Mirabegron (Betmiga) is a new class of drug for the treatment of overactive bladder. In our New products review, Steve Chaplin presents the clinical data relating to its efficacy and adverse events, and Professor Chapple discusses its place in treatment compared with anticholinergics.

The NICE guideline on the management of lower urinary tract symptoms (LUTS) in men recommends drug treatment when conservative measures alone are ineffective. The drug treatment of first choice is an alpha-blocker for moderate to severe LUTS symptoms, an antimuscarinic for overactive bladder syndrome (OAB) and a 5-alpha reductase inhibitor for men with an enlarged prostate.

For women with urinary incontinence and OAB, NICE recommends oxybutynin, followed by other antimuscarinic agents, as first-line drug therapy if nonpharmacological measures and lifestyle change are unsuccessful.

Mirabegron
Mirabegron (Betmiga) is a selective beta3-agonist that relaxes the bladder detrusor muscle and enhances urine storage. It is licensed for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence in adults with overactive bladder.

NICE has recommended mirabegron for treating the symptoms of OAB for people in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side-effects.

The recommended dose is 50mg once daily. This should be halved in patients with moderate hepatic impairment or severe renal impairment; mirabegron is contraindicated in patients with severe hepatic impairment or end-stage renal disease, and in patients with uncontrolled hypertension.

Its metabolism is reduced by strong inhibitors of CYP3A, eg, itraconazole, clarithromycin, and the dose should be reduced or treatment avoided in patients taking these drugs who also have impaired renal or hepatic function (see SPC for details). The cost of one month’s treatment is £29.

Clinical trials
Mirabegron has been evaluated in three similar 12-week phase 3 trials in patients with OAB (urinary frequency and urgency with or without incontinence) of at least three months’ duration. The primary endpoints were the change in number of
incontinence and micturition episodes per day (both based on a three-day micturition diary). One study included tolterodine as an active control but was not powered to compare efficacy. Two studies included the unlicensed dose of 100mg per day; these data are not reported below.

Randomised patients were mostly women (72–83 per cent) with a median age of about 60 who reported moderately severe OAB (averaging 11–12 micturitions per day, two or three incontinence episodes and moderate to severe urgency). About half had previously been treated with an antimuscarinic drug.3

The three trials have been pooled for analysis showing that, overall, mirabegron is broadly as effective as other drugs for OAB.3 Compared with placebo, mirabegron 50mg per day significantly reduced the number of micturition episodes by a mean of 0.55 per day and the number of incontinence episodes by a mean of 0.4. One study evaluated the 25mg per day dose, for which the corresponding mean reductions were 0.47 and 0.4. These effects were evident within four weeks.

Mirabegron also significantly reduced the frequency of nocturia by a mean of 0.14 episodes per 24 hours.

Mirabegron reduced urgency and the mean number of urgency incontinence episodes. After 12 weeks, it significantly increased the odds of improving continence: the proportion of patients reporting no incontinence episodes was 44 per cent with mirabegron and 38 per cent with placebo; the proportions with ≥50 per cent reduction in incontinence episodes were 70 and 60 per cent respectively.

About one-third of patients taking mirabegron reported eight or fewer micturitions per day compared with about one-quarter of those taking placebo. These changes were associated with significant improvements in bothersome symptoms and health-related quality of life.

**Adverse effects**

Mirabegron does not increase intraocular pressure or prolong the QT interval.2 The most frequently reported adverse events were urinary tract infection (2.9 per cent) and tachycardia (1.2 per cent). Mirabegron was associated with a lower frequency of dry mouth than tolterodine (1.7 vs 10.4 per cent; placebo 1.7 per cent).3

Four per cent of patients discontinued mirabegron due to adverse events, about the same as those assigned to placebo.4

**References**


**Place in therapy**

The storage symptom component of LUTS encapsulated by the term OAB is now recognised to be an important clinical symptom complex affecting approximately 10 per cent of the population at some time.

The cardinal symptom of OAB is urgency (a compelling desire to void that is difficult to defer) accompanied by urinary frequency of more than eight voids per day and nocturia of two or more voids per night and, in up to one-third of cases (usually female), urgency incontinence.

In up to two-third of these patients there is the underlying functional abnormality on urodynamic testing of bladder (detrusor) overactivity.

Over the last 40 years the primary pharmacotherapy for OAB has been anticholinergic (antimuscarinic) therapy, which many patients find lacks efficacy or is poorly tolerated due to side-effects. Mirabegron is a new class of drug that acts via beta_3_ adrenoceptors to relax bladder smooth muscle.

This is an interesting development as it heralds the introduction of a class of therapy that appears to have similar efficacy to anticholinergics without the usual side-effects seen with anticholinergic agents, namely dry mouth, heartburn, visual effects, constipation and potential cognitive dysfunction, particularly in the elderly who may be on other therapy with anticholinergic activity.

Mirabegron has been shown in the phase 3 studies to be devoid of these side-effects with no evident cardiovascular safety concerns. It looks to be equally effective as primary therapy or in patients who have failed prior anticholinergic therapy either as a consequence of poor tolerability or lack of efficacy.

In the first instance it will be useful to see how effective this therapy is in real-life clinical practice, and it will initially be used as second-line therapy after failed treatment with anticholinergic agents.

**Common (1/100–1/10)**

- Urinary tract infection
- Tachycardia

**Uncommon (1/1000–1/100)**

- Vaginal infection, cystitis
- Palpitation, atrial fibrillation
- Dyspepsia, gastritis
- Urticaria, rash, macular rash, papular rash, pruritus
- Joint swelling, vulvovaginal pruritus
- Raised blood pressure, increased GGT, AST, ALT

**Rare (1/10 000–1/1000)**

- Eyelid oedema
- Lip oedema
- Leukocytoclastic vasculitis, purpura

Table 1. Adverse reactions recorded in the three 12-week phase 3 clinical trials


**Declaration of interests**

Steve Chaplin has received payment for contributing to publications commissioned by Astellas Pharma.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics.
It may well subsequently be more widely used as first-line therapy and perhaps particularly indicated in male patients (no concern over inducing retention) and the elderly (no concern over cognitive dysfunction). In addition one can speculate that it may prove efficacious in the management of OAB as a combination therapy, potentially with a lower dose of anticholinergic drug than might otherwise need to be the case.

**Declaration of interests**
Professor Chapple has acted as a speaker for Ranbaxy, a consultant for AMS, Lilly and ONO, and as a consultant, researcher, speaker and trial participant for Allergan, Astellas, Pfizer and Recordati.

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