Mirabegron (Betmiga™) for overactive bladder

London New Drugs Group
APC/DTC Briefing Document

Mirabegron (Betmiga™) for overactive bladder
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Summary
- Mirabegron is first of a new class of drug, beta-3-adrenoceptor agonists, for the treatment of overactive bladder.
- NICE recommend first-line treatment for OAB is with an antimuscarinic agent.
- Phase III studies have shown that mirabegron provides an effective treatment option for OAB in patients who discontinued antimuscarinic treatment because of e.g. insufficient effect or poor tolerability.
- Mirabegron has a lower incidence of dry mouth and cardiac arrhythmias than tolterodine, but otherwise its side effect profile is comparable.
- Mirabegron use is forecast to grow modestly, representing 1% of the OAB market in year 1, 2% in year 2 and 3.5% in year 3. The resulting total budget impact estimate in year 1 is £1,242, in year 2 is £2,485 and in year 3 is £4,348. These estimates do not consider any potential savings from lower rates of healthcare professional contact, avoidance of surgery, or avoidance of OAB symptom management.

1. Background and introduction
In January 2013, mirabegron (Betmiga™) was approved for use in the EU for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence that may occur in patients with overactive bladder. Mirabegron will be supplied as 25mg and 50mg (recommended dose) prolonged-release tablets and should be swallowed whole, not chewed or crushed.

Overactive bladder syndrome (OAB) is defined as urgency with or without urge urinary incontinence (UI) and is usually combined with frequency and nocturia. Prevalence is difficult to determine due to differences in study populations, definition and measurement of UI, and survey method used. For women, most studies estimates range from 25% to 45% in those aged ≥15 years, with more severe UI prevalent in 4% to 7% in women <65 years and in 4% to 17% in those >65 years. Studies have shown that the prevalence increases up to middle age, plateaus or fall between 50-70 years, then increases steadily with advancing age. About 20% of women aged ≥40 years (about 5 million people in the UK), require medical treatment for OAB; in women this increases up to 35.6% in those ≥80 years. Lower urinary tract symptoms (LUTS) occur in up to 30% of men over the age of 65 years, and these include UI. Several common chronic conditions have been associated with OAB, such as depression, constipation, neurologic conditions and erectile dysfunction.

Guidelines and alternative treatments
Lifestyle interventions and conservative management tend to be first line therapy, then followed by pharmacological treatment. The mainstay of pharmacological therapy is controlling detrusor muscle overactivity by inhibiting muscarinic receptors on the bladder. Acetylcholine activates muscarinic receptors to mediate normal detrusor contraction required for voiding urine; anticholinergics (antimuscarinics) block the action of acetylcholine and treat OAB symptoms. NICE (2006) recommends that the antimuscarinic agent, immediate-release oxybutynin, is the first-line pharmacological therapy to treat OAB in women; this is based on cost-effectiveness because of the lack of evidence of clinically important differences in efficacy between the antimuscarinic drugs. If this is not well tolerated, then alternate antimuscarinic drugs that can be tried include solifenacin, tolterodine or an extended release / transdermal formulation of oxybutynin. For men, an anticholinergic should be used to manage OAB symptoms.

Mirabegron
Mirabegron is a potent and selective beta-3-adrenoceptor agonist and causes relaxation of the bladder smooth muscle. By stimulating the beta-3 adrenoceptors in the bladder, mirabegron increases mean voided volume per micturition and decreases the frequency of non-voiding contractions.

2. Proposed place in therapy
Currently, the market leader for the treatment of OAB in the UK is the antimuscarinic agent, solifenacin, with approximately one-third of patients treated with it. Mirabegron is not an antimuscarinic drug and therefore is thought to be less likely to have the muscarinic effects which can affect a number of body systems. Astellas Pharma anticipates that mirabegron will be used in a similar position to solifenacin, either as first- or second-line therapy. Note that in the studies, there was an active control (tolterodine) rather than comparator.

3. Evidence selected for inclusion
Three main phase III studies have evaluated the efficacy and safety of mirabegron: ARIES, SCORPIO and TAUrus. In all three...
studies, the primary endpoints were recorded in a micturition diary by the patient for the three days preceding a study visit. In the two efficacy studies (ARIES and SCORPIO), the primary endpoints were the change in the mean number of incontinence episodes/24 hours and the change in the mean number of micturitions/24 hours. In all three studies, the primary endpoint was assessed in all randomised patients taking ≥1 dose of study drug and with baseline and ≥1 post-baseline micturition measurements (Full Analysis Set, FAS).

**ARIES** was a multicentre, randomised, parallel-group, double-blind, placebo-controlled study in 1329 adults with OAB who were randomly assigned to treatment with mirabegron 50mg OD (n=312), mirabegron 100mg OD (n=296) or placebo (n=325) for 12 weeks.\(^7\) A sample size of 362 patients would provide 90% power to detect a reduction of 0.7 in the mean number of micturitions/24 hours over placebo. Although the co-primary endpoints were statistically significantly greater with mirabegron treatment, the differences were not very large due to the high placebo response rate.

- **Mean number of incontinence episodes/24 hours**: placebo, -1.13; mirabegron 50mg, -1.47 (p<0.05) and mirabegron 100mg, -1.63 (p<0.05).
- **Mean number of micturitions/24 hours**: placebo, -1.05; mirabegron 50mg, -1.66 (p<0.05) and mirabegron 100mg, -1.75 (p<0.05).

**SCORPIO** was a double-blind, parallel-group, placebo- and active-controlled trial in 1978 adults with OAB who were randomly assigned treatment with placebo (n=494), mirabegron 50mg OD (n=493), mirabegron 100mg OD (n=494) or tolterodine SR 4mg OD (n=495) for 12 weeks.\(^6\) About 50% had previously been treated with an anticholinergic. The study was powered (90%) to compare mirabegron treatment with placebo but not with tolterodine. As in the ARIES study, the co-primary endpoints were statistically significantly greater with mirabegron treatment, but the differences were not very large due to the high placebo response rate. Although this was not a head-to-head comparison, mirabegron was as good as tolterodine, the active control.

- **Mean number of incontinence episodes/24 hours**: placebo, -1.13; mirabegron 50mg, -1.62 (p<0.003); mirabegron 100mg, -1.51 (p<0.01) and tolterodine, -1.21 (p=NS).
- **Mean number of micturitions/24 hours**: placebo, -1.37; mirabegron 50mg, -1.94 (p<0.001); mirabegron 100mg, -1.75 (p=0.005) and tolterodine, -1.57 (p=NS).

**TAURUS** was a phase III trial that assessed the long-term (12 month) safety and tolerability of mirabegron in 2444 adults with OAB, of whom 81% had participated in previous mirabegron phase 3 trials.\(^6\) Patients were randomised to treatment with mirabegron 50mg OD (n=812) or 100mg OD (n=820) or tolterodine SR 4mg OD (n=812). The primary endpoint was the incidence and severity of treatment-emergent adverse events (TEAEs), which is discussed in Section 4.2 (Safety). The efficacy of long-term treatment of mirabegron relative to tolterodine was a secondary endpoint. The study was not designed to demonstrate a statistically significant difference in efficacy between the treatment groups. Numerical improvements in the mean number of micturitions/24 hours, the mean number of incontinence episodes/24 hours and the mean volume voided per micturition were evident from month 1 (first visit) and maintained through to month 12. Improvements with mirabegron were comparable to those seen with tolterodine. Results were presented graphically with no actual figures or P values.

### 4. Critical evaluation

#### 4.1: Clinical application

- **SCORPIO and ARIES** were short studies (12 weeks) and give little indication of how effective mirabegron will be in treating OAB in the long-term. In both studies, mirabegron treatment was associated with a small but statistically significant improvement from baseline in terms of numbers of incontinence episodes and micturitions compared to placebo: over a 2-day period when compared with placebo, there was approximately one fewer incontinence episode and approximately one less micturition with mirabegron 50mg OD.
- **Urgency**, a key symptom of OAB, was a secondary, not primary endpoint of ARIES and SCORPIO. Mirabegron 50mg and tolterodine 4mg SR both significantly reduced the mean number of grade 3/4 urgency episodes compared with placebo (p<0.05), but mirabegron 100mg did not. Urgency was not assessed in TAURUS.
- **Long-term (12 month) therapy** showed an initial large improvement in symptoms by month 1, which were sustained over 12 months. Efficacy of mirabegron was comparable to that of tolterodine with respect to reductions in the mean numbers of micturitions and of incontinence episodes/24 hours, and mean volume voided.
- In all three studies, the approximately three-quarters of patients enrolled were women, which reflects the higher prevalence in women.
- In clinical practice, continued therapy with antimuscarinic drugs is much lower than in clinical trials, where adherence can be >80%.\(^9\) A 12-month study analysing UK-based prescription data (n=4833 taking antimuscarinics) showed that at 3 months, 28-58% continued antimuscarinic therapy, falling to 16-46% at 6 months and 13-35% at 12 months.\(^9\) Other systematic reviews and prescription monitoring studies have found discontinuation rates ranging from 43% to 83% within the first 30 days of therapy and <25% continuing at 1 year. Discontinuations rates in the TAURUS study, where patients had trial visits every 3 months, were 5.9%-6.4% with mirabegron and 6% with tolterodine because of adverse events and
3.0%-4.2% and 5.5% respectively because of lack of efficacy. Most people discontinued because of withdrawn consent (7.9%-9.1%). Persistence with treatment will need to be assessed in clinical practice.

4.2: Safety
- In the studies most adverse events (AEs) were mild to moderate and comparable across groups.\(^6\)\(^8\)
- The main advantage mirabegron appears to have over tolterodine with respect to side effects, is the lower incidence of dry mouth. This was reported by <3% of patients treated with mirabegron in all three studies, but by 8.6-10.1% of those treated with tolterodine.
- A slightly lower incidence of cardiac arrhythmias occurred patients treated with mirabegron in the TAURUS study (3.9-4.1%), compared with those treated with tolterodine (6%).
- No difference in the incidence of other side effects, such as hypertension, urinary tract infection or constipation, was seen between the groups in TAURUS.
- Antimuscarinic drugs can increase ocular pressure, making them unsuitable for use in patients with uncontrolled narrow-angle glaucoma.\(^7\)^\(^10\) Mirabegron has been shown to have no effect on intraocular pressure (IOP) in an 8-week, placebo-controlled trial in 320 healthy volunteers.\(^10\) The primary outcome assessment, mean change from baseline to day 56 in IOP, was -0.3mmHg with mirabegron vs. -0.2mmHg with placebo. No subject had an increase in IOP of ≥6mmHg.

Limitations of the study are its short duration (8 weeks), lack of active control and patient population (healthy subjects).

4.3: Potential advantages and disadvantages over existing technologies

4.3.1: Convenience
Mirabegron is an oral formulation taken once a day, which can be started in primary care. Mirabegron is not an antimuscarinic agent and therefore does not have antimuscarinic side effects, which are often the reason for patients discontinuing therapy. The main advantage in terms of the side effect profile with mirabegron appears to be a lower incidence of dry mouth than with tolterodine.

4.3.2: Drug cost
Mirabegron will cost £29 per 30 day pack for both the 25mg and 50mg doses. Mirabegron is expected to displace medicines of a broadly similar cost, as shown in the budget impact estimate detailed in 4.2.5.

4.3.3: Healthcare resource utilisation
Mirabegron can be initiated in primary care in place of antimuscarinics where they are contraindicated or after antimuscarinics have been tried. Use may potentially delay the requirement for hospital consultations and tests, although this is yet to be proven in clinical practice.

4.3.4: Suitability for shared care
None required.

4.5.5: Likely budgetary impact
The budget impact calculation provided by the manufacturer is based on a population of 100,000.\(^11\) Prevalence rates are quoted for adults over the age of 40 years. When applied to an adjusted population of ≥40yrs the manufacturer estimates approximately 12,000 patients to be suffering with OAB. Of these, 19% are expected to seek medical help and be prescribed a pharmacological treatment. Therefore 3,213 patients are estimated to receive pharmacotherapy.

A simplified picture of the OAB market is presented in which mirabegron is expected to displace the use of the three market leading comparators in equal proportions, namely solifenacin(5mg), tolterodine (4mg ER) and oxybutynin (10mg IR). Mirabegron is forecast to grow modestly within this market, representing 1% of the market in year 1, 2% in year 2 and 3.5% in year 3. The resulting total budget impact estimate in year 1 is £1,242, in year 2 is £2,485 and in year 3 is £4,348. These estimates do not consider any potential savings from lower rates of healthcare professional contact, avoidance of surgery, or avoidance of OAB symptom management.

**Mirabegron (Betmiga™) budget impact calculation\(^{11}\)**
(based on the budget impact estimate submitted for NICE single technology appraisal - ID542)

| **Step One: Population details** |
|-----------------|----------------|
| Population      | 100,000        |
| Population (≥ 40 years) | 62,640 |
| Prevalence (clinically significant symptoms in adults ≥ 40 years) | 19% |
| Patients currently on medication | 27% |
| Patients eligible for treatment (n) | 11,902 |
| Patients likely to present for treatment (n) | 3,213 |
Step Two: Comparator details

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Pack price</th>
<th>Annual cost (*based on 180 days treatment)</th>
<th>Cost difference (vs. mirabegron)</th>
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<tbody>
<tr>
<td>SOLIFENACIN (5mg od 30 tablet pack price used)</td>
<td>£27.62</td>
<td>£165.72</td>
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<tr>
<td>TOLTERODINE (XL 4mg od 28 tablet pack price used)</td>
<td>£25.78</td>
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<tr>
<td>OXYBUTYNIN (5mg tds 84 tablet pack price (generic))</td>
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<td>£74.57</td>
<td>£99.43</td>
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<tr>
<td>MIRABEGRON (50mg od 30 tablet pack)</td>
<td>£29.00</td>
<td>£174.00</td>
<td></td>
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</table>

Average annual* price difference £38.66

Step Three: Mirabegron local budget impact

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients likely to present for treatment (n)</th>
<th>Predicted mirabegron share (of antimuscarinic market)</th>
<th>Average annual cost difference per patient</th>
<th>Annual budget impact</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>3,213</td>
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<td>£4,348.09</td>
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5. Health Economics

A de novo Markov model was developed to analyse the cost-effectiveness of mirabegron 50mg vs. appropriate antimuscarinics for the treatment of OAB as part of single technology appraisals to both NICE and SMC.²² The model simulated the therapeutic management, the course of disease, and complications in hypothetical cohorts of patients with OAB and was used to predict costs and QALYs over 5 years. Base case analysis of the general OAB population compared mirabegron 50mg with tolerodine ER 4mg, based on results from SCORPIO. Subgroup analyses for male vs. female and previously treated vs. treatment-naïve populations were also conducted. Secondary analyses compared mirabegron 50 mg with alternative comparators (solifenacin 5mg and 10mg, fesoterodine 4mg, trospium chloride 60mg MR and oxybutynin 10mg IR and ER), based on results of a mixed treatment comparison (MTC).

The following incremental cost-effectiveness ratios (ICERs) were submitted to NICE, but have not yet been formally accepted (decision expected in June 2013):

- In the base case analyses of the general OAB population, the ICER for mirabegron 50mg vs. tolerodine 4mg was £4,386 per QALY gained.
- Using further data from the MTC, mirabegron 50mg was found to be cost-effective when compared with other relevant antimuscarinics resulting in the following ICERs (cost per QALY gained); solifenacin 10 mg: £340, fesoterodine 4 mg: £3,607, tolerodine 4 mg: £3,715, oxybutynin 10 mg ER: £3,878, trospium 60 mg MR: £8,881, solifenacin 5mg: £12,493, and oxybutynin 10 mg IR: £21,796.
- In the subgroup analysis, mirabegron 50mg was shown to be cost-effective vs. tolerodine 4mg ER in both previously treated (£3,836) and treatment-naïve (£5,315) populations.

6. Likely commissioning and funding pathway

Mirabegron will be in tariff.

7. Proposed recommendation

Mirabegron is a new treatment option for the symptoms of overactive bladder. It may be useful in patients who discontinue anticholinergics because of dry mouth, which has been the main advantage over tolerodine seen in clinical trials or in those where antimuscarinics are contraindicated. A lower incidence of arrhythmias with mirabegron compared with tolerodine has been seen in studies, but this will need to be evaluated in clinical practice.

Reference List


Produced by the London New Drugs Group. Correspondence to Alexandra Denby, Regional MI Manager, London Medicines Information Centre, Northwick Park Hospital, Watford Road, Harrow, Middlesex. HA1 3UJ. e-mail: alexandra.denby@nhs.net. Astellas Pharma Ltd has commented on this review. Accessed via https://www.evidence.nhs.uk.