

Darifenacin: first M3 receptor antagonist for overactive bladder

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PRODUCT PROFILE

Proprietary name: Emselex

Constituents: darifenacin

Indication: symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder (OAB) syndrome

Dosage and method of administration:

adults: initially 7.5mg daily; may be increased to 15mg daily after two weeks in patients requiring greater symptom relief; *elderly* – initially 7.5mg daily; may be increased to 15mg daily after two weeks for those patients who have an acceptable tolerability profile but require greater symptom relief; *children* – not recommended in patients under 18

Contraindications: patients hypersensitive to darifenacin or its excipients; patients with: urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, myasthenia gravis, severe hepatic impairment (Child-Pugh C), severe ulcerative colitis, toxic megacolon, concomitant treatment with potent CYP3A4 inhibitors

Precautions: administer Emselex with caution in patients with: autonomic neuropathy, hiatus hernia, clinically significant bladder outflow obstruction, risk for urinary retention, severe constipation or GI obstructive disorders, eg pyloric stenosis; use Emselex with caution in patients with: narrow-angle glaucoma, risk of decreased GI motility, gastro-oesophageal reflux and/or who are concurrently taking medicinal products, eg oral bisphosphonates, that can cause/exacerbate oesophagitis

Pregnancy and lactation: not recommended during pregnancy; caution should be exercised before administering Emselex to a nursing woman

Interactions: digoxin, inhibitors of CYP2D6 (eg paroxetine, terbinafine, cimetidine, quinidine) or CYP3A4 (eg ketoconazole, itraconazole, protease inhibitors such as ritonavir), moderate CYP3A4 inhibitors (eg erythromycin, clarithromycin, telithromycin, fluconazole, grapefruit juice), substrates of CYP2D6 (eg flecainide, thioridazine, imipramine) or CYP3A4 (eg midazolam), inducers of CYP3A4 (eg rifampicin, carbamazepine, barbiturates, St John's wort), P-glycoprotein inhibitors (eg ciclosporin, verapamil), antimuscarinic agents (eg oxybutynin, tolterodine, flavoxate)

Side-effects: *very common:* dry mouth, constipation; *common:* abdominal pain, headache; nausea, dyspepsia; dry eyes

Presentation/cost: 7.5mg, 15mg prolonged-release tablets; 7.5mg – 28, £26.13; 15mg – 28, £26.13



Darifenacin (Emselex) is the first antimuscarinic agent to target the M3 receptor that is associated with detrusor muscle contraction. In our New products review Steve Chaplin presents the clinical data relating to its efficacy and adverse effects, and Professor Christopher Chapple comments on its place in the treatment of overactive bladder.

The International Continence Society defines overactive bladder (OAB) as urgency, with or without urge incontinence, usually with frequency and nocturia.¹ The prevalence of OAB in the UK is about 20 per cent overall^{2,3} and increases with age.⁴ OAB has a marked impact on quality of life.⁵ A European survey found that many people with OAB symptoms have not been formally diagnosed and, though half of those diagnosed have been prescribed medication at some time, only one-quarter continue to take it.²

The National Institute for Health and Clinical Excellence (NICE) clinical guideline for the management of urinary incontinence in women includes the management of OAB.⁶ (The Scottish Intercollegiate Guidelines Network,

Dose	N	Median baseline	Median change from baseline	Median difference from placebo	95% CI	p value
placebo	271	16.6	-7.0	-	-	-
darifenacin 7.5mg od	335	16.0	-8.8	-2.0	(-3.6,-0.7)	0.004
placebo	384	16.6	-7.5	-	-	-
darifenacin 15mg od	330	16.9	-10.6	-3.2	(-4.5, -2.0)	<0.001
placebo	123	14.0	-6.0	-	-	-
darifenacin 7.5mg → 15mg	261	16.0	-8.2	-1.4	(-2.9,-0.0)	0.035

Table 1. Pooled analysis of clinical studies showing efficacy of darifenacin 7.5mg and 15mg once daily in reducing median number of incontinence episodes per week

SIGN, has published a management guideline for urinary incontinence in both men and women.⁷) Initial management comprises lifestyle change (weight loss if overweight, modifying fluid intake, avoiding caffeine), pelvic floor muscle training, bladder training and treatment with an antimuscarinic agent.⁶

The drug of first choice is immediate-release oxybutynin; if this is not tolerated, the alternatives are darifenacin (Emselex), solifenacin (Vesicare), tolterodine (Detrusitol) or trospium (Regurin), or modified-release (Lyrinel XL) or transdermal (Kentera) oxybutynin. Propiverine (Detrunorm) may also be considered for urinary frequency.

Meta-analysis of clinical trials of antimuscarinic agents has revealed a high placebo response to treatment (about 40 per cent) but antimuscarinic agents improve or stop symptoms in a further 15 per cent of patients; they also offer a modest improvement in quality of life.⁸

The technology⁹

Darifenacin is an antagonist at muscarinic receptors, with selectivity within the therapeutic range for M3 receptors (the predominant receptor subtype in the bladder). It is licensed for the symptomatic treatment of urge incontinence and/or increased urinary fre-

quency and urgency as may occur in patients with OAB syndrome. The recommended dose is 7.5mg per day initially; this should be assessed after two weeks and may be increased to 15mg per day if required. The dose should be increased in older patients only when tolerability is acceptable.

Darifenacin is metabolised by hepatic CYP2D6 and CYP3A4 enzymes. It should be prescribed with caution in patients taking other drugs that inhibit or induce these enzymes and should not be prescribed for patients taking potent inhibitors of CYP3A4 such as verapamil, itraconazole or ritonavir (Norvir). Like other antimuscarinic agents, darifenacin may potentiate the anticholinergic effects of TCAs and drugs for Parkinson's disease.

Emselex is a modified-release formulation. Peak plasma levels of darifenacin occur seven hours after administration and steady state levels are achieved on the sixth day.

Clinical trials

Three similar randomised, fixed-dose, double-blind trials have been pooled for analysis;^{10,11} a randomised flexible-dose trial has also been published.¹²

In the pooled analysis, a total of 1059 patients (85 per cent women, 95 per cent idiopathic OAB) with

frequency, urgency and urge incontinence of at least six months' duration were randomised to placebo or darifenacin 7.5 or 15mg per day. The primary end-point was the median change in number of incontinence episodes per week.

At baseline, the median number of incontinence episodes per week was 16-17. After 12 weeks, the median change was -8.8 episodes per week for darifenacin 7.5mg per day (2.0 fewer than placebo)¹³ and -10.6 episodes per week for 15mg per day (3.2 fewer than placebo);¹³ both differences were statistically significant (see Table 1).

Darifenacin also significantly improved secondary end-points including the number of daily voids or urgency episodes (0.8-0.9 episodes fewer than placebo), the severity of urgency episodes, incontinence episodes requiring a change of pad (1.8-2.0 fewer per week), and - at the 15mg per day dose only - nocturnal awakenings (0.7 per week).

The proportions of patients experiencing at least three dry days per week were 55 per cent at 7.5mg per day and 65 per cent at 15mg per day, both of which were significantly greater than placebo (43 and 48 per cent respectively).¹⁰ Similar findings were reported in a subgroup analysis of 317 patients aged 65 or over.¹¹

In the flexible dose study, treatment with darifenacin was initiated at a dose of 7.5mg per day and increased to 15mg per day after two weeks if additional efficacy was required. Fifty-nine per cent of patients increased their dose; outcomes at each dose were similar after 12 weeks and comparable with those reported in the pooled analysis.

A nonblinded uncontrolled extension study involving 716 patients who had participated in two of the 12-week trials showed that the number of incontinence episodes per week was further reduced after two years and over 40 per cent of patients experienced at least a reduction in weekly incontinence episodes of at least 90 per cent.¹⁴

Two small short-term trials suggest that the efficacy of darifenacin may be comparable with that of immediate-release oxybutynin 2.5-5mg three times daily.^{15,16}

Adverse effects

In seven-day studies in healthy volunteers, including older people, darifenacin has been shown to have no effect on cognitive function, cardiac function or vision.¹⁷⁻¹⁹

The adverse anticholinergic effects of darifenacin are dose-dependent.⁹ In clinical trials, as with other antimuscarinic agents, dry mouth (placebo 8 per cent, 7.5mg per day 20 per cent, 15mg

per day 35 per cent) and constipation (6, 15 and 21 per cent respectively) were the commonest adverse events associated with darifenacin.¹⁰ The incidence of cardiovascular and CNS effects was comparable with placebo and there was no evidence of an effect on cardiac conduction.¹³

The frequency of discontinuation due to treatment-related adverse events was 1.3 per cent with placebo and 1.2 and 4.5 per cent for 7.5mg and 15mg per day darifenacin.¹⁰

In the nonblinded extension study, 66 per cent of patients completed two years' treatment with darifenacin. The commonest adverse events were dry mouth (23 per cent) and constipation (21 per cent).¹⁴

Summary

Darifenacin is an antimuscarinic agent for OAB. It reduces the number of incontinence episodes by about one per week and the number of urgency episodes by about one per day, in addition to improving other OAB symptoms. Its common adverse effects are typical of antimuscarinic agents; in clinical trials, darifenacin was not associated with an increased risk of clinically significant adverse cardiovascular or CNS effects. Long-term trials comparing darifenacin with other treatments for OAB are lacking.

Key points

- the prevalence of OAB in the UK is about 20 per cent; drug treatment is one component of management
- darifenacin is an M3 receptor antagonist for the treatment of OAB
- it reduces the number of episodes of weekly incontinence and daily urgency, and reduces urgency severity
- the commonest adverse effects of darifenacin are dry mouth and constipation, affecting about 20 per cent of patients in long-term use
- darifenacin does not appear to be associated with significant adverse cardiovascular or CNS effects
- its effectiveness compared with other antimuscarinic agents is uncertain

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By Steve Chaplin, a pharmacist who specialises in writing on therapeutics

Place in therapy

OAB is a term applied to the troublesome urinary storage symptoms of urgency (a sudden and strong desire to void) with or without urgency incontinence, usually with increased frequency of micturition (over eight micturitions per 24 hours) and nocturia.¹ It is a highly prevalent, chronic and debilitating disease that affects men and women of all ages. The symptoms occur in the absence of pathological (*eg* urinary tract infection, urinary stones or interstitial cystitis) or metabolic factors (*eg* diabetes mellitus) that would explain them.

The prevalence of OAB in Europe and the USA has been estimated. One population-based survey of 16 776 men and women aged 40 years and older conducted in six countries estimated the prevalence of OAB in Europe to be 15.6 and 17.4 per cent respectively for men and women, with an overall prevalence of 16.6 per cent.²

The prevalence of OAB was also assessed in a large population-based survey in the USA: the National Overactive BLadder

Evaluation (NOBLE) survey.³ A sample of 5204 adults over 18 years of age and representative of the US population by sex, age and geographical region was assessed. The overall prevalence of OAB was similar between men (16.0 per cent) and women (16.9 per cent) and was quite similar to the results reported earlier from Europe.²

Overall, from these studies it can be concluded that of these patients with OAB, approximately one-third are troubled by incontinence (OAB 'wet') and two-thirds are not (OAB 'dry').

Clearly, OAB impacts on all aspects of patients' everyday activities, including emotional, physical, social, occupational and domestic functions, and shows similar prevalence to several other chronic medical conditions such as asthma and chronic bronchitis, yet many patients with OAB do not seek medical help for their symptoms. Reasons include embarrassment and misconceptions, such as lack of effective treatment options. Consequently, many patients with OAB resort to elaborate coping strategies in order to manage their symptoms, such as frequent void-

ing, mapping the location of toilets, restricting fluid intake and/or the use of absorbent pads. OAB therefore accounts for a considerable socioeconomic burden.

Muscarinic receptors

The symptoms of OAB can be explained by abnormal increases in bladder detrusor muscle contractility during the filling phase of the micturition cycle. Although the exact aetiology of OAB remains largely unknown, it is well recognised that the underlying abnormal detrusor muscle contractions (together with those associated with normal voiding) are at least in part mediated by acetylcholine-mediated stimulation of bladder muscarinic receptors. Consequently, antimuscarinic agents have become the treatment of choice for OAB.⁴

However, existing agents of this class are not highly selective for the muscarinic M3 receptor subtype that has been shown to be primarily responsible for mediating human detrusor muscle contraction.⁵ This explains their potential to cause a number of side-effects given that five muscarinic receptor subtypes are known to exist and

such subtypes are located in many other tissues throughout the body (including the salivary glands, GI tract, heart, CNS and eye).⁶ Such effects often give rise to tolerability and safety problems.

Antimuscarinic agents selective for the muscarinic M₃ receptor might therefore on theoretical grounds be expected to have clinical efficacy in the treatment of OAB with a lower propensity for side-effects and safety concerns related to blockade of other receptor subtypes, including cognitive impairment and tachycardia (primarily M₁ and M₂ receptor-mediated, respectively).⁷

Darifenacin

Darifenacin is a novel agent that was identified on the basis of this subtype-selectivity rationale, and represents the first M₃ selective receptor antagonist to undergo extensive clinical evaluation for the treatment of patients with OAB. It appears to have similar efficacy to the other agents that are currently available and the presence of two doses allows flexible dosing. Potential advantages over other

contemporary agents in terms of increased safety relating to pharmacological selectivity in the context of both the cardiovascular and CNS have been suggested, but definitive comments on this await the results of adequately powered head-to-head clinical studies.

To summarise, at this juncture darifenacin has to be considered to be a new agent with similar efficacy to other agents, with the possibility of flexible dosing and similar tolerability to other contemporary agents.

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