Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

mirabegron 25mg and 50mg prolonged-release tablets (Betmiga®)

SMC No. (862/13)

## Astellas Pharma Ltd

05 April 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE**: following a full submission

**mirabegron (Betmiga®)** is accepted for use within NHS Scotland.

**Indication under review:** for symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

Mirabegron was associated with modest treatment benefits over placebo in reducing symptoms associated with overactive bladder syndrome, including frequency and incontinence.

Alternative treatments are available at a lower drug acquisition cost.

Overleaf is the detailed advice on this product.

**Chairman,**
**Scottish Medicines Consortium**

*Published 13 May 2013*

## Indication

Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

## Dosing Information

Mirabegron 50mg orally once daily with or without food. The summary of product characteristics (SPC) provides recommendations on when it is appropriate to reduce the dose to 25mg daily depending on renal or hepatic impairment in the absence and presence of strong CYP3A inhibitors.

## Product availability date

22 February 2013

## Summary of evidence on comparative efficacy

Overactive bladder (OAB) syndrome describes a complex of lower urinary tract symptoms (including urinary urgency, with or without urge incontinence, and usually frequency and nocturia) that occur in the absence of pathologic or metabolic causative factors. OAB includes patients with and without a possible neurological cause for their symptoms. Mirabegron is the first of a new therapeutic class of medicine, a beta 3-adrenoceptor agonist, which is thought to enhance urine storage function by stimulating beta 3-adrenoceptors in the bladder.[1]

The evidence to support the efficacy of mirabegron comes from the results of three, randomized, double-blind, placebo-controlled, phase III studies.[1-4] Each study comprised a two-week single-blind, placebo run-in period, after which eligible patients were randomised to study drug for 12 weeks. Eligible patients were men and women aged ≥18 years with symptoms of OAB (urinary frequency and urgency with or without incontinence) for ≥3 months. During the run-in period, they had a micturition frequency of ≥8 times per 24 hours and ≥3 episodes of urgency with or without incontinence during a 3-day micturition diary period. Patients were randomised to receive oral treatment with mirabegron 50mg, mirabegron 100mg, tolterodine extended release (ER) 4mg or placebo daily in the first study, mirabegron 50mg, mirabegron 100mg or placebo daily in the second study, or mirabegron 25mg, mirabegron 50mg or placebo daily in the third study. In the first study, tolterodine was included as an active control and there was no statistical comparison with mirabegron. Study patients could continue bladder training and pelvic floor exercises if they had started ≥30 days before study entry.

All studies had two co-primary outcomes: (i) change from baseline to week 12 in the mean number of micturitions per 24 hours analysed in the full analysis set (FAS, defined as all randomised patients who took ≥1 dose of study drug and had ≥1 baseline and post-treatment micturition measurement) and (ii) change from baseline to week 12 in the mean number of incontinence episodes per 24 hours analysed in the FAS-incontinence set (FAS-I, defined as FAS patients who had ≥1 incontinence episode at baseline). Missing data were imputed using last observation carried forward (LOCF). Results for the co-primary endpoints including only the licensed 50mg dose of mirabegron are detailed in table 1 below.

**Table 1: results for co-primary outcomes in three, pivotal, 12-week, efficacy studies**[1-4]

| | Study 1 | | | Study 2 | | Study 3 | |
|---|---|---|---|---|---|---|---|
| | **Mirabegron 50mg** | **Placebo** | **Tolterodine** | **Mirabegron 50mg** | **Placebo** | **Mirabegron 50mg** | **Placebo** |
| **Mean number of micturitions per 24 hours in FAS** | | | | | | | |
| Patient numbers | 473 | 480 | 475 | 425 | 433 | 426 | 415 |
| Baseline | 11.65 | 11.71 | 11.55 | 11.80 | 11.51 | 11.66 | 11.48 |
| Final visit | 9.70 | 10.35 | 9.97 | 10.09 | 10.51 | 10.04 | 10.33 |
| Adjusted mean change | -1.93 | -1.34 | -1.59 | -1.66 | -1.05 | -1.60 | -1.18 |
| Mean difference vs placebo [95% CI], p-value | -0.60 [-0.90 to -0.29] p<0.001 | - | -0.25 [-0.55 to 0.06], p=0.11 | -0.61 [-0.98 to -0.24], p=0.001 | - | -0.42 [-0.76 to -0.08], p=0.015 | - |
| **Mean number of incontinence episodes per 24 hours in FAS-I** | | | | | | | |
| Patient numbers | 293 | 291 | 300 | 312 | 325 | 257 | 262 |
| Baseline | 2.83 | 2.67 | 2.63 | 2.77 | 3.03 | 2.51 | 2.43 |
| Final visit | 1.22 | 1.54 | 1.42 | 1.33 | 1.81 | 1.13 | 1.54 |
| Adjusted mean change | -1.57 | -1.17 | -1.27 | -1.47 | -1.13 | -1.38 | -0.96 |
| Mean difference vs placebo [95% CI], p-value | -0.41 [-0.72 to -0.09], p=0.003 | - | -0.10 [-0.42 to 0.21], p=0.11 | -0.34 [-0.66 to -0.03], p=0.026 | - | -0.42 [-0.76 to -0.08], p=0.001 | - |

vs= versus, CI=confidence interval

Secondary outcomes also significantly favoured mirabegron compared with placebo including the mean volume voided per micturition, the mean level of urgency, the mean number of urgency incontinence episodes per 24 hours and the mean number of episodes with grade 3 or 4 urgency per 24 hours.[1-4]

Quality of life was assessed using the OAB questionnaire (OABq) symptom bother score (range 0 to 100), the Patient Perception of Bladder Condition (PPBC) (6-point Likert scale) and the Treatment Satisfaction Visual Analog Scale (TS-VAS) (range 0 to 10). Patients treated with mirabegron 50mg had statistically significantly greater improvements from baseline to final visit in each measure compared with placebo in two of the studies. [2-4]

Pooled analyses were performed on the primary and secondary outcomes from the three studies. At baseline, the mean number of micturitions, incontinence episodes, volume voided, level of urgency, urgency incontinence episodes and nocturia were comparable across the three studies. The adjusted mean changes from baseline to final visit for mirabegron 50mg versus placebo were -0.55 micturitions per 24 hours, -0.40 incontinence episodes per 24 hours, +11.9mL volume voided per micturition, -0.11 in level of urgency, -0.40 urgency incontinence episodes and -0.14 nocturia. All differences were significantly greater than placebo. There were also significant differences between mirabegron 50mg and placebo in adjusted change from baseline in OABq symptom bother score (-4.51), health-related quality of life total score (2.46) and TS-VAS (0.76).[1] Analysis of the pooled population in the subgroup previously treated with antimuscarinics found a mean change from baseline versus placebo of -0.74 micturitions per 24 hours and -0.57 incontinence episodes per 24 hours.

A 12 month study compared mirabegron 50mg, 100mg and tolterodine 4mg ER primarily in terms of safety and results are presented below. However secondary efficacy outcomes suggested that treatment benefits were maintained in the longer term.[4]

## Summary of evidence on comparative safety

There are limited comparative safety data from the three pivotal 12-week studies as only one included tolterodine as an active control and differences between active treatments were not tested.[2]

In the 12 month safety study, treatment-emergent adverse events were reported in 60% (485/812) mirabegron 50mg and 63% (508/812) tolterodine patients and were mostly mild to moderate in severity.[4] Discontinuations due to treatment-emergent adverse events were reported in 6.4% and 6.0% of patients respectively. The most frequently reported treatment-emergent adverse events were hypertension (9.2% and 9.6%, respectively), urinary tract infection (5.9% and 6.4%), nasopharyngitis (3.9% and 3.1%), dry mouth (2.8% and 8.6%), headache (4.1% and 2.5%) and constipation (2.8% and 2.7%). During the study, cardiovascular events were closely monitored. QTc prolongation was reported in 0.4% of both mirabegron 50mg and tolterodine patients and cardiac arrhythmia in 3.9% and 6.0% respectively.

During clinical studies, mirabegron 50mg was associated with a modest, not clinically significant, increase in pulse rate (1 bpm versus placebo) and in blood pressure (≤1mm Hg versus placebo). This did not translate into clinical adverse events distinct from those reported with tolterodine or in most cases placebo.[1] The SPC states that mirabegron is not recommended in patients with severe uncontrolled hypertension (SBP ≥180mm Hg and/or DBP ≥110mm Hg).

## Summary of clinical effectiveness issues

The three pivotal efficacy studies have demonstrated that mirabegron significantly reduced micturition and incontinence episodes compared with placebo. However there are several limitations. Only one study included an active control (tolterodine ER) and this study was not designed or powered to test the difference between mirabegron and tolterodine.[2] The 12 month safety study also included tolterodine as an active control but efficacy outcomes were secondary and were not statistically analysed.[4]

In all studies, the treatment benefits in clinical outcomes produced by mirabegron over placebo were modest. It was not necessary for all patients to have incontinence episodes at baseline. Therefore analysis of the co-primary outcome of incontinence episodes per 24 hours was performed in a subset of the FAS (the FAS-I). If this analysis was performed in the full FAS, the overall treatment effect was reduced. This is considered a limitation of the study designs.[1]

Since OAB is not a life-threatening condition, the patient's perception of the quantitative outcomes measured should be a main objective of the studies to determine the impact on the patient's daily life. However, in each of the three studies, the quality of life measures were secondary outcomes only.[1] The assessments of patient perception of treatment reached statistical significance with mirabegron 50mg versus placebo in the majority of the individual studies and in the pooled analyses, but failed to reach minimally important differences over placebo. The European Medicines Agency (EMA) European Public Assessment Report acknowledges that although there was no clear improvement in patient perception with mirabegron, there was a trend in line with the modest effects on clinical outcomes.[1] Patients in the pivotal studies recorded events in diaries over 3-day periods. EMA guidance recommends that diaries are recorded over a week.[1]

The incidence of dry mouth was similar in patients treated with mirabegron and placebo but was higher in the tolterodine treated patients. This is considered a troublesome antimuscarinic adverse effect. However, it is unclear if this lower incidence in the mirabegron group would translate into less discontinuation or treatment switching in clinical practice. The proportions of patients discontinuing study medication because of adverse events were similar across study groups.

Although tolterodine was included as an active control in two of the studies described, there was no statistical analysis so comparative data with mirabegron are lacking. The submitting company presented a Bayesian mixed treatment comparison (MTC) of 40 studies to assess mirabegron versus immediate and extended release formulations of tolterodine and oxybutynin, as well as solifenacin, fesoterodine and trospium in patients with general overactive bladder (OAB). The MTC assessed a number of different efficacy outcomes (micturition frequency, incontinence episodes, urge incontinence) and safety outcomes (dry mouth, constipation, blurred vision). There were differences between the studies in duration, primary outcomes measured and previous treatment. The results suggest that mirabegron 50mg was not significantly different from comparators in efficacy outcomes, with the exception of being less effective than solifenacin 10mg in micturition frequency and urge incontinence. However, the inconsistency testing indicates that direct data of mean change in micturition and incontinence for mirabegron versus placebo were lower than the indirect results, suggesting that the model may be overestimating the effect of mirabegron. The results also suggest that mirabegron 50mg was associated with significantly less dry mouth and, in some comparisons, constipation, than other antimuscarinics. However, data inputted after different durations of follow-up may affect the validity of these results.

SMC clinical experts advised that over active bladder syndrome can be difficult to treat and can adversely impact the quality of life of patients. They also noted that side effects associated with antimuscarinic agents may limit the use of current treatments. The introduction of mirabegron would therefore offer an alternative therapeutic option with a different side effect profile.

## Summary of comparative health economic evidence

The company submitted a cost-utility analysis over a five year time horizon comparing mirabegron with tolterodine ER and solifenacin 5mg in patients with OAB. Secondary analyses were also conducted using alternative comparators: solifenacin 10mg, fesoterodine, trospium chloride and oxybutynin. A Markov model with monthly cycles was used, with health states defined in terms of the two primary endpoints within the pivotal studies: frequency of micturitions and incontinence episodes. Both of these symptoms were categorised into 5 levels of severity (based on the range of frequencies in the pivotal studies) to give 25 possible health states.

For the comparison with tolterodine ER, the transition probabilities and adverse event rates were based on the results of study 1 described above, where a comparison with tolterodine was provided but the study was not powered to detect a difference between mirabegron and tolterodine. The transition probabilities from months 2 to 3 were assumed to apply for the remainder of the 5 year time horizon. For all other comparisons, the main clinical data inputs were based on the results of the MTC. A second-line antimuscarinic was included in the model and was assumed to be either solifenacin or tolterodine. Botulinum toxin was included as a third-line option.

Utility values were included in the model according to symptom severity and were derived from EQ-5D data collected in the clinical study. The utility value for the least severe health state was estimated to be 0.85 and the most severe was 0.73. Resource use was estimated based largely on expert opinion and included drug acquisition costs for first-line and subsequent lines of therapy, GP visits, specialist visits, incontinence pads, and botulinum toxin administration costs.

The results of the two base case analyses are summarised in the table below:

| Mirabegron 50mg vs | Incremental cost | Incremental quality-adjusted life years (QALY) | Cost per QALY |
|---|---|---|---|
| Tolterodine ER 4mg | £33.18 | 0.00864 | £3,842 |
| Solifenacin 5mg | £51.12 | 0.00466 | £10,975 |

The results of the secondary analyses were:

| Mirabegron 50mg vs | Incremental cost | Incremental QALY | Cost per QALY |
|---|---|---|---|
| Solifenacin 10mg | -£8.70 | 0.0104 | Dominant |
| Fesoterodine 4mg | £32.95 | 0.0106 | £3,120 |
| Tolterodine ER 4mg | £32.97 | 0.0102 | £3,236 |
| Oxybutynin 10mg ER | £36.08 | 0.0109 | £3,321 |
| Trospium chloride 60mg MR | £75.72 | 0.0094 | £8,016 |
| Oxybutynin 10mg IR | £199.01 | 0.0146 | £13,606 |

The economic model estimated relatively low incremental cost-effectiveness ratios (ICER) based on small differences in costs and QALYs between mirabegron and the comparator treatments. However, there were some important weaknesses with the analysis:

- The clinical study was not designed to show a difference versus tolterodine but the non-significant differences were used in the economic model. Similarly, the MTC showed there were no significant differences between mirabegron and most of the comparator treatments but the numerical differences were used in the economic model. On request, the company provided an additional analysis where the non-significant differences were removed and this resulted in ICERs of £6,192 and £4,384 per QALY for the comparisons with tolterodine and solifenacin respectively.
- The company was also asked to provide a sensitivity analysis where the cost of tolterodine was based a weighted average 75:25 split between the ER and IR formulations. This increased the cost per QALY to £18,383.
- When the non-significant differences were removed the model still estimated a QALY gain with mirabegron. The company explained that this was due to the discontinuation rates used in the model, as fewer patients were estimated to discontinue treatment with mirabegron due to fewer adverse events. Additional threshold analyses were provided which showed for the comparison with tolterodine ER/IR the probability of dry mouth could increase from 2.8% to 3.75% and 6.67% and the probability of constipation could increase from 1.6% to 2.47% and 5.4% before the ICER increased to £20k and £30k respectively.

In conclusion, despite the weaknesses highlighted above, the economic case has been demonstrated.

## Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- B&BF (Bladder and Bowel Foundation)
- The Cystitis & Overactive Bladder Foundation

## Additional information: guidelines and protocols

In August 2012, the National Institute for Health and Clinical Excellence (NICE) published a guideline on urinary incontinence in neurological disease.[5] This recommends offering antimuscarinics to patients with spinal cord disease and symptoms of OAB, considering antimuscarinics for patients with conditions affecting the brain and symptoms of OAB and for patients with urodynamic investigations showing impaired bladder storage. Botulinum toxin type A injections are recommended for patients in whom antimuscarinics were ineffective or poorly tolerated.

In February 2012, the European Association of Urology published a guideline on assessment and non-surgical management of urinary incontinence recommending the use of antimuscarinic drugs.[6] It was noted that there is no consistent evidence for the superiority of one antimuscarinic agent over another for the cure or improvement of urinary incontinence. Recent trials with incontinence as the primary outcome suggest that fesoterodine, 8 mg daily, is superior to tolterodine ER, 4 mg daily, but meta-analysis is required to determine the size of effect. More than half of patients will stop antimuscarinic agents within the first 3 months because of ineffectiveness, adverse events and cost. Local oestrogen therapy in post-menopausal women can at least temporarily improve or cure urinary incontinence.

In May 2010, NICE published a guideline on the management of lower urinary tract symptoms (LUTS) in men.[7] This recommends offering drug treatment only to men with bothersome LUTS when conservative management options have been unsuccessful or are not appropriate. This recommends offering an anticholinergic to men to manage the symptoms of OAB and to consider offering an anticholinergic as well as an alpha blocker to men who still have storage symptoms after treatment with an alpha blocker alone. This also recommends offering an alpha blocker to men with moderate to severe LUTS.

In October 2006, NICE published a guideline on the management of urinary incontinence in women.[8] It notes that there is no evidence of a clinically important difference in efficacy between antimuscarinic drugs. If bladder training is ineffective, it recommends the use of immediate release (IR) non-proprietary oxybutynin as the most cost-effective option in women with OAB or mixed UI. If not tolerated, alternatives are darifenacin, solifenacin, tolterodine, trospium or other formulations of oxybutynin. Propiverine should be considered as an option to treat frequency of urination in women with OAB, but is not recommended for the treatment of UI. Flavoxate, propantheline and imipramine should not be used for the treatment of urinary incontinence or OAB in women.

In December 2004, the Scottish Intercollegiate Guidelines Network (SIGN) published a national clinical guideline on management of urinary incontinence in primary care.[9] It recommended that a trial of oxybutynin, propiverine, tolterodine or trospium be given to patients with significant urgency with or without urge incontinence. The dose should be titrated to combat adverse effects. Antimuscarinic therapy should be tried for a period of six weeks to enable an assessment of the benefits and side-effects. Treatment should be reviewed after six months to ascertain continuing need.

## Additional information: comparators

The main comparators are other antimuscarinic drugs: oxybutynin, tolterodine, solifenacin darifenacin and trospium. Pelvic floor muscle exercise and bladder training are also recommended for OAB.

## Cost of relevant comparators

| Drug | Dose regimen | Cost per year (£) |
|---|---|---|
| **Mirabegron prolonged release tablets** | **50mg once daily** | **352** |
| Oxybutynin prolonged release tablets (Lyrinel XL®) | 5 to 20mg daily | 167 to 668 |
| Solifenacin tablets | 5 to 10mg daily | 335 to 436 |
| Oxybutynin transdermal patch (Kentera®) | One patch twice weekly | 354 |
| Fesoterodine prolonged release tablets (Toviaz®) | 4 to 8mg daily | 335 |
| Tolterodine prolonged release capsules (Detrusitol XL®) | 4mg daily | 335 |
| Trospium prolonged release capsules (Regurin XL®) | 60mg once daily | 300 |
| Darifenacin prolonged release tablets (Emselex®) | 7.5 to 15mg daily | 272 |
| Trospium tablets | 20mg twice daily | 221 |
| Oxybutynin tablets (non-proprietary) | 2.5mg twice daily (initial dose in elderly) to 5mg four times daily | 57 to 180 |
| Tolterodine tablets (non-proprietary) | 2mg twice daily | 73 |

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 4 February 2013.

## Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 83,526 in all years with an estimated uptake rate of 1% in year 1 and 9% in year 5. The company has also estimated that there will be a discontinuation rate of 50% in all years.

The gross impact on the medicines budget was estimated to be £147k in year 1 and £1.326m in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £7k in year 1 and £63k in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. European Medicines Agency European Public Assessment Report (EPAR) for Betmiga® EMEA/H/C/002388 www.ema.europa.eu [accessed 15 January 2013]

2. Khullar V, Amarenco G, Angulo JC et al. Efficacy and tolerability of mirabegron, a β3-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. European Urology 2013;63:283-295.

3. Nitti V, Auerbach S, Martin N et al. Results of a randomised phase III trial of mirabegron in patients with overactive bladder. Accepted manuscript. J Urology 2012, doi: 10.1016/j.juro.2012.10.017.

4. Chapple CR, Kaplan SA, Mitcheson D et al. Randomised double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a β3-adrenocpetor agonist, in overactive bladder. European Urology 2013;63:283-295

5. National Institute for Health & Clinical Excellence. Urinary incontinence in neurological disease. NICE clinical guideline 148. August 2012.

6. Lucas MG, Bosch RJL, Burkahrd FC et al. EAU guidelines on assessment and nonsurgical management of urinary incontinence. Eurpoean Urology 2012; doi.org/10.1016/j.eururo.2012.08.047.

7. National Institute for Health & Clinical Excellence. The management of lower urinary tract symptoms in men. NICE clinical guideline 97. May 2010.

8. National Institute for Health & Clinical Excellence. Urinary incontinence. The management of urinary incontinence in women. NICE clinical guideline 40. October 2006.

9. The Scottish Intercollegiate Guidelines Network (SIGN). Guideline number 79: Management of urinary incontinence in primary care. December 2004.

This assessment is based on data submitted by the applicant company up to and including 18 March 2013.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

***Advice context:***

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*