drug information perspectives

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Contents

DARIFENACIN

TRADE NAME: Enablex

CLASSIFICATION: Anticholinergic; muscarinic receptor antagonist; antispasmodic

ACTION

- Muscarinic receptor antagonist.
- Inhibits contractions of bladder detrusor muscle by antagonism of M3 muscarinic receptors, thus potentially reduces urinary urge and incontinence.
- There are 5 muscarinic receptor subtypes, M1-M5. Tissues generally contain more than one subtype: brain (mostly M1 but also M3 and M4); salivary glands (M1 stimulation produces lubricating secretions while both M1 and M3 stimulation produce low viscosity secretions); heart (mostly M2 but also M3); eye ciliary muscle (M3 and M5); bladder (most detrusor muscle contraction is due to M3 stimulation, also M2); gastrointestinal tract (M2 and M3); gastric acid secretion (M1).
- Selectivity: Darifenacin selectively antagonizes M3 muscarinic receptors. *In vivo* selectivity of darifenacin for human muscarinic receptors is M3 > M1/M4/M5 > M2.
- Toxicity potential: Darifenacin has a 5-fold greater affinity for M3 receptors than M1 receptors, suggesting a low potential for anticholinergic-related cognition deficits. M3 receptors are present in salivary glands, eyes and gastrointestinal tract, thus dry mouth, blurred vision and constipation are expected.

PHARMACOKINETICS
Half-life: 12-16 hours.
Absorption: 97% absorption, but undergoes extensive saturable first-pass metabolism, resulting in a bioavailability of 15-18%. Maximum serum concentration after 5-12 hours. Absorption is not altered by food.
Distribution: 98% plasma protein bound. Low levels in brain in animals.
Metabolism: Extensively metabolized by CYP2D6 and CYP3A4 (mainly by CYP3A4 in CYP2D6 Poor Metabolizers). Three major metabolites; only one has antimuscarinic action but it is unlikely to contribute to effect. Possible saturation of metabolism by CYP2D6 and 3A4 in the GI tract wall produces dose-dependent kinetics, with a double dose producing more than double the AUC (bioavailability).
Elimination: Urine 60%, feces 40%, mainly as metabolites; only 3% excreted unchanged. Substrate for P-glycoprotein.

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Special populations:

- **Elderly**: Increased bioavailability with age.
- **Hepatic impairment**: Mild hepatic impairment: No change in pharmacokinetics. Moderate hepatic impairment (Child Pugh B): Unbound drug AUC is increased 4.7-fold, Cmax is increased 4-fold. Severe hepatic impairment: No data.
- **Renal impairment**: No alteration in pharmacokinetics detected.
- **Sex difference**: 31% lower clearance in females than in males.
- **Race**: 56% lower bioavailability in Japanese.
- **Pharmacogenetics: In CYP2D6 Poor Metabolizers** (7% of Caucasians, up to 2% of Asians and Black people), the drug is metabolized by CYP3A4. Bioavailability is increased by 40% in heterozygous Extensive Metabolizers and by 90% in Poor Metabolizers, relative to homozygous Extensive Metabolizers.

USES AND EFFICACY

Uses: Symptomatic treatment of overactive bladder.

Compared with placebo, it reduces the urge to void by about 1 urge/day, reduces the number of episodes of incontinence by 10-20%, reduces significant leaks by 1-2 episodes per week, and slightly reduces the number of voids by about 1/day. There is a strong placebo response. Effects are consistent with documented improvements in quality of life, particularly with an increased ability to be active outside the home. Nocturnal wakening to void and warning times have not been consistently improved, and the average volume of urine per void increases only by 10-30mL. Response rate: Approximately 75% of patients can achieve a 50% or greater decrease in incontinence episodes, compared with 49% of patients taking placebo.

Clinical course: Benefit is detectable within 2 weeks, and may improve even more over the first 2-3 months.

Major clinical trials

In a randomized, placebo-controlled, double-blind study of patients with overactive bladder, 1095 adults (age 19-88) were given darifenacin 7.5mg once daily, darifenacin 15mg once daily, or placebo for 12 weeks. The number of incontinence episodes was reduced from about 16/week at baseline by 8.8 or 10.6 with darifenacin 7.5mg or 15mg, respectively. This represented a statistically significant reduction of 68-77% compared with 54-58% in the placebo groups. Significant leaks requiring a change of clothing or pads were statistically significantly reduced by 4-5 episodes per week, compared with 2-2.7 episodes/week with placebo. The number of urges and voids per day were significantly reduced by 0.8-0.9 episodes/day compared with placebo. A 90% reduction in incontinence episodes was achieved by 27-28% of patients in the darifenacin groups compared with 17% in the placebo groups. Dry mouth and constipation were common side effects. *Study limitations*: The placebo response was very high. Some patients were using bladder training.

Comparisons

Vs. oxybutynin

Oxybutynin 5mg three times daily has similar efficacy (reduced incontinence, reduced urge) to darifenacin 15mg after 2 weeks; long-term comparisons are not available. At these doses, adverse effects were more common with oxybutynin than with darifenacin: dizziness 1.6% of patients versus 0%; blurred vision 3.3% of patients versus 0%; dry mouth 36% of patients versus 13%; no difference in rates of constipation.

Advantages:

- Simple once daily administration independent of meals.
- M3 muscarinic receptor selectivity may reduce the potential for cognitive impairment.
- Long-term effectiveness and tolerability documented.
- Since pharmacokinetics are not altered in patients with reduced renal function, dosing is simplified in patients with renal impairment.
- Available in Europe since the 1980's.

Disadvantages:

- Many drug interactions.
- Dry mouth and constipation are common.

***Place in therapy*:**
Modestly reduces incontinence, including significant leaks, in patients with overactive bladder. Compared with other drugs for overactive bladder, darifenacin has the theoretical advantage of little effect on M1 muscarinic receptors, which should lead to few CNS side effects. A lack of effect on cognition has been seen in trials, and will be an advantage if verified in real world usage. Direct comparisons with other drugs have not been adequately conducted. There is a strong placebo response, and there is evidence that behavioural training is as effective as, or more effective than, drug therapy. A trial of bladder training with encouragement should be attempted prior to initiating drug therapy with its common side effects of dry mouth and constipation.

Investigational/Unapproved Uses:

- ***Irritable bowel syndrome**:* Studies are being done.

CONTRAINDICATIONS AND PRECAUTIONS

***Contraindications*:**

- **Hypersensitivity**
- **Urinary retention** (may cause acute urinary retention)
- **Gastric retention** (may reduce gastric motility)
- **Uncontrolled narrow-angle glaucoma**
- **Severe liver impairment** (no data; highly eliminated by metabolism)

***Precautions*:**

- Patients with **bladder outflow obstruction** (risk of developing urinary retention)
- Patients with **decreased gastrointestinal motility or gastrointestinal obstructive disorders** such as pyloric stenosis, myasthenia gravis, severe constipation, ulcerative colitis (risk of decreased gastric motility)
- Patients with controlled **narrow angle glaucoma**
- **Moderate liver impairment** (maximum dose 7.5mg/day)
- **Xerostomia, Sjogren's Syndrome** (risk of dry mouth)
- **Report** unexpected or serious reactions to Canada Vigilance, Canada's adverse drug reaction monitoring program.

PREGNANCY AND LACTATION

- Not teratogenic in animals. Delayed ossification in rats at high doses. No human data. Consider risk:benefit.
- No data on presence in breast milk in humans. Possible anticholinergic adverse effects in the breast-feeding infant; caution.

SIDE EFFECTS:
Most common effects are dry mouth and constipation, due to anticholinergic effects, with onset in the first two weeks.

Cardiovascular:

- Tachycardia (less than 1%). No QT interval prolongation.

CNS:

- Dizziness (0.9-2.1% versus placebo 1.3%).
- Headache 6% versus placebo 2%) .
- Cognitive impairment has not occurred in studies done in adults or in the elderly.
- Confusion, dementia (1 case).

Gastrointestinal:

- Dry mouth (20-40% versus placebo 6-8%, dose-related).
- Constipation (14-25% versus placebo 5-7%, dose-related, some patients may require laxatives, may be severe).
- Dyspepsia (at 15mg daily, 8% versus placebo 2%).
- Abdominal pain (2-4% versus placebo 0.5%).

Genitourinary:

- Urinary tract infection (5% versus placebo 3%).
- Acute urinary retention (cases).

Other:

- Dry eyes (1.5-2.1% versus placebo 0.5%).
- Abnormal vision (less than 2%).
- Lack of efficacy (case reports); drug delivery system malfunction (1 case).

INTERACTIONS:

Extensively metabolized by CYP2D6 and CYP3A4 (mainly by CYP3A4 in people who are Poor Metabolizers of CYP2D6). A moderate inhibitor of CYP2D6, with less inhibition of CYP3A4. Does not induce or inhibit CYP1A2 or CYP2C9**.**

DRUG	EFFECT	MECHANISM	IMPORTANCE
Acetylcholinesterase inhibitors (donepezil, rivastigmine)	Decreased efficacy of both drugs	Antagonism	Caution
Anticholinergic drugs	Increased anticholinergic adverse effects	Additive	Caution
Cimetidine	Increased darifenacin levels	Decreased metabolism	Caution
Digoxin	Increased digoxin levels	Unknown; possibly P-glycoprotein competition	Caution, monitor digoxin level when starting or stopping either drug
Drugs that induce CYP3A4 (rifampicin, carbamazepine, St. John's wort, barbiturates)	Decreased darifenacin levels	Increased metabolism	Caution
Drugs that inhibit CYP2D6 (paroxetine, terbinafine, quinidine)	Increased darifenacin levels in extensive metabolizers	Decreased metabolism (CYP2D6)	Caution
Drugs that inhibit CYP3A4*	Increased darifenacin levels in both extensive and poor metabolizers	Decreased metabolism (CYP3A4)	Maximum dose of darifenacin 7.5mg/day for strong inhibitors or avoid; caution with moderate inhibitors

Drugs that are metabolized by CYP2D6**	Increased drug levels	Decreased metabolism	Caution
Drugs that are metabolized by CYP3A4***	Increased drug levels	Decreased metabolism	Caution; unlikely to interact; controversial

*** Drugs that strongly inhibit CYP3A4 include**: Clarithromycin, itraconazole, ketoconazole, miconazole, troleandomycin, nelfinavir, nefazodone and ritonavir. Less interaction occurs with moderate inhibitors (diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil).

**** Drugs that are metabolized by CYP2D6 include**: Carvedilol, clozapine, codeine, cyclobenzaprine, dextromethorphan, donepezil, flecainide, galantamine, hydrocodone, metoprolol, oxycodone, propafenone, propranolol, risperidone, thioridazine, tolterodine, the tricyclic antidepressants imipramine, nortriptyline, desipramine, trimipramine, and venlafaxine.

***** Drugs that are metabolized by CYP3A4 include**: Alfentanil, alprazolam, amiodarone, amitriptyline, amprenavir, aprepitant, atazanavir, atorvastatin, bosentan, bromocriptine, budesonide, buprenorphine, buspirone, busulfan, cabergoline, carbamazepine, cisapride, cyclophosphamide, cyclosporine, darunavir, delavirdine, dexamethasone, diltiazem, disopyramide, donepezil, dutasteride, ergot derivatives, estrogens, felodipine, fentanyl, fluticasone, fosamprenavir, galantamine, hydrocortisone, ifosfamide, imatinib, imipramine, indinavir, irinotecan, itraconazole, lidocaine, lovastatin, maraviroc, methadone, methylprednisolone, midazolam, nelfinavir, pimozide, progestogens, propafenone, quetiapine, quinidine, rifabutin, ritonavir, saquinavir, sibutramine, sildenafil, simvastatin, sirolimus, solifenacin, tacrolimus, tadalafil, tamoxifen, taxanes, teniposide, terfenadine, testosterone, tipranavir, tolterodine, triazolam, vardenafil, vinblastine, vincristine, voriconazole, zopiclone.

Interactions lacking
A lack of pharmacokinetic interaction has been documented with

- Oral contraceptives containing levonorgestrel, ethinyl estradiol.
- Warfarin

DOSAGE:

Adults:
Initially 7.5mg once daily. After 2 weeks, dose may be increased to 15mg once daily if tolerated and required.

Children: No data.

Elderly: No dosage adjustment required.

Hepatic impairment:
Mild hepatic impairment (Child Pugh A): No dosage adjustment required. Moderate hepatic impairment (Child Pugh B): Maximum dose 7.5mg daily. Severe hepatic impairment: Not recommended due to lack of data.

Renal impairment: No dosage adjustment required. No data.

Concurrent potent CYP3A4 inhibitors (ketoconazole, itraconazole, miconazole, troleandomycin, clarithromycin, nefazodone and ritonavir): Maximum dose 7.5mg once daily.

Pharmacogenetics:
CYP2D6 Poor Metabolizers: In CYP2D6 poor metabolizers (7% of Caucasians, up to 2% of Asians and Black people) the drug is metabolized by CYP3A4, and drug exposure is increased 55%. No dosage adjustment required.

NURSING IMPLICATIONS:
Darifenacin may be administered with food or milk, or on an empty stomach.

Extended-release tablets must be swallowed whole. They should not be chewed, crushed or broken.

Monitor urine output. Darifenacin may cause urinary retention. If urinary retention or skin rash occur, stop giving the drug. Notify physician immediately.

The elderly may be especially sensitive to the anticholinergic side effects: severe dry mouth, blurred vision, drowsiness, constipation, urinary retention.

Supervise ambulation. Encourage fluids and dietary fibre intake. Dry mouth may be relieved by sucking on ice chips or by chewing sugarless gum.

Clinical monitoring parameters: improvement in urinary frequency, urgency, nocturia, and urge incontinence.

Store at room temperature. Protect from light.

Keep out of reach of children.

PATIENT INSTRUCTIONS:
Darifenacin (dar-ee-FEN-a-sin) is used to control the symptoms of an overactive bladder. Symptoms can include the frequent need to urinate or the inability to control urination.

Before taking this medication for the first time, be sure that your physician is aware if you have any of the following conditions: liver impairment, narrow angle glaucoma, urinary outflow problems, gastrointestinal problems such as constipation or gastric obstruction; Sjogren's syndrome.

Take this medication exactly as prescribed. It is taken once a day. Taking it at the same time each day will help you to remember. It may be taken with or without food.

If you forget to take a dose, take it as soon as you remember unless it is almost time for the next dose. In that case, skip the missed dose and just take the next dose. Do not take a double dose to make up for a missed dose.

Swallow each tablet whole, do not crush or chew it.

This medication may take several weeks to produce an effect. Full effect may be seen after 8-12 weeks.

Tell your physician or pharmacist if you are taking any prescription medications or over-the-counter medications. Darifenacin can interact with various medications.

If you are pregnant or breast-feeding, discuss the use of this medication with your physician.

Some patients may experience dizziness. Do not drive a car or operate dangerous machinery until you know how this medication affects you.

This medication may cause you to have a dry mouth. Sucking on ice chips or chewing sugarless gum may help.

This medication may cause constipation. Fluid and dietary fibre intake may help prevent the constipation. Check with your physician if this persists or is bothersome.

Other common side effects that can be seen with darifenacin include headache, dizziness, or dry eyes. Check with your physician if these side effects persist or are bothersome.

If you develop swelling of the throat or face, or difficulty urinating, stop taking this product and contact your physician as soon as possible.

In a hot environment, this drug can reduce sweating and increase the risk of heat stroke. Drink plenty of fluids.

If you have experienced an unexpected or serious reaction to this drug, this can be reported to Health Canada's monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789). Note that this is not an emergency number.

Store this drug in its original container, away from heat, light and moisture, and out of the reach of children.

PRESENTATION:
Extended release tablets: 7.5, 15mg.

References are available on request.

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