

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-513

Approved Labeling

1 **ENABLEX[®]**

2 (darifenacin)

3 Extended-release tablets

4 **Rx**

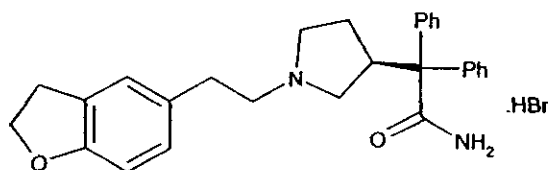
5 **Prescribing Information**

6 **DESCRIPTION**

7 ENABLEX[®] (darifenacin) is an extended-release tablet which contains 7.5 mg or 15 mg
8 darifenacin as its hydrobromide salt. The active moiety, darifenacin, is a potent muscarinic
9 receptor antagonist.

10 Chemically, darifenacin hydrobromide is (*S*)-2-[1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-
11 pyrrolidinyl]-2,2-diphenylacetamide hydrobromide. The empirical formula of darifenacin
12 hydrobromide is C₂₈H₃₀N₂O₂.HBr.

13 The structural formula is



15 Darifenacin hydrobromide is a white to almost white, crystalline powder, with a molecular
16 weight of 507.5.

17 ENABLEX is a once-a-day extended-release tablet, and contains the following inactive
18 ingredients: dibasic calcium phosphate anhydrous, hydroxypropyl methylcellulose
19 (hypromellose), lactose monohydrate, magnesium stearate, titanium dioxide and triacetin. The
20 15-mg tablet also contains FD&C Yellow No. 6 Aluminum Lake.

21 **CLINICAL PHARMACOLOGY**

22 **General**

23 Darifenacin is a competitive muscarinic receptor antagonist. Muscarinic receptors play an
24 important role in several major cholinergically mediated functions, including contractions of
25 the urinary bladder smooth muscle and stimulation of salivary secretion.

26 In vitro studies using human recombinant muscarinic receptor subtypes show that darifenacin
27 has greater affinity for the M₃ receptor than for the other known muscarinic receptors (9 and
28 12-fold greater affinity for M₃ compared to M₁ and M₅, respectively, and 59-fold greater
29 affinity for M₃ compared to both M₂ and M₄). M₃ receptors are involved in contraction of
30 human bladder and gastrointestinal smooth muscle, saliva production, and iris sphincter
31 function. Adverse drug effects such as dry mouth, constipation and abnormal vision may be
32 mediated through effects on M₃ receptors in these organs.

1

2 **Pharmacodynamics**

3 In three cystometric studies performed in patients with involuntary detrusor contractions,
4 increased bladder capacity was demonstrated by an increased volume threshold for unstable
5 contractions and diminished frequency of unstable detrusor contractions after ENABLEX®
6 (darifenacin) extended-release tablet treatment. These findings are consistent with an
7 antimuscarinic action on the urinary bladder.

8 **Pharmacokinetics**

9 **Absorption**

10 After oral administration of ENABLEX to healthy volunteers, peak plasma concentrations of
11 darifenacin are reached approximately seven hours after multiple dosing and steady state
12 plasma concentrations are achieved by the sixth day of dosing. The mean (SD) steady state
13 time course of ENABLEX 7.5 mg and 15 mg extended-release tablets is depicted in Figure 1.

14

15 A summary of mean (standard deviation, SD) steady state pharmacokinetic parameters of
16 ENABLEX 7.5 mg and 15 mg extended-release tablets in extensive (EM) and poor (PM)
17 metabolizers of CYP2D6 is provided in Table 1.

18 **Table 1: Mean (SD) Steady State Pharmacokinetic Parameters From ENABLEX®**
19 **7.5 mg And 15 mg Extended-Release Tablets Based On Pooled Data By**
20 **Predicted CYP2D6 Phenotype**

	ENABLEX® 7.5 mg (N = 68 EM, 5 PM)					ENABLEX® 15 mg (N = 102 EM, 17 PM)				
	AUC ₂₄ (ng.h/ml)	C _{max} (ng/ml)	C _{avg} (ng/ml)	T _{max} (h)	t _{1/2} (h)	AUC ₂₄ (ng.h/ml)	C _{max} (ng/ml)	C _{avg} (ng/ml)	T _{max} (h)	t _{1/2} (h)
EM	29.24 (15.47)	2.01 (1.04)	1.22 (0.64)	6.49 (4.19)	12.43 (5.64) ^a	88.90 (67.87)	5.76 (4.24)	3.70 (2.83)	7.61 (5.06)	12.05 (12.37) ^b
PM	67.56 (13.13)	4.27 (0.98)	2.81 (0.55)	5.20 (1.79)	19.95 ^c	157.71 (77.08)	9.99 (5.09)	6.58 (3.22)	6.71 (3.58)	7.40 ^d

21 ^aN=25; ^bN=8; ^cN= 2; ^dN=1; AUC₂₄ = Area under the plasma concentration versus time curve for
22 24h; C_{max} = Maximum observed plasma concentration; C_{avg} = Average plasma concentration at steady
23 state; T_{max} = Time of occurrence of C_{max}; t_{1/2} = Terminal elimination half-life.

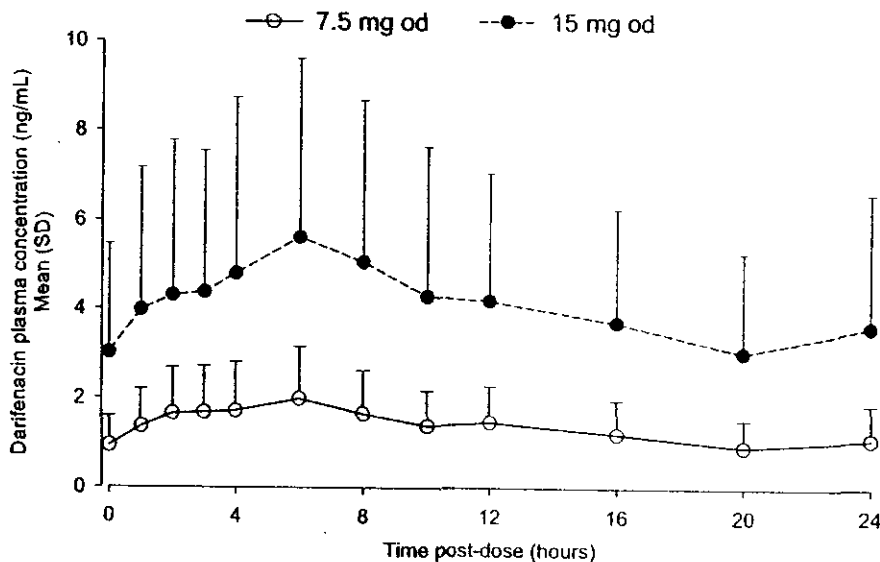
24 Regarding EM and PM, see CLINICAL PHARMACOLOGY, Pharmacokinetics, *Variability in*
25 *Metabolism*.

26

27

28 The mean oral bioavailability of ENABLEX in EMs at steady state is estimated to be 15% and
29 19% for 7.5 mg and 15 mg tablets, respectively.

1 **Figure 1. Mean (SD) Steady State Darifenacin Plasma Concentration-Time**
 2 **Profiles For ENABLEX 7.5 And 15 Mg In Healthy Volunteers Including**
 3 **Both CYP2D6 EMs And PMs***



4
 5 *Includes 95 EMs and 6 PMs for 7.5 mg; 104 EMs and 10 PMs for 15 mg.

6 **Effect of Food:**

7 There is no effect of food on multiple-dose pharmacokinetics from ENABLEX extended-
 8 release tablets.

9 **Distribution**

10 Darifenacin is approximately 98% bound to plasma proteins (primarily to alpha-1-acid-
 11 glycoprotein). The steady-state volume of distribution (V_{ss}) is estimated to be 163 L.

12 **Metabolism**

13 Darifenacin is extensively metabolized by the liver following oral dosing.

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

- 16 (i) monohydroxylation in the dihydrobenzofuran ring;
- 17 (ii) dihydrobenzofuran ring opening;
- 18 (iii) N-dealkylation of the pyrrolidine nitrogen.

19 The initial products of the hydroxylation and N-dealkylation pathways are the major
 20 circulating metabolites but they are unlikely to contribute significantly to the overall clinical
 21 effect of darifenacin.

22
 23 **Variability in Metabolism:**

24 A subset of individuals (approximately 7% Caucasians and 2% African Americans) are poor
 25 metabolizers (PMs) of CYP2D6 metabolized drugs. Individuals with normal CYP2D6

1 activity are referred to as extensive metabolizers (EMs). The metabolism of darifenacin in
2 PMs will be principally mediated via CYP3A4. The darifenacin ratios (PM:EM) for C_{max} and
3 AUC following darifenacin 15 mg once-daily at steady state were 1.9 and 1.7, respectively.

4 **Excretion**

5 Following administration of an oral dose of ^{14}C -darifenacin solution to healthy volunteers,
6 approximately 60% of the radioactivity was recovered in the urine and 40% in the feces.
7 Only a small percentage of the excreted dose was unchanged darifenacin (3%). Estimated
8 darifenacin clearance is 40 L/h for EMs and 32 L/h for PMs. The elimination half-life of
9 darifenacin following chronic dosing is approximately 13-19 hours.

10 **Pharmacokinetics in Special Populations**

11 **Age:** No dose adjustment is recommended for the elderly.

12 A population pharmacokinetic analysis of patient data indicated a trend for clearance of
13 darifenacin to decrease with age (6% per decade relative to a median age of 44). Following
14 administration of ENABLEX 15 mg once-daily, darifenacin exposure at steady state was
15 approximately 12%-19% higher in volunteers between 45 and 65 years of age compared to
16 younger volunteers aged 18 to 44 years (see PRECAUTIONS, Geriatric Use).

17 **Pediatric:** The pharmacokinetics of ENABLEX have not been studied in the pediatric
18 population.

19 **Gender:** No dose adjustment is recommended based on gender. PK parameters were
20 calculated for 22 male and 25 female healthy volunteers. Darifenacin C_{max} and AUC at steady
21 state were approximately 57%-79% and 61%-73% higher in females than in males,
22 respectively.

23 **Race:** The effect of race on the pharmacokinetics of ENABLEX has not been characterized.

24 **Renal Insufficiency:** No dose adjustment is recommended for patients with renal
25 impairment. A study of subjects with varying degrees of renal impairment (creatinine
26 clearance between 10 and 136 mL/min) given ENABLEX 15 mg once daily to steady state
27 demonstrated no clear relationship between renal function and darifenacin clearance.

28 **Hepatic Insufficiency:** The daily dose of ENABLEX should not exceed 7.5 mg once daily
29 for patients with moderate hepatic impairment (Child Pugh B) (see PRECAUTIONS and
30 DOSAGE AND ADMINISTRATION). No dose adjustment is recommended for patients with
31 mild hepatic impairment (Child Pugh A).

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

1 Subjects with severe hepatic impairment (Child Pugh C) have not been studied, therefore
2 ENABLEX is not recommended for use in these patients (see PRECAUTIONS and DOSAGE
3 AND ADMINISTRATION).

4 **Drug-Drug Interactions**

5 ***Effects of Other Drugs on Darifenacin***

6 Darifenacin metabolism is primarily mediated by the cytochrome P450 enzymes CYP2D6 and
7 CYP3A4. Therefore, inducers of CYP3A4 or inhibitors of either of these enzymes may alter
8 darifenacin pharmacokinetics.

9 **CYP2D6 Inhibitors:** No dosing adjustments are recommended in the presence of CYP2D6
10 inhibitors. Darifenacin exposure following 30 mg once daily at steady state was 33% higher
11 in the presence of the potent CYP2D6 inhibitor paroxetine 20 mg.

12 **CYP3A4 Inhibitors:** The daily dose of ENABLEX should not exceed 7.5 mg when
13 coadministered with potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir,
14 nelfinavir, clarithromycin and nefazodone) (see PRECAUTIONS and DOSAGE AND
15 ADMINISTRATION). In a drug interaction study, when a 7.5 mg once-daily dose of
16 ENABLEX was given to steady state and coadministered with the potent CYP3A4 inhibitor
17 ketoconazole 400 mg, mean darifenacin C_{max} increased to 11.2 ng/mL for EMs (n=10) and
18 55.4 ng/mL for one PM subject (n=1). Mean AUC increased to 143 and 939 ng.h/mL for
19 EMs and for one PM subject, respectively. When a 15 mg daily dose of ENABLEX was
20 given with ketoconazole, mean darifenacin C_{max} increased to 67.6 ng/mL and 58.9 ng/mL for
21 EMs (n=3) and one PM subject (n=1), respectively. Mean AUC increased to 1110 and 931
22 ng.h/mL for EMs and for one PM subject, respectively.

23 No dosing adjustments are recommended in the presence of moderate CYP3A4 inhibitors
24 (e.g., erythromycin, fluconazole, diltiazem and verapamil). The mean C_{max} and AUC of
25 darifenacin following 30 mg once daily dosing at steady state were 128% and 95% higher,
26 respectively, in the presence of erythromycin. Coadministration of fluconazole and
27 darifenacin 30 mg once daily at steady state increased darifenacin C_{max} and AUC by 88% and
28 84%, respectively.

29 The mean C_{max} and AUC of darifenacin following 30 mg once-daily at steady state were 42%
30 and 34% higher, respectively, in the presence of cimetidine, a mixed CYP P450 enzyme
31 inhibitor.

1 **Effects of Darifenacin on Other Drugs**

2 **In vitro Studies:** Based on in vitro human microsomal studies, ENABLEX is not expected to
3 inhibit CYP1A2 or CYP2C9 at clinically relevant concentrations.

4 **In vivo Studies:** The potential for clinical doses of ENABLEX to act as inhibitors of
5 CYP2D6 or CYP3A4 substrates was investigated in specific drug interaction studies.

6 **CYP2D6 Substrates:** Caution should be taken when ENABLEX is used concomitantly with
7 medications that are predominantly metabolized by CYP2D6 and which have a narrow
8 therapeutic window, such as flecainide, thioridazine and tricyclic antidepressants (see
9 PRECAUTIONS, Drug Interactions).

10 The mean C_{max} and AUC of imipramine, a CYP2D6 substrate, were increased 57% and
11 70%, respectively, in the presence of steady-state darifenacin 30 mg once daily. This was
12 accompanied by a 3.6-fold increase in the mean C_{max} and AUC of desipramine, the active
13 metabolite of imipramine.

14 **CYP3A4 Substrates:** Darifenacin (30 mg daily) coadministered with a single oral dose of
15 midazolam 7.5 mg resulted in 17% increase in midazolam exposure.

16 Darifenacin (10 mg t.i.d.) had no effect on the pharmacokinetics of the combination oral
17 contraceptives containing levonorgestrel and ethinylestradiol.

18 **Other Drugs:** Darifenacin had no significant effect on prothrombin time when a single dose
19 of warfarin 30 mg was coadministered with darifenacin (30 mg daily) at steady state.
20 Standard therapeutic prothrombin time monitoring for warfarin should be continued.

21 Routine therapeutic drug monitoring for digoxin should be continued. Darifenacin (30 mg
22 daily) coadministered with digoxin (0.25 mg) at steady state resulted in 16% increase in
23 digoxin exposure.

24 **Electrophysiology**

25 The effect of six-day treatment of 15 mg and 75 mg ENABLEX on QT/QTc interval was
26 evaluated in a multiple-dose, double-blind, randomized, placebo- and active-controlled
27 (moxifloxacin 400 mg) parallel-arm design study in 179 healthy adults (44% male, 56%
28 female) aged 18 to 65. Subjects included 18% PMs and 82% EMs. The QT interval was
29 measured over a 24-hour period both pre-dosing and at steady state. The 75 mg ENABLEX
30 dose was chosen because this achieves exposure similar to that observed in CYP2D6 poor
31 metabolizers administered the highest recommended dose (15 mg) of darifenacin in the
32 presence of a potent CYP3A4 inhibitor. At the doses studied, ENABLEX did not result in
33 QT/QTc interval prolongation at any time during the steady state, while moxifloxacin
34 treatment resulted in a mean increase from baseline QTcF of about 7.0 msec when compared
35 to placebo. In this study, darifenacin 15 mg and 75 mg doses demonstrated a mean heart rate
36 change of 3.1 and 1.3 bpm, respectively, when compared to placebo. However, in the phase
37 II/III clinical studies, the change in median HR following treatment with ENABLEX was no
38 different from placebo.

1 **CLINICAL STUDIES**

2 ENABLEX[®] (darifenacin) extended-release tablets were evaluated for the treatment of
3 patients with overactive bladder with symptoms of urgency, urge urinary incontinence, and
4 increased urinary frequency in three randomized, fixed-dose, placebo-controlled, multicenter,
5 double-blind, 12-week studies (Studies 1, 2 and 3) and one randomized, double-blind,
6 placebo-controlled, multicenter, dose-titration study (Study 4). For study eligibility in all four
7 studies, patients with symptoms of overactive bladder for at least six months were required to
8 demonstrate at least eight micturitions and at least one episode of urinary urgency per day,
9 and at least five episodes of urge urinary incontinence per week. The majority of patients were
10 white (94%) and female (84%), with a mean age of 58 years, range 19 to 93 years. 33% of
11 patients were ≥ 65 years of age. These characteristics were well balanced across treatment
12 groups. The study population was inclusive of both naïve patients who had not received prior
13 pharmacotherapy for overactive bladder (60%) and those who had (40%).

14 Table 2 shows the efficacy data collected from 7- or 14-day voiding diaries in the three fixed-
15 dose placebo-controlled studies of 1059 patients treated with placebo, 7.5 mg or 15 mg once
16 daily ENABLEX for 12 weeks. A significant decrease in the primary endpoint, change from
17 baseline in average weekly urge urinary incontinence episodes was observed in all three
18 studies. Data is also shown for two secondary endpoints, change from baseline in the average
19 number of micturitions per day (urinary frequency) and change from baseline in the average
20 volume voided per micturition.

1 **Table 2: Difference Between ENABLEX® (7.5 mg, 15 mg) And Placebo For The**
 2 **Week 12 Change From Baseline (Studies 1, 2 And 3)**

3

	Study 1			Study 2			Study 3	
	ENABLEX® 7.5 mg	ENABLEX® 15 mg	Placebo	ENABLEX® 7.5 mg	ENABLEX® 15 mg	Placebo	ENABLEX® 15 mg	Placebo
No. of Patients Entered	229	115	164	108	107	109	112	115
Incontinence Episodes per Week								
Median Baseline	16.3	17.0	16.6	14.0	17.3	16.1	16.2	15.5
Median Change from Baseline	-9.0	-10.4	-7.6	-8.1	-10.4	-5.9	-11.4	-9.0
Median Difference to Placebo	-1.5 *	-2.1 *	-	-2.8 *	-4.3 *	-	-2.4*	-
Micturitions per Day								
Median Baseline	10.1	10.1	10.1	10.3	11.0	10.1	10.5	10.4
Median Change from Baseline	-1.6	-1.7	-0.8	-1.7	-1.9	-1.1	-1.9	-1.2
Median Difference to Placebo	-0.8 *	-0.9 *	-	-0.5	-0.7 *	-	-0.5	-
Volume of Urine Passed per Void (mL)								
Median Baseline	160.2	151.8	162.4	161.7	157.3	162.2	155.0	147.1
Median Change from Baseline	14.9	30.9	7.6	16.8	23.6	7.1	26.7	4.6
Median Difference to Placebo	9.1 *	20.7 *	-	9.2	16.6 *	-	20.1 *	-

* Indicates statistically significant difference, versus placebo ($p < 0.05$, Wilcoxon rank-sum test)

4 Table 3 shows the efficacy data from the dose-titration study in 395 patients who initially
 5 received 7.5 mg ENABLEX or placebo daily with the option to increase to 15 mg ENABLEX
 6 or placebo daily after 2 weeks.

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Table 3: Difference Between ENABLEX® (7.5 mg/15 mg) And Placebo For The Week 12 Change From Baseline (Study 4)

	ENABLEX® 7.5 mg / 15 mg	Placebo
No. of Patients Treated	268	127
Incontinence Episodes per Week		
Median Baseline	16.0	14.0
Median Change from Baseline	-8.2	-6.0
Median Difference to Placebo	-1.4*	-
Micturitions per Day		
Median Baseline	9.9	10.4
Median Change from Baseline	-1.9	-1.0
Median Difference to Placebo	-0.8 *	-
Volume of Urine Passed per Void (mL)		
Median Baseline	173.7	177.2
Median Change from Baseline	18.8	6.6
Median Difference to Placebo	13.3 *	-

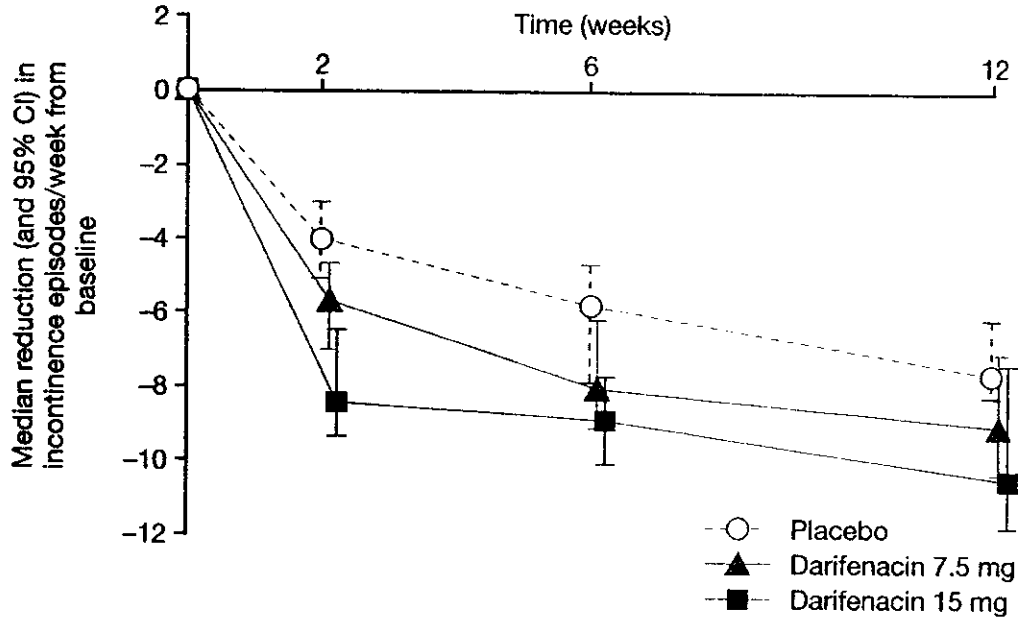
* Indicates statistically significant difference versus placebo (p<0.05, Wilcoxon rank-sum test)

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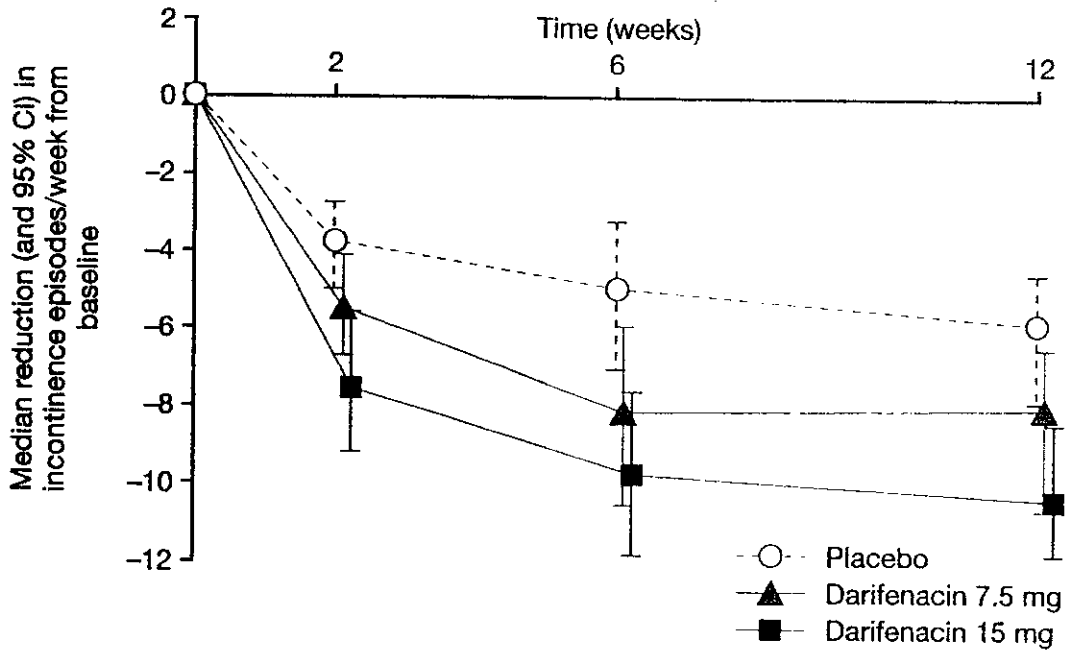
As seen in Figures 2 a, b and c, reductions in the number of incontinence episodes per week was observed within the first two weeks in patients treated with ENABLEX 7.5 mg and 15 mg once daily compared to placebo. Further, these effects were sustained throughout the 12-week treatment period.

1 **Figure 2 a,b,c Median Change From Baseline At Weeks 2, 6, 12 For Number Of**
2 **Incontinence Episodes Per Week (Study 1, 2 and 3)**

3 **Figure 2a Study 1**



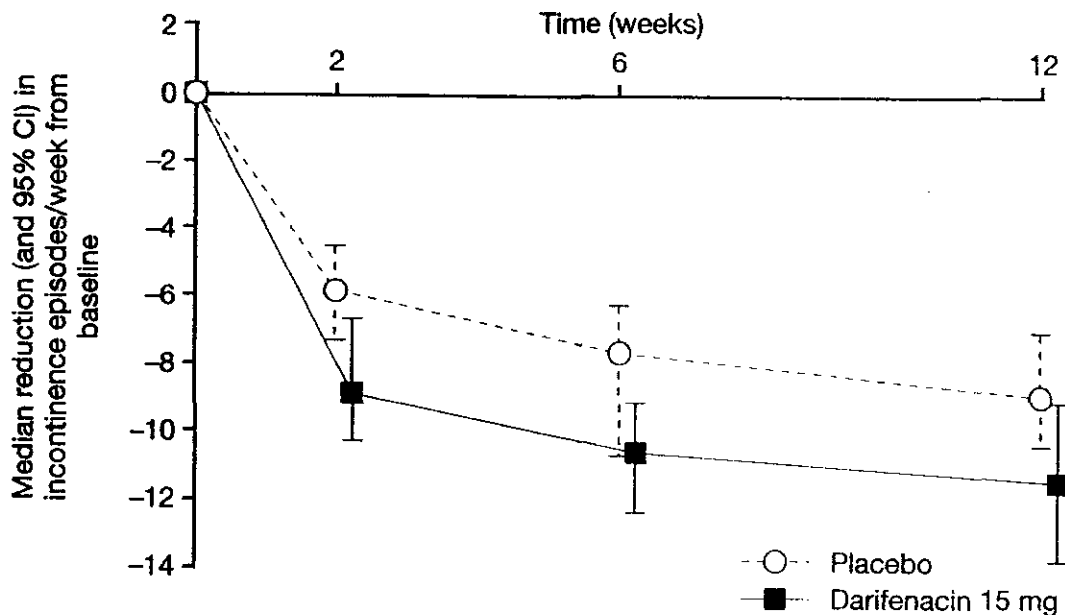
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5 **Figure 2b Study 2**



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Figure 2c Study 3



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5 **INDICATIONS AND USAGE**

6 ENABLEX® (darifenacin) extended-release tablets are indicated for the treatment of
7 overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.

8 **CONTRAINDICATIONS**

9 ENABLEX® (darifenacin) extended-release tablets are contraindicated in patients with urinary
10 retention, gastric retention or uncontrolled narrow-angle glaucoma and in patients who are at
11 risk for these conditions. ENABLEX is also contraindicated in patients with known
12 hypersensitivity to the drug or its ingredients.

13 **PRECAUTIONS**

14 **General**

15 *Risk of Urinary Retention*

16 ENABLEX® (darifenacin) extended-release tablets should be administered with caution to
17 patients with clinically significant bladder outflow obstruction because of the risk of urinary
18 retention.

19 *Decreased Gastrointestinal Motility*

20 ENABLEX should be administered with caution to patients with gastrointestinal obstructive
21 disorders because of the risk of gastric retention. ENABLEX, like other anticholinergic

1 drugs, may decrease gastrointestinal motility and should be used with caution in patients with
2 conditions such as severe constipation, ulcerative colitis, and myasthenia gravis.

3 **Controlled Narrow-Angle Glaucoma**

4 ENABLEX should be used with caution in patients being treated for narrow-angle glaucoma
5 and only where the potential benefits outweigh the risks.

6 **Patients with Hepatic Impairment**

7 There are no dosing adjustments for patients with mild hepatic impairment. The daily dose of
8 ENABLEX should not exceed 7.5 mg for patients with moderate hepatic impairment.
9 ENABLEX has not been studied in patients with severe hepatic impairment and therefore is
10 not recommended for use in this patient population (see CLINICAL PHARMACOLOGY,
11 Pharmacokinetics in Special Populations and DOSAGE AND ADMINISTRATION).

12 **Information for Patients**

13 Patients should be informed that anticholinergic agents, such as ENABLEX, may produce
14 clinically significant adverse effects related to anticholinergic pharmacological activity
15 including constipation, urinary retention and blurred vision. Heat prostration (due to
16 decreased sweating) can occur when anticholinergics such as ENABLEX are used in a hot
17 environment. Because anticholinergics, such as ENABLEX, may produce dizziness or
18 blurred vision, patients should be advised to exercise caution in decisions to engage in
19 potentially dangerous activities until the drug's effects have been determined. Patients should
20 read the patient information leaflet before starting therapy with ENABLEX.

21 ENABLEX extended-release tablets should be taken once daily with liquid. They may be
22 taken with or without food, and should be swallowed whole and not chewed, divided or
23 crushed.

24 **Drug Interactions**

25 The daily dose of ENABLEX should not exceed 7.5 mg when coadministered with potent
26 CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin and
27 nefazadone) (see CLINICAL PHARMACOLOGY and DOSAGE AND
28 ADMINISTRATION).

29 Caution should be taken when ENABLEX is used concomitantly with medications that are
30 predominantly metabolized by CYP2D6 and which have a narrow therapeutic window, such
31 as flecainide, thioridazine and tricyclic antidepressants (see CLINICAL
32 PHARMACOLOGY).

33 The concomitant use of ENABLEX with other anticholinergic agents may increase the
34 frequency and/or severity of dry mouth, constipation, blurred vision and other anticholinergic
35 pharmacological effects. Anticholinergic agents may potentially alter the absorption of some
36 concomitantly administered drugs due to effects on gastrointestinal motility.

37 **Drug Laboratory Test Interactions**

38 Interactions between darifenacin and laboratory tests have not been studied.

1 **Carcinogenesis/Mutagenesis/Impairment of Fertility**

2 Carcinogenicity studies with darifenacin were conducted in mice and rats. No evidence of
3 drug-related carcinogenicity was revealed in a 24-month study in mice at dietary doses up to
4 100 mg/kg/day or approximately 32 times the estimated human free AUC_{0-24h} reached with 15
5 mg, the maximum recommended human dose (AUC at MRHD) and in a 24-month study in
6 rats at doses up to 15 mg/kg/day or up to approximately 12 times the AUC at MRHD in
7 female rats and approximately eight times the AUC at MRHD in male rats.

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

11 There was no evidence for effects on fertility in male or female rats treated at oral doses up to
12 50 mg/kg/day. Exposures in this study correspond to approximately 78 times the AUC at
13 MRHD.

14 **Pregnancy Category C**

15 Darifenacin was not teratogenic in rats and rabbits at doses up to 50 and 30 mg/kg/day
16 respectively. At the dose of 50 mg/kg in rats, there was a delay in the ossification of the sacral
17 and caudal vertebrae which was not observed at 10 mg/kg (approximately 13 times the AUC
18 of free plasma concentration at MRHD). Exposure in this study at 50 mg/kg corresponds to
19 approximately 59 times the AUC of free plasma concentration at MRHD. Dystocia was
20 observed in dams at 10 mg/kg/day (17 times the AUC of free plasma concentration at
21 MRHD). Slight developmental delays were observed in pups at this dose. At 3 mg/kg/day
22 (five times the AUC of free plasma concentration at MRHD) there were no effects on dams or
23 pups. At the dose of 30 mg/kg in rabbits, darifenacin was shown to increase post-implantation
24 loss but not at 10 mg/kg (nine times the AUC of free plasma concentration at MRHD).
25 Exposure to unbound drug at 30 mg/kg in this study corresponds to approximately 28 times
26 the AUC at MRHD. In rabbits, dilated ureter and/or kidney pelvis was observed in offspring
27 at 30 mg/kg/day and one case was observed at 10 mg/kg/day along with urinary bladder
28 dilation consistent with pharmacological action of darifenacin. No effect was observed at 3
29 mg/kg/day (2.8 times the AUC of free plasma concentration at MRHD). There are no studies
30 of darifenacin in pregnant women. Because animal reproduction studies are not always
31 predictive of human response, ENABLEX should be used during pregnancy only if the benefit
32 to the mother outweighs the potential risk to the fetus.

33 **Nursing Mothers**

34 Darifenacin is excreted into the milk of rats. It is not known whether darifenacin is excreted
35 into human milk and therefore caution should be exercised before ENABLEX is administered
36 to a nursing woman.

37 **Pediatric Use**

38 The safety and effectiveness of ENABLEX in pediatric patients have not been established.

39 **Geriatric Use**

40 In the Phase III fixed-dose, placebo-controlled, clinical studies, 30% of patients treated with
41 ENABLEX were over 65 years of age. No overall differences in safety or efficacy were

1 observed between these patients (n= 207) and younger patients <65 years (n= 464). No dose
2 adjustment is recommended for elderly patients (see CLINICAL PHARMACOLOGY,
3 *Pharmacokinetics in Special Populations* and CLINICAL STUDIES).

4 **ADVERSE REACTIONS**

5 During the clinical development of ENABLEX® (darifenacin) extended-release tablets, a total
6 of 7,363 patients and volunteers were treated with doses of darifenacin from 3.75 mg to 75 mg
7 once daily.

8 The safety of ENABLEX was evaluated in Phase II and III controlled clinical trials in a total
9 of 8,830 patients, 6001 of whom were treated with ENABLEX. Of this total, 1,069 patients
10 participated in three, 12-week, Phase III, fixed-dose efficacy and safety studies. Of this total,
11 337 and 334 patients received ENABLEX 7.5 mg daily and 15 mg daily, respectively. In all
12 long term trials combined, 1,216 and 672 patients received treatment with ENABLEX for at
13 least 24 and 52 weeks, respectively.

14 In all placebo-controlled trials combined, the incidence of serious adverse events for 7.5 mg,
15 15 mg and placebo was similar.

16 In all fixed-dose Phase III studies combined, 3.3% of patients treated with ENABLEX
17 discontinued due to all adverse events versus 2.6% in placebo. Dry mouth leading to study
18 discontinuation occurred in 0%, 0.9%, and 0% of patients treated with ENABLEX 7.5 mg
19 daily, ENABLEX 15 mg daily and placebo, respectively. Constipation leading to study
20 discontinuation occurred in 0.6%, 1.2%, and 0.3% of patients treated with ENABLEX 7.5 mg
21 daily, ENABLEX 15 mg daily and placebo, respectively.

22 Table 4 lists the adverse events reported (regardless of causality) in 2% or more of patients
23 treated with 7.5 or 15 mg ENABLEX extended-release tablets and greater than placebo in the
24 three, fixed-dose, placebo-controlled Phase III studies (Studies 1, 2 and 3). Adverse events
25 were reported by 54% and 66% of patients receiving 7.5 and 15 mg once daily ENABLEX
26 extended-release tablets, respectively, and by 49% of patients receiving placebo. In these
27 studies, the most frequently reported adverse events were dry mouth and constipation. The
28 majority of adverse events in ENABLEX-treated subjects were mild or moderate in severity
29 and most occurred during the first two weeks of treatment.

1

2 **Table 4: Incidence Of Adverse Events* Reported In $\geq 2.0\%$ Of Patients Treated**
 3 **With ENABLEX[®] Extended- Release Tablets And More Frequent With**
 4 **ENABLEX[®] Than With Placebo In Three, Fixed-Dose, Placebo-**
 5 **Controlled, Phase III Studies (Studies 1, 2, and 3)**

Body System	Adverse Event	Percentage of subjects with adverse event (%)		
		ENABLEX [®] 7.5 mg N = 337	ENABLEX [®] 15 mg N = 334	Placebo N = 388
Digestive	Dry Mouth	20.2	35.3	8.2
	Constipation	14.8	21.3	6.2
	Dyspepsia	2.7	8.4	2.6
	Abdominal Pain	2.4	3.9	0.5
	Nausea	2.7	1.5	1.5
	Diarrhea	2.1	0.9	1.8
Urogenital	Urinary Tract Infection	4.7	4.5	2.6
Nervous	Dizziness	0.9	2.1	1.3
Body as a Whole	Asthenia	1.5	2.7	1.3
Eye	Dry eyes	1.5	2.1	0.5

*Regardless of causality

6

7 Other adverse events reported, regardless of causality, by $\geq 1\%$ of ENABLEX patients in
 8 either the 7.5 mg or 15 mg once-daily darifenacin dose groups in these fixed-dose, placebo-
 9 controlled Phase III studies include: abnormal vision, accidental injury, back pain, dry skin,
 10 flu syndrome, pain, hypertension, vomiting, peripheral edema, weight gain, arthralgia,
 11 bronchitis, pharyngitis, rhinitis, sinusitis, rash, pruritus, urinary tract disorder and vaginitis.

12 Study 4 was a 12-week, placebo-controlled, dose-titration regimen study in which ENABLEX
 13 was administered in accordance with dosing recommendations (see DOSAGE and
 14 ADMINISTRATION). All patients initially received placebo or ENABLEX 7.5 mg daily,
 15 and after two weeks, patients and physicians were allowed to adjust upward to ENABLEX
 16 15mg if needed. In this study, the most commonly reported adverse events were also
 17 constipation and dry mouth. The incidence of discontinuation due to all adverse events was
 18 3.1% and 6.7% for placebo and for ENABLEX, respectively. Table 5 lists the adverse events
 19 (regardless of causality) reported in $>3\%$ of patients treated with ENABLEX extended-release
 20 tablets and greater than placebo.

1

2 **Table 5: Number (%) Of Adverse Events* Reported In >3% Of Patients Treated**
3 **With ENABLEX® Extended-Release Tablets, And More Frequent With**
4 **ENABLEX® Than Placebo, In The Placebo-Controlled, Dose-Titration,**
5 **Phase III Study (Study 4).**

Adverse Event	ENABLEX®7.5 mg/15 mg N = 268	Placebo N = 127
Constipation	56 (20.9%)	10 (7.9%)
Dry Mouth	50 (18.7%)	11 (8.7%)
Headache	18 (6.7%)	7 (5.5%)
Dyspepsia	12 (4.5%)	2 (1.6%)
Nausea	11 (4.1%)	2 (1.6%)
Urinary Tract Infection	10 (3.7%)	4 (3.1%)
Accidental Injury	8 (3.0%)	3 (2.4%)
Flu Syndrome	8 (3.0%)	3 (2.4%)

*Regardless of causality

6

7 Acute urinary retention (AUR) requiring treatment was reported in a total of 16 patients in the
8 ENABLEX phase I-III clinical trials. Of these 16 cases, 7 were reported as serious adverse
9 events, including one patient with detrusor hyperreflexia secondary to a stroke, one patient
10 with benign prostatic hypertrophy (BPH), one patient with irritable bowel syndrome (IBS)
11 and four OAB patients taking darifenacin 30 mg daily. Of the remaining nine cases, none
12 were reported as serious adverse events. Three occurred in OAB patients taking the
13 recommended doses, and two of these required bladder catheterization for 1-2 days.

14

15 Constipation was reported as a serious adverse event in six patients in the ENABLEX phase I-
16 III clinical trials, including one patient with benign prostatic hypertrophy (BPH), one OAB
17 patient taking darifenacin 30 mg daily, and only one OAB patient taking the recommended
18 doses. The latter patient was hospitalized for investigation with colonoscopy after reporting
19 nine months of chronic constipation that was reported as being moderate in severity.

20 OVERDOSAGE

21 Overdosage with antimuscarinic agents, including ENABLEX® (darifenacin) extended-release
22 tablets can result in severe antimuscarinic effects. Treatment should be symptomatic and
23 supportive. In the event of overdosage, ECG monitoring is recommended. ENABLEX has
24 been administered in clinical trials at doses up to 75 mg (five times the maximum therapeutic
25 dose) and signs of overdose were limited to abnormal vision.

1 **DOSAGE AND ADMINISTRATION**

2 **Administration**

3 The recommended starting dose of ENABLEX® (darifenacin) extended-release tablets is 7.5
4 mg once daily. Based upon individual response, the dose may be increased to 15 mg once
5 daily, as early as two weeks after starting therapy.

6 ENABLEX extended-release tablets should be taken once daily with liquid. They may be
7 taken with or without food, and should be swallowed whole and not chewed, divided or
8 crushed.

9 For patients with moderate hepatic impairment or when coadministered with potent CYP3A4
10 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin and
11 nefazadone), the daily dose of ENABLEX should not exceed 7.5 mg. ENABLEX is not
12 recommended for use in patients with severe hepatic impairment (see CLINICAL
13 PHARMACOLOGY and PRECAUTIONS).

14 **HOW SUPPLIED**

15 ENABLEX® 7.5 mg extended-release tablets are round, shallow, convex, white-colored
16 tablets, and are identified with "DF" on one side and "7.5" on the reverse.

17 Bottle of 30 (NDC 0078-0419-15)

18 Bottle of 90 (NDC 0078-0419-34)

19 Unit-Dose Package of 100, 10 blisters per strip (NDC 0078-0419-06)

20
21 ENABLEX® 15 mg extended-release tablets are round, shallow, convex, light peach-colored
22 tablets, and are identified with "DF" on one side and "15" on the reverse.

23 Bottle of 30 (NDC 0078-0420-15)

24 Bottle of 90 (NDC 0078-0420-34)

25 Unit-Dose Package of 100, 10 blisters per strip (NDC 0078-0420-06)

26 **Storage**

27 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room
28 Temperature]. Protect from light.

29
30 Manufactured by:

31 Pfizer Inc.

32 Brooklyn, New York 11206

33
34 Distributed by:

35 Novartis Pharmaceutical Corporation

1 East Hanover, New Jersey 07936

2

3 ©Novartis

PATIENT INFORMATION

ENABLEX® (*ĕn-ā-blĕx*)

(darifenacin)

Extended-release tablets

7.5 mg or 15 mg

Rx only

Read the Patient Information that comes with ENABLEX® before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor or other healthcare professional about your medical condition or your treatment. Only your doctor or healthcare professional can determine if treatment with ENABLEX is right for you.

What is ENABLEX?

ENABLEX is a prescription medicine used in adults to treat the following symptoms due to a condition called overactive bladder:

- having a strong need to go to the bathroom right away (also called “urgency”)
- leaking or wetting accidents (also called “urinary incontinence”)
- having to go to the bathroom too often (also called “urinary frequency”)

What is overactive bladder?

Overactive bladder happens when you cannot control your bladder contractions. When these muscle contractions happen too often or cannot be controlled, you get symptoms of overactive bladder, which are urinary urgency, urinary incontinence (leakage) and urinary frequency.

Who should not take ENABLEX?

Do not take ENABLEX if you:

- are not able to empty your bladder (also called “urinary retention”)
- have delayed or slow emptying of your stomach (also called “gastric retention”)
- have an eye problem called “uncontrolled narrow-angle glaucoma”
- are allergic to ENABLEX or to any of its ingredients. See the end of this leaflet for a complete list of ingredients.

ENABLEX® has not been studied in children.

What should I tell my doctor before starting ENABLEX?

Before starting ENABLEX, tell your doctor or healthcare professional about all of your medical conditions including if you:

- have any stomach or intestinal problems, or problems with constipation
- have trouble emptying your bladder or if you have a weak urine stream
- have an eye problem called narrow-angle glaucoma
- have liver problems
- are pregnant or planning to become pregnant. It is not known if ENABLEX can harm your unborn baby.
- are breastfeeding. It is not known if ENABLEX passes into breast milk and if it can harm your baby.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. ENABLEX and certain other medicines can interact with each other, causing side effects. Especially tell your doctor if you take:

- ketoconazole (Nizoral[®]) or itraconazole (Sporonox[®]), antifungal medicines
- clarithromycin (Biaxin[®]), an antibiotic medicine
- ritonavir or nelfinavir (Viracept[®]), antiviral medicines
- nefazadone (Serzone[®]), a depression medicine
- flecainide (Tambocor[™]), an abnormal heartbeat (antiarrhythmia) medicine
- thioridazine (Mellaril[®]), a mental disorder (antipsychotic) medicine
- a medicine called a tricyclic antidepressant

Know all the medicines you take. Keep a list of them with you to show your doctor and pharmacist each time you get a new medicine.

How should I take ENABLEX?

Take ENABLEX exactly as prescribed. Your doctor will prescribe the dose that is right for you. Your doctor may prescribe the lowest dose if you have certain medical conditions such as liver problems.

- You should take ENABLEX once daily with liquid.
- **ENABLEX should be swallowed whole and not chewed, divided or crushed.**
- ENABLEX may be taken with or without food.
- If you miss a dose of ENABLEX, begin taking ENABLEX again the next day. Do not take two doses of ENABLEX in the same day.
- If you take too much ENABLEX, call your local Poison Control Center or emergency room right away.

What are the possible side effects of ENABLEX?

The most common side effects with ENABLEX are:

- dry mouth
- constipation.

ENABLEX may cause other less common side effects, that include:

- blurred vision. Use caution while driving or doing dangerous activities until you know how ENABLEX affects you.
- heat prostration. Heat prostration (due to decreased sweating) can occur when drugs such as ENABLEX are used in a hot environment.

These are not all the side effects with ENABLEX. For more information, ask your doctor, healthcare professional or pharmacist.

How do I store ENABLEX?

- **Keep ENABLEX and all medicines out of the reach of children.**
- Store ENABLEX at room temperature, 59 to 86° F (15 to 30° C). Protect from light.
- Safely dispose of ENABLEX that is out of date or no longer needed.

General information about ENABLEX

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not give ENABLEX to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about ENABLEX. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about ENABLEX that is written for health professionals. You can also call the product information department at 1-888-44 ENABLEX (1 888-443-6225) or visit the website at www.ENABLEX.com.

What are the ingredients in ENABLEX?

Active Ingredient: darifenacin

Inactive Ingredients: dibasic calcium phosphate anhydrous, hydroxypropyl methylcellulose (hypromellose), lactose monohydrate, magnesium stearate, titanium dioxide and triacetin. The 15 mg tablet also contains FD&C Yellow No. 6 Aluminum Lake.

Appearance:

The 7.5-mg tablet is round and white-colored with "DF" on one side and "7.5" on the other side

The 15-mg tablet is round and peach-colored with "DF" on one side and "15" on the other side.

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