

PrENABLEX*

(darifenacin extended release tablets)
7.5 mg and 15 mg darifenacin (as darifenacin hydrobromide)



Prescribing Summary



Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Muscarinic M₃ selective receptor antagonist

INDICATIONS AND CLINICAL USE: ENABLEX* (darifenacin) is indicated for the treatment of overactive bladder—a collection of urinary symptoms composed of urgency, with or without urge incontinence, usually with frequency and nocturia, in the absence of proven infection or other obvious pathology.

Geriatrics > 65 Years of Age: In clinical studies (31.4% of patients were > 65 years of age), the safety and efficacy profile of darifenacin 7.5 mg and 15 mg in patients aged over 65 years are comparable to the younger population and were not affected by age.

Geriatrics >75 Years of Age: In clinical studies, the safety and efficacy profile of darifenacin 7.5 mg and 15 mg in patients aged over 75 years are comparable to the younger population and were not affected by age. This information is based on 75 patients over 75 years of age that were included in the four pivotal darifenacin phase III studies (see **PRECAUTIONS**).

Pediatrics: The safety and effectiveness of ENABLEX* in pediatric patients have not been established.

CONTRAINDICATIONS: Patients with, or at risk of, urinary retention, gastric retention, uncontrolled narrow-angle glaucoma; patients with known hypersensitivity to the drug or its ingredients.



Safety Information

WARNINGS AND PRECAUTIONS

Risk of Urinary Retention and Gastrointestinal Obstructive Disorders

ENABLEX* (darifenacin) should be administered with caution to: patients with clinically significant bladder outflow obstruction, as it may worsen symptoms of urinary retention; patients with gastrointestinal obstructive disorders (i.e., pyloric stenosis), due to the risk of gastrointestinal obstruction; patients with severe constipation (≤ 2 bowel movements per week) (see **CONTRAINDICATIONS**); patients with risk of decreased gastrointestinal motility.

Narrow-Angle Glaucoma: ENABLEX* should be used with caution in patients with narrow-angle glaucoma.

Hepatic: No special dosing requirements for patients with mild hepatic impairment (Child Pugh A). (Child Pugh scores, see REFERENCES – References # 1, 2 and 4 in Enablex* Product Monograph) The daily dose of ENABLEX* (darifenacin) should not exceed 7.5 mg for patients with moderate hepatic impairment (Child Pugh B). ENABLEX* has not been studied in patients with severe hepatic impairment (Child Pugh C) and therefore is not recommended for use in this patient population (see **DOSAGE AND ADMINISTRATION**).

Renal: Insufficient evidence to determine whether a dose reduction is necessary in patients with severe renal failure.

Special Populations

Pregnant women: There are no studies of ENABLEX* in pregnant women. ENABLEX* should be used during pregnancy only if the benefit to the mother outweighs the potential risk to the fetus.

Nursing Women: ENABLEX* is excreted into the milk of rats. It is not known whether ENABLEX* is excreted into human milk; therefore caution should be exercised before administering to a nursing woman.

Pediatrics: The safety and effectiveness of ENABLEX* in pediatric patients have not been established.

Geriatrics: The recommended starting dose for the elderly is 7.5 mg daily. After 2 weeks of starting therapy, patients should be reassessed for efficacy and safety. For those patients who have an acceptable tolerability profile but

require greater symptom relief, the dose may be increased to 15 mg daily, based on individual response.

ADVERSE REACTION SERIOUSNESS AND INCIDENCE

During the clinical development of ENABLEX* (darifenacin), a total of 7,271 patients and healthy volunteers have been treated with doses of darifenacin from 3.75 mg to 60 mg once daily (recommended doses are 7.5 and 15 mg once daily) for up to one year duration of therapy, resulting in more than 2,000 patient-years exposure, for overactive bladder and other indications.

In fixed-dose, placebo-controlled Phase III studies, the adverse events (regardless of causality) reported in 3% or more patients treated with 7.5 mg or 15 mg ENABLEX* Extended Release Tablets, respectively, were as follows: dry mouth (20.2%; 35.3%), constipation (14.8%; 21.3%), dyspepsia (2.7%; 8.4%), headache (4.5%; 5.1%), respiratory tract infection (2.7%; 5.1%), urinary tract infection (4.7%; 4.5%), abdominal pain (2.4%; 3.9%), asthenia (1.5%; 2.7%), flu syndrome (2.1%; 2.1%), dizziness (0.9%; 2.1%), dry eyes (1.5%; 2.1%), back pain (2.4%; 1.5%), nausea (2.7%; 1.5%), pharyngitis (2.7%; 1.2%) and diarrhea (2.1%; 0.9%).

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 dose studied. There is a tendency for adverse reactions, particularly those classified as mild to moderate, to increase with increasing dose.

The most frequently reported adverse events in the pivotal trials 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 in the population tested. The incidence of cardiovascular adverse events such as tachycardia, were less than 1% at all doses and did not increase with dose.

No clinically significant changes in QT interval were observed in clinical trials of volunteers and patients (n = 964 treated, n = 261 placebo) with ENABLEX* up to and including doses of 60 mg (4 times the recommended dose).

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.

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

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

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

Abnormal Hematologic and Clinical Chemistry Findings: There was no indication of an increased incidence of laboratory test abnormalities in subjects treated with darifenacin in long-term studies.

Post-Market Adverse Drug Reaction: The following events have been reported in association with darifenacin use in worldwide post-marketing experience: Generalized Hypersensitivity reactions including angioedema. 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.

DRUG INTERACTIONS

Drug-Drug Interactions

Effects of other drugs on darifenacin: Darifenacin metabolism is primarily mediated by the cytochrome P450 enzymes CYP 2D6 and CYP 3A4. Therefore,

inducers of CYP 3A4 or inhibitors of either of these enzymes may alter darifenacin pharmacokinetics.

CYP 2D6 inhibitors: No special dosing requirements are necessary in the presence of CYP 2D6 inhibitors. Darifenacin exposure following 30 mg once daily dosing (twice the maximum recommended therapeutic dose) was 33% higher in the presence of the potent CYP 2D6 inhibitor paroxetine 20 mg.

CYP 3A4 inhibitors: The daily dose of darifenacin should not exceed 7.5 mg when co-administered with potent CYP 3A4 inhibitors (e.g., ketoconazole, itraconazole, miconazole, troleandomycin, clarithromycin, nefazodone and ritonavir) (see **DOSAGE AND ADMINISTRATION**). When the 7.5 mg once-daily dose of darifenacin was given to steady-state and co-administered with the potent CYP 3A4 inhibitor ketoconazole, mean darifenacin exposure was increased 5.3-fold. No special dosing requirements are necessary in the presence of moderate CYP 3A4 inhibitors. Darifenacin exposure following 30 mg once daily dosing (twice the maximum recommended therapeutic dose) was 34%, 84% and 95% higher in the presence of cimetidine, fluconazole and erythromycin, respectively.

Effects of darifenacin on other drugs: The potential for clinical doses of darifenacin to act as inhibitors of CYP 2D6 or CYP 3A4 substrates was investigated in specific clinical interaction studies.

CYP 2D6 substrates: Caution should be taken when darifenacin is used concomitantly with medications that are predominantly metabolized by CYP 2D6 and which have a narrow therapeutic window (i.e., flecainide, thioridazine and tricyclic antidepressants). The mean exposure of imipramine, a CYP 2D6 substrate, was increased 70% in the presence of steady-state darifenacin 30 mg once daily (twice the maximum recommended therapeutic dose). This was accompanied by a 3.6-fold increase in the exposure of desipramine, the active metabolite of imipramine.

CYP 3A4 substrates: Darifenacin (30 mg once daily) had no clinically relevant effect on the exposure of the CYP 3A4 substrate midazolam. Darifenacin (30 mg once daily) had no effect on the pharmacokinetics of the oral contraceptives levonorgestrel or ethinylestradiol.

Other Drugs:

Warfarin: The effect of warfarin on prothrombin time was not significantly altered when co-administered with darifenacin 30 mg/day (twice the maximum daily recommended dose).

Digoxin: Routine therapeutic drug monitoring for digoxin should be continued. Darifenacin 30 mg qd (twice the maximum dose) co-administered with digoxin at steady-state resulted in a small but potentially clinically significant, 16%, increase in digoxin exposure. Therapeutic drug monitoring for digoxin should be performed when initiating and ending darifenacin treatment, as well as changing the darifenacin dose.

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

In vitro studies: In vitro human microsomal studies have shown that darifenacin does not inhibit CYP 1A2 or CYP 2C9 up to concentrations of $1 \cdot 10^5$ nM. In comparison, the average peak unbound concentration of darifenacin at steady state following 15 mg dosing is 0.24 nM.

Effect of food: There is no effect of food on multiple dose pharmacokinetics from extended release tablets.

Effects on ability to drive and use machines: No studies of the effects of ENABLEX* on the ability to drive and use machines have been performed. However, antimuscarinics such as ENABLEX* may produce dizziness or blurred vision. Patients experiencing these side effects should not drive or use machines.

To report an adverse event, contact your Regional Adverse Reaction Monitoring Office at 1-866-234-2345.



Dosage and Administration

Recommended Dose and Dosage Adjustment: The recommended starting dose of ENABLEX* (darifenacin) Extended Release Tablets is 7.5 mg once daily. For those patients starting on 7.5 mg daily and 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* Extended Release Tablets should be taken once daily. They may be taken with or without food, and should be swallowed whole and not chewed, divided or crushed.

Dosing Considerations

There are no special dosing requirements for the elderly, for male versus female patients, or for patients with renal impairment.

Use in Children: The safety and effectiveness of ENABLEX* in pediatric patients with overactive bladder or any other condition have not been investigated.

Hepatic Impairment: There is a risk of increased exposure in this population; however, 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 CYP 3A4 inhibitors (e.g., ketoconazole, itraconazole, miconazole, troleandomycin and nefazodone), 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).



References

1. Enablex* Product Monograph, Novartis Pharmaceuticals Canada Inc., January 5, 2009.

Product Monograph available on request:

Triton Pharma Inc
665 Milway Avenue, Suite 31B
Concord, Ontario L4K 3T8
Tel: 1-866-429-9707
www.tritonpharma.ca



NOVARTIS

Manufactured and distributed by
Novartis Pharmaceuticals Canada Inc.
Dorval, Quebec H9S 1A9



Marketed by Triton Pharma Inc.
Concord, Ontario L4K 3T8

*Enablex is a registered trademark.



Supplemental Product Information

ADVERSE REACTIONS

The following adverse events were also reported, regardless of causality, by less than 2% of ENABLEX* patients in either the 7.5 mg or 15 mg once daily darifenacin dose groups in the fixed-dose, placebo-controlled Phase III studies: accidental injury, pain, face edema, hypertension, vomiting, flatulence, ulcerative stomatitis, peripheral edema, weight gain, ALT increased, AST increased, edema, arthralgia, insomnia, somnolence, thinking abnormal, bronchitis, rhinitis, sinusitis, cough increased, rash, dry skin, pruritus, sweating, abnormal vision, taste perversion, urinary tract disorder, vaginitis, impotence and bladder pain, urinary retention.

OVERDOSAGE

No cases of overdose were recorded in the ENABLEX* (darifenacin) clinical development program that included doses as high as 60 mg daily (4 times the recommended maximum daily dose). Moreover, in a study evaluating the interaction between ketoconazole and daily doses of 30 mg darifenacin, the systemic plasma exposure exceeded the systemic exposure observed after a 60 mg dose by a factor of two, with no reported SAEs. The most commonly reported adverse events were typical of those expected from a drug with antimuscarinic M₃ receptor antagonist activity. Overdosage with antimuscarinic agents can potentially result in severe antimuscarinic effects. Treatment should be symptomatic and supportive when necessary, and aimed at reversing the antimuscarinic symptoms under careful medical supervision.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

STORAGE AND STABILITY

ENABLEX* Extended Release Tablets should be stored at 15 to 30°C and protected from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ENABLEX* is formulated as a once-a-day extended release tablet for oral use containing 7.5 mg or 15 mg of darifenacin as darifenacin hydrobromide.

ENABLEX* (darifenacin as darifenacin hydrobromide) 7.5 mg Extended Release Tablets: White, round shallow convex film-coated tablets, debossed with "DF" on one side and "7.5" on the reverse. The inactive ingredients are dibasic calcium phosphate anhydrous, hypromellose, magnesium stearate, titanium dioxide, PEG 400 and talc. Blister packs of 28 tablets (7 or 14 tablets per blister).

ENABLEX* (darifenacin as darifenacin hydrobromide) 15 mg Extended Release Tablets: Light peach, round shallow convex film-coated tablets, debossed with "DF" on one side and "15" on the reverse. The inactive ingredients are dibasic calcium phosphate anhydrous, hypromellose, magnesium stearate, titanium dioxide, iron oxide yellow, iron oxide red, PEG 400 and talc. Blister packs of 28 tablets (7 or 14 tablets per blister).