1 % to < 10 %	> 1 % to < 10 %
Hernia	-	-	0,1 %
Hot flushes, pain, photosensitivity reaction	-	0,1 %	-
Cardiovascular			
Angina pectoris, atrial fibrillation, a.v. block, bundle	0,1 %	-	-

Body system	Incidence of adverse events by dose		
	7,5 mg	15 mg	7,5/15*
branch block			
Bradycardia, palpitation, vasodilatation	-	0,1 %	-
Hypertension	> 0,1 % to < 1 %	-	> 1 % to < 10 %
Migraine	-	-	0,1 %
Digestive			
Diarrhoea	> 0,1 % to < 1 %	-	> 0,1 % to < 1 %
Dyspepsia	> 1 % to < 10 %	> 1 % to < 10 %	> 1 % to < 10 %
Dysphagia, rectal disorder	-	-	0,1 %
Flatulence	-	> 0,1 % to < 1 %	0,1 %
Gastritis, gastrointestinal disorder, stomatitis	0,1 %	-	-
Increased appetite, tongue oedema, vomiting	-	0,1 %	-
Nausea	> 1 % to < 10 %	0,1 %	> 1 % to < 10 %
Ulcerative stomatitis	-	> 0,1 % to < 1 %	-
Haemic and lymphatic			
Leukopenia	0,1 %	-	-
Metabolic and nutritional			
Increased alkaline phosphatase, thirst, weight gain	-	0,1 %	-
Increased SGOT	> 0,1 % to < 1 %	-	-
Increased SGPT	> 0,1 % to < 1 %	0,1 %	-
Oedema	-	-	> 0,1 % to < 1 %

Body system	Incidence of adverse events by dose		
	7,5 mg	**15 mg**	**7,5/15***
Peripheral oedema	0,1 %	> 0,1 % to < 1 %	-
Musculoskeletal			
Arthralgia	-	-	0,1 %
Myalgia	-	0,1 %	-
Nervous			
Abnormal thinking	0,1 %	0,1 %	-
Agitation, amnesia, depression, extrapyramidal syndrome, paresthesia, stupor, vertigo	-	0,1 %	-
Dizziness	> 0,1 % to < 1 %	0,1 %	> 1 % to < 10 %
Insomnia	0,1 %	0,1 %	> 0,1 % to < 1 %
Somnolence	0,1 %	0,1 %	> 0,1 % to < 1 %
Twitching	-	-	0,1 %
Respiratory			
Increased cough, dyspnoea	0,1 %	0,1 %	-
Pharyngitis	-	-	0,1 %
Respiratory disorder, sinusitis	-	0,1 %	-
Rhinitis	-	> 1 % to < 10 %	> 0,1 % to < 1 %
Skin and appendages			
Alopecia, herpes simplex, urticaria	-	0,1 %	-
Dry skin	-	> 1 % to < 10 %	-
Pruritus	-	> 0,1 % to < 1 %	-
Rash	> 0,1 % to < 1 %	-	0,1 %

Body system	Incidence of adverse events by dose		
	7,5 mg	15 mg	7,5/15*
Sweating	0,1 %	-	0,1 %
Special senses			
Abnormal vision	> 0,1 % to < 1 %	> 1 % to < 10 %	> 0,1 % to < 1 %
Dry eyes	> 1 % to < 10 %	> 1 % to < 10 %	-
Taste perversion	-	> 0,1 % to < 1 %	-
Tinnitus	-	0,1 %	-
Urogenital			
Bladder pain	-	-	> 0,1 % to < 1 %
Breast pain, urinary hesitancy, urine abnormality	-	0,1 %	-
Dysuria, menstrual disorder, urinary tract disorder	-	-	0,1 %
Impotence	0,1 %	0,1 %	0,1 %
Urinary retention	0,1 %	-	-
Urinary tract infection	0,1 %	0,1 %	0,1 %
Urinary tract disorder	-	> 1 % to < 10 %	0,1 %
Vaginitis	0,1 %	-	0,1 %

*Dose titration from 7,5 mg to 15 mg

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

No overdosages were recorded in the ENABLEX clinical development programme. However, overdosage with ENABLEX can potentially lead to severe anticholinergic effects and should be treated accordingly. Therapy should be aimed at reversing the anticholinergic symptoms under careful medical supervision. The use of medicines such as physostigmine can assist in

reversing such symptoms.

IDENTIFICATION

ENABLEX 7,5 mg: White, shallow, round, biconvex film-coated tablets debossed with “DF” on one side and “7.5” on the other side.

ENABLEX 15 mg: Peach, shallow, round, biconvex film-coated tablets, debossed with “DF” on one side and “15” on the other side.

PRESENTATION

14, 28, 56 or 98 film-coated controlled-release tablets are packed in a clear polyvinylchloride and polyvinylidene chloride film sealed with an aluminium foil backing. One or more blister strips are packed into an outer cardboard carton.

14, 28, 56 or 98 film-coated controlled-release tablets are packed in a clear polyamide, aluminium and polyvinylchloride film sealed with an aluminium foil backing. One or more blister strips are packed into an outer cardboard carton.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Protect from light.

Keep the blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

ENABLEX 7,5 mg: A38/5.4/0699

ENABLEX 15 mg: A38/5.4/0700

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Dates of registration:

ENABLEX 7,5 mg: 17 February 2006

ENABLEX 15 mg: 17 February 2006

Date of the most recent amendment to the professional information as approved by the Authority: 17 February 2006

Botswana:	S2
7,5 mg	BOT1101793
15 mg	BOT1101794

Namibia:	NS2
7,5 mg	08/5.4/0120
15 mg	08/5.4/0121

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