

NEW DRUG EVALUATION

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DARIFENACIN

Darifenacin is an antimuscarinic licensed for overactive bladder syndrome. It has been shown to significantly reduce the number of incontinence episodes experienced per week compared with placebo. The main adverse effects are dry mouth and constipation, but it is not known how these adverse effects compare to other controlled-release anticholinergics. NICE states that oxybutynin is the first-line drug treatment after non-pharmacological interventions. Darifenacin should be reserved for use only after other second-line agents have been given an adequate therapeutic trial (e.g. oxybutynin SR and tolterodine), and until further comparative studies have been undertaken.

What is it?

Darifenacin hydrobromide (Emsalex®, Novartis) is a muscarinic M₃ selective antagonist,¹ licensed for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency in patients with overactive bladder syndrome (OAB).² Around 16% of adults have symptoms of overactive bladder (urgency with frequency and/or urge incontinence), and prevalence increases with age.³ Darifenacin is available as 7.5 mg or 15 mg prolonged-release tablets and the recommended starting dose is 7.5 mg daily; after two weeks the dose may be increased to 15 mg daily if required.² Currently, the most widely prescribed and studied anticholinergic drugs for OAB are oxybutynin and tolterodine.⁴

How effective is it?

A pooled analysis of three phase III studies was undertaken in 1,059 patients (85% women) with OAB symptoms, who were randomised to once daily treatment with darifenacin 7.5 mg or 15 mg, or matching placebo for 12 weeks.⁵ Compared to baseline, both darifenacin 7.5 mg and 15 mg significantly reduced the number of incontinence episodes per week (the primary endpoint). The median changes were -8.8 (-68.4%, $p = 0.004$) for darifenacin 7.5 mg, and -10.6 (-76.8%, $p < 0.001$) for darifenacin 15 mg.⁵

A 12-week study of 561 OAB patients compared darifenacin 3.75 mg, 7.5 mg and 15 mg with placebo, using the same primary endpoint as above.⁶ Median changes at week 12 were -9.0 (-67.7%, $p = 0.010$) and -10.4 (-72.8%, $p = 0.017$) for 7.5 mg and 15 mg darifenacin respectively compared with -7.6 (-55.9%) for placebo.⁶

One small study compared darifenacin 15 mg and 30 mg daily with oxybutynin (5 mg three times daily) and placebo in OAB patients (93.4% of whom were female).⁷ Fifty-eight patients were included in the efficacy analysis.⁷ OAB improvement with darifenacin 15 mg and oxybutynin was comparable. Mean number of incontinence episodes per week was 10.93 with darifenacin 15 mg, 9.45 with oxybutynin and 14.64 with placebo ($p < 0.05$ vs placebo).⁷

In a two year open-label extension trial of two 12-week studies,⁸ darifenacin's efficacy improved or was maintained throughout this period.⁸

How safe is it?

Adverse events (A/E) experienced by $\geq 3\%$ of patients in the pooled analysis of placebo controlled trials are shown below:⁵

A/E	Darifenacin 7.5mg n (%)	Darifenacin 15mg n (%)	Placebo n (%)
All A/E	182 (54.0)	219 (65.6)	189 (48.7)
Dry mouth	68 (20.2)	118 (35.3)	32 (8.2)
Constipation	50 (14.8)	71 (21.3)	24 (6.2)
Headache	15 (4.5)	17 (5.1)	21 (5.4)
Dyspepsia	9 (2.7)	28 (8.4)	10 (2.6)

As expected, the incidences of dry mouth and constipation were significantly higher with both darifenacin strengths than placebo. However, there were also high incidences of A/E with placebo. Three patients had at least one treatment-related A/E resulting in hospitalisation; two placebo and one darifenacin patient (which was considered unrelated to the A/E).⁵

Similar incidences of A/E were seen in other trials.^{6,7}

The oxybutynin comparative trial demonstrated a lower incidence of dry mouth with darifenacin 15 mg daily compared with oxybutynin 5 mg three times daily (13.1% and 36.1% respectively, $p < 0.05$), but comparable to that with 30 mg darifenacin (34.4% vs 36.1% respectively). Constipation was comparable (9.8% and 8.2% for darifenacin 15 mg and oxybutynin respectively) but was higher with darifenacin 30 mg (21.3% vs 8.2% respectively).⁷ Darifenacin has a high selectivity for M₃ receptors, whilst sparing M₁ and M₂ receptors. Oxybutynin shows a high affinity for M₃ and M₁ receptors, which may explain its more pronounced effect on salivation and consequently increased incidence of dry mouth relative to darifenacin.⁷

What other options are there?

NICE recently issued a guideline on urinary incontinence in women, recommending that first-line options include non-pharmacological methods (e.g. bladder training).⁹ Non-proprietary, immediate-release oxybutynin should be offered as first-line antimuscarinic if bladder training is ineffective. If this is not tolerated, darifenacin, solifenacin, tolterodine, trospium or an extended-release or transdermal formulations of oxybutynin should be considered. NICE states that there is no evidence of clinically important efficacy differences among antimuscarinic drugs, but immediate-release non-proprietary oxybutynin is the most cost-effective of the available options.⁹

When should it be used?

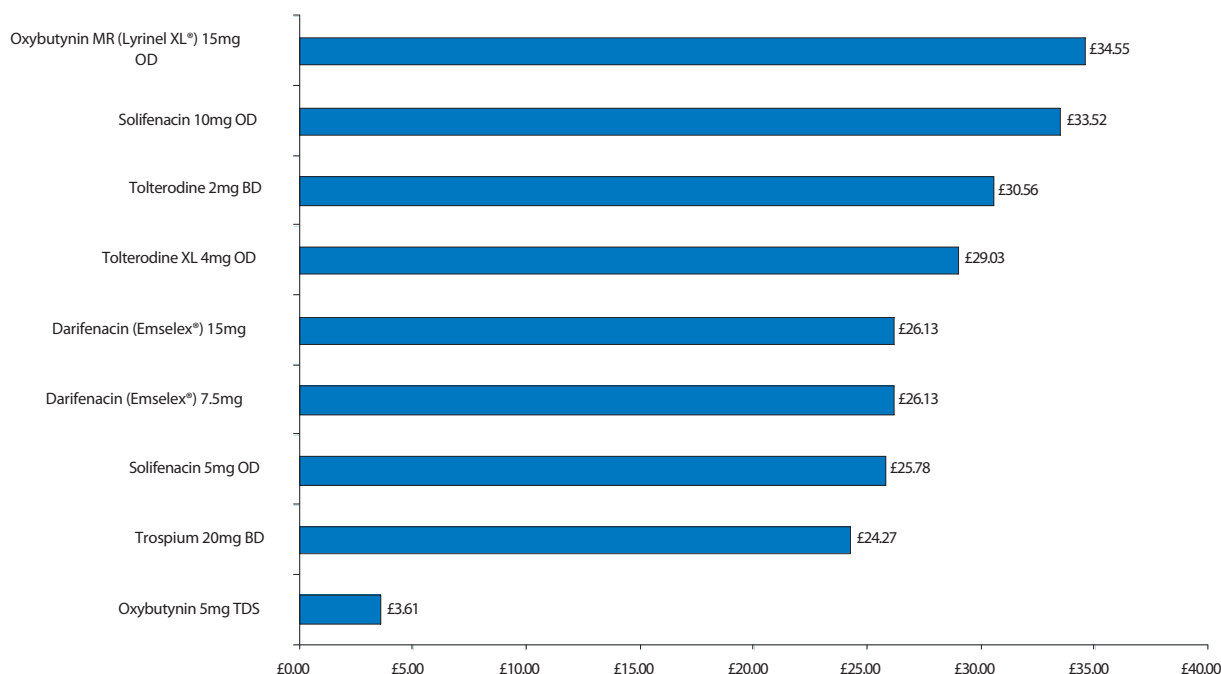
Oxybutynin is still considered the treatment of choice in OAB and should be used first line once non-pharmacological therapies have failed or are inappropriate. There is

insufficient evidence to recommend one second-line anticholinergic over another, but tolterodine has the greatest body of evidence. Darifenacin could be considered as an option once other second-line agents had been given an adequate therapeutic trial, taking into consideration its black triangle status, lack of long-term data, adverse effect profile and cost compared to the other anticholinergics.

The Committee for Medicinal Products for Human Use concluded that darifenacin showed a similar effectiveness to other anticholinergic drugs used in OAB.¹⁰ A Cochrane review found that there were insufficient trials and data to reach any conclusions about the relative efficacy of different doses of oxybutynin, trospium, propiverine, darifenacin or solifenacin and more data are needed to support prescribing of these drugs.⁴ Any new anticholinergic drug should be compared to oxybutynin or tolterodine to establish its comparative efficacy and cost compared to either of these more established agents.

How much does it cost?

Cost for 28 days treatment (MIMS / Drug Tariff March 2007)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence

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KEY RCT - randomised controlled trial, G-guideline, O-open study, R-review

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