NICE National Institute for Health and Care Excellence

NICE guidance

Mirabegron for treating symptoms of overactive bladder

Technology appraisal guidance
Published: 26 June 2013

www.nice.org.uk/guidance/ta290

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Mirabegron is recommended as an option for treating the symptoms of overactive bladder only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects.

1.2 People currently receiving mirabegron that is not recommended for them in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

2 The technology

2.1 Mirabegron (Betmiga, Astellas Pharma) has a marketing authorisation in the UK for the 'symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in patients with overactive bladder (OAB)'. It is a beta-3-adrenoceptor agonist, which activates beta-3-adrenoceptors causing the bladder to relax, which helps it to fill and also to store urine. It is administered orally. Mirabegron will be available as 25 mg and 50 mg tablets, with the recommended dose being 50 mg daily, and 25 mg if there is renal or hepatic impairment.

2.2 The summary of product characteristics lists the following adverse reactions for mirabegron: urinary tract infection, tachycardia, vaginal infection, cystitis, palpitation, atrial fibrillation, dyspepsia, gastritis, urticaria, rash, rash macular, rash papular, pruritus, joint swelling, vulvovaginal pruritis, increased blood pressure, increased gamma-glutamyl transpeptidase, increased aspartate aminotransferase, increased alanine aminotransferase, eyelid oedema, lip oedema, leukocytoclastic vasculitis and purpura (rash). For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The list price indicated in the manufacturer's submission is £0.97 (excluding VAT) per 50 mg or 25 mg tablet, or an average cost of £27.06 per 28 days (assuming 1 tablet per day). Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of mirabegron and a review of this submission by the Evidence Review Group (ERG).

Clinical effectiveness

3.1 The manufacturer conducted 2 systematic reviews to identify published randomised and non-randomised controlled trial evidence on the efficacy and safety of mirabegron in adults with symptoms of overactive bladder (OAB). The clinical evidence submitted by the manufacturer consisted of 3 trials identified by the manufacturer as pivotal (SCORPIO, ARIES and CAPRICORN) and 4 supporting trials (DRAGON, 178-CL-045 and 178-CL-048, and TAURUS, which was a safety study). Additionally, a mixed-treatment comparison was performed of mirabegron against placebo, tolterodine tartrate, oxybutynin hydrochloride, solifenacin succinate, fesoterodine fumarate and trospium chloride.

3.2 SCORPIO, ARIES and CAPRICORN were randomised controlled trials that compared mirabegron (at varying doses) with placebo and tolterodine tartrate modified release (MR) 4 mg (as an active control in SCORPIO only). The supporting studies included TAURUS, a long-term safety study that compared mirabegron with tolterodine tartrate MR 4 mg (no placebo control), which examined adverse events over 52 weeks and recruited patients mainly from SCORPIO and ARIES; DRAGON, a randomised controlled trial of 12 weeks' duration comparing mirabegron with placebo and tolterodine tartrate MR 4 mg; and 2 randomised controlled trials (178-CL-045 and 178-CL-048) performed in Japan. Trial 178-CL-045 compared mirabegron with placebo and 178-CL-048 compared mirabegron with tolterodine tartrate MR 4 mg and placebo. The manufacturer presented individual results for SCORPIO, ARIES and CAPRICORN and a pooled analysis of the 3 trials with multiplicity adjustments made during the analysis of all outcomes.

3.3 SCORPIO was a 12-week trial comparing mirabegron (50 mg and 100 mg once daily) and placebo, with tolterodine tartrate MR 4 mg as an active control in adults with symptoms of OAB. The trial population was 72% female, and 63% of

all trial participants were under 65 years old. The trial took place in 189 sites in 27 EU (including the UK) and non-EU countries (in Europe, as well as Russia and Australia). There were 1987 participants, with patients randomised to mirabegron 50 mg (n=497), mirabegron 100 mg (n=498), tolterodine tartrate MR 4 mg (n=495), and placebo (n=497) in a 1:1:1:1 ratio. Assessments were conducted at weeks 4, 8 and 12.

3.4 ARIES was a 12-week trial that compared mirabegron (50 mg and 100 mg) with placebo in adults with symptoms of OAB. The trial had 74.8% female participants, and 60.3% of all trial participants were under 65 years old. The trial was conducted in 132 sites in the USA and Canada. There were 1329 participants, with patients randomised to mirabegron 50 mg (n=442), mirabegron 100 mg (n=433) and placebo control (n=454) in a 1:1:1 ratio. Assessments were conducted at weeks 4, 8 and 12.

3.5 CAPRICORN was a 12-week trial that compared mirabegron (25 mg and 50 mg) with placebo in adults with symptoms of OAB. The trial had 68.5% female participants, and 62.8% of all trial participants were under 65 years old. The trial took place in 151 sites in Europe (not including the UK) and North America. There were 1306 participants, with patients randomised to mirabegron 25 mg (n=433), mirabegron 50 mg (n=440), and placebo (n=433) in a 1:1:1 ratio. Assessments were conducted at weeks 4, 8 and 12.

3.6 TAURUS was a safety trial that compared mirabegron (50 mg and 100 mg) with tolterodine tartrate MR 4 mg as an active control in adults with symptoms of OAB. The trial duration was 2 weeks in a single-blind placebo run-in, followed by 12 months on randomised treatment. The trial took place in 306 sites globally, including the UK. There were 2452 participants, with patients randomised to mirabegron 50 mg (n=815), mirabegron 100 mg (n=824) and tolterodine tartrate MR 4 mg (n=813) in a 1:1:1 ratio. Assessments were conducted at screening, baseline and in months 1, 3, 6, 9 and 12.

3.7 DRAGON was a 12-week randomised controlled trial that compared mirabegron (25 mg, 50 mg, 100 mg and 200 mg) with placebo, and with tolterodine tartrate MR 4 mg as an active control, in adults with symptoms of OAB, in 14 European countries, including the UK (n=928). The 178-CL-045 randomised controlled trial carried out in Japan compared 25 mg, 50 mg and 100 mg mirabegron with

placebo in adults with symptoms of OAB over 12 weeks (n=842). The 178-CL-048 randomised trial carried out in Japan compared 50 mg mirabegron with placebo or tolterodine tartrate MR 4 mg as an active control in adults with symptoms of OAB over 12 weeks (n=1139).

3.8 The 2 primary outcomes of SCORPIO, ARIES and CAPRICORN were change from baseline to end point for mean number of micturitions per 24 hours and mean number of incontinence episodes per 24 hours. Secondary outcomes were mean volume voided per micturition; mean number of urgency episodes (grade 3 or 4) per 24 hours (grade 3 is severe urgency [I could not postpone voiding, but had to rush to the toilet in order not to wet myself] and grade 4 is urge incontinence [I leaked before arriving at the toilet]); mean level of urgency (associated urgency according to the 5-point categorical scale Patient Perception of Intensity of Urgency Scale); mean number of urge incontinence episodes (involuntary leakage accompanied by or immediately preceded by urgency) per 24 hours; and mean number of nocturia episodes per 24 hours.

3.9 For the 3 trials (SCORPIO, ARIES and CAPRICORN), results were reported for several populations. The primary population used in the submission was the full analysis set (patients who had at least 1 post-dose assessment). Other analyses included the intention-to-treat population (all patients randomised to receive treatment), the modified intention-to-treat set for health-related quality of life (patients who were randomised, received at least 1 dose of double-blind study medication and completed the EQ-5D questionnaire at baseline and at least once post-baseline, but excluding any patients who presented serious deviations from the protocol or for whom the EQ-5D questionnaire data was not available at 12 weeks), the incontinence full analysis set (patients who had at least 1 post-dose assessment, but only those with incontinence; these data were used for incontinence outcomes), and the safety analysis set (all randomised patients who took 1 or more doses of double-blind study drug). The doses of mirabegron used in the trials ranged from 25 mg to 100 mg. The manufacturer focused its submission on mirabegron 50 mg as the anticipated licensed dose.

Comparisons with placebo

3.10 Urinary frequency was measured as change from baseline in mean number of

micturitions in 24 hours (measured by micturition diary). The results from the full set analyses of SCORPIO, ARIES and CAPRICORN all indicated statistically significant improvements in change from baseline to week 12 in the mean number of micturitions in 24 hours in the mirabegron groups compared with placebo (SCORPIO mean difference −0.60, 95% confidence interval [CI] −0.90 to −0.29; ARIES mean difference −0.61, 95% CI −0.98 to −0.24; CAPRICORN mean difference −0.42, 95% CI −0.76 to −0.08). In the DRAGON and 178-CL-048 trials there was no statistically significant difference between mirabegron and tolterodine tartrate. In the 178-CL-045 trial significant improvements were seen with mirabegron compared with placebo (mean difference −0.74, 95% CI −1.12 to −0.36). The results of the manufacturer's pooled analysis of 3 trials (ARIES, CAPRICORN and SCORPIO) showed a statistically significant difference between mirabegron 50 mg and placebo (adjusted mean difference −0.55, 95% CI −0.75 to −0.36, $p<0.001$).

3.11 Frequency of incontinence was measured as the mean number of incontinence episodes per 24 hours and assessed in the manufacturer's submission by the full analysis set – incontinence population. The results from the SCORPIO, ARIES and CAPRICORN trials all indicated statistically significant improvements in change from baseline to week 12 in mean number of incontinence episodes per 24 hours versus placebo (SCORPIO mean difference −0.41, 95% CI −0.72 to −0.09; ARIES mean difference −0.34, 95% CI −0.66 to −0.03; CAPRICORN mean difference −0.42, 95% CI −0.76 to −0.08). In the DRAGON and 178-CL-048 trials there was no statistically significant difference between mirabegron and tolterodine tartrate. In the 178-CL-045 trial significant improvements were seen with mirabegron compared with placebo (mean difference −0.40, 95% CI −0.67 to −0.13). The results of the manufacturer's pooled analysis for the 3 trials showed a statistically significant difference between mirabegron 50 mg and placebo (mean difference −0.40, 95% CI −0.58 to −0.21 $p<0.001$).

3.12 The manufacturer presented results for the secondary outcomes reported in the trials. These were mean volume voided per micturition, frequency of urge urinary incontinence, mean level of urgency, the number of urgency episodes (grade 3 or 4) per 24 hours, and nocturia episodes per 24 hours.

Subgroup analyses

3.13 The manufacturer performed pooled subgroup analyses (from SCORPIO, ARIES and CAPRICORN) for men versus women, for the 2 primary outcomes. Mirabegron 50 mg was numerically more effective in the female subgroup than the male subgroup for the pooled trial data for the change in the number of incontinence episodes and micturitions per 24 hours between baseline and final visit. The adjusted mean difference versus placebo for incontinence episodes per 24 hours (incontinence full analysis set) in the male mirabegron 50 mg treatment group was −0.07 (95% CI −0.50 to 0.36), which was not statistically significant. The change in the adjusted mean difference versus placebo for incontinence episodes per 24 hours (incontinence full analysis set) in the female mirabegron 50 mg treatment group was −0.47 (95% CI −0.67 to −0.26), which was statistically significant. The adjusted mean difference versus placebo in the mean number of micturitions per 24 hours was −0.37 (95% CI −0.74 to −0.01) in the male mirabegron 50 mg treatment group, which was statistically significant. The adjusted mean difference versus placebo in the mean number of micturitions per 24 hours in the female mirabegron 50 mg treatment group was −0.62 (95% CI −0.85 to −0.39), which was statistically significant. Tests for treatment by sex interactions were non-significant for both outcomes (p value=0.22 for the change in the mean number of incontinence episodes per 24 hours; p=0.16 for change in the mean number of micturitions per 24 hours) indicating that there was no differential treatment effect between men and women.

3.14 The manufacturer also performed a pooled subgroup analysis using data from SCORPIO, CAPRICORN and ARIES comparing previously treated and treatment-naive groups. Mirabegron 50 mg was effective in both populations for the 2 primary outcomes. The change in the mean number of incontinence episodes per 24 hours between baseline and final visit (incontinence full analysis set) in the previously treated mirabegron 50 mg treatment group was −1.49 (95% CI −1.66 to −1.32) and the adjusted mean difference versus placebo was −0.57 (95% CI −0.81 to −0.33). The change in the mean number of incontinence episodes per 24 hours between baseline and final visit (incontinence full analysis set) in the treatment-naive mirabegron 50 mg treatment group was −1.50 (95% CI −1.71 to −1.29) and the adjusted mean difference versus placebo was −0.15 (95% CI −0.44 to 0.14). The change in the mean number of micturitions per 24 hours between baseline and final visit (full analysis set) in the previously treated

mirabegron 50 mg treatment group was −1.67 (95% CI −1.86 to −1.48) and the adjusted mean difference versus placebo was −0.74 (95% CI −1.01 to −0.47). The change in the mean number of micturitions per 24 hours between baseline and final visit (full analysis set) in the treatment-naive mirabegron 50 mg treatment group was −1.84 (95% CI −2.04 to −1.64) and the adjusted mean difference versus placebo was −0.33 (95% CI −0.62 to −0.05). Mirabegron 50 mg was effective in reducing the mean number of incontinence episodes and micturitions per 24 hours from baseline to final visit for both previously treated and treatment-naive patients. Tests for interaction indicated no treatment effect for either outcome (p=0.095 for the change in the mean number of incontinence episodes and p=0.10 for the mean number of micturitions).

Safety outcomes

3.15 Data on adverse events presented in the manufacturer's submission were largely derived from the 52-week study TAURUS (mirabegron versus tolterodine tartrate). Additionally, information was available from the SCORPIO, ARIES and CAPRICORN trials. Treatment-emergent adverse events were adverse events that occurred after treatment, while treatment-related adverse events were directly linked to treatment, although the criteria used by the manufacturer for establishing a direct link with treatment were unclear. The incidence of treatment-related adverse events was similar in the 2 groups, with 26.2% in the mirabegron 50 mg group and 27.6% in the tolterodine tartrate group in TAURUS. In TAURUS the overall incidence of treatment-emergent adverse events was similar across the mirabegron 50 mg (59.7%) and tolterodine tartrate (62.6%) groups. Most treatment-emergent adverse events were mild or moderate in all treatment groups. The overall incidence of treatment-emergent severe adverse events was 5.2% in the mirabegron 50 mg group and 5.4% in the tolterodine tartrate group in TAURUS (safety analysis set). For treatment-emergent adverse events leading to permanent discontinuation of the study drug the rates were 5.9% in the mirabegron 50 mg group and 5.7% in the tolterodine tartrate group in TAURUS (safety analysis set). In SCORPIO, ARIES and CAPRICORN the incidence of treatment-emergent adverse events was similar across all the treatment groups (safety analysis set population).

3.16 The adverse events that were designated of interest because of their association

with antimuscarinic drugs were dry mouth and constipation. The rates of constipation by treatment group for TAURUS were 2.8% and 2.7% for mirabegron and tolterodine tartrate respectively. For dry mouth, the rates were 2.8% and 8.6% for mirabegron and tolterodine tartrate respectively. In SCORPIO, the rates of dry mouth by treatment group were 1.8% and 9.5% for mirabegron and tolterodine tartrate respectively. The rates were not given for SCORPIO for constipation, or for either adverse event in ARIES and CAPRICORN.

Mixed treatment comparison

3.17 Based on the 40 studies identified in the manufacturer's literature review, the manufacturer conducted a Bayesian mixed treatment comparison (MTC) to estimate the relative efficacy and safety of mirabegron compared with oxybutynin hydrochloride (5 mg and 10 mg), fesoterodine fumarate (4 mg and 8 mg), trospium chloride (60 mg), tolterodine tartrate (4 mg), solifenacin succinate (5 mg and 10 mg) and placebo. This was done through a network analysis, using direct comparisons when available, or indirect comparison via placebo when available, or through another comparator if necessary. Oxybutynin hydrochloride and tolterodine tartrate have both MR and immediate-release formulations available, which were examined together for efficacy, but separately for safety, by the manufacturer. Analyses were conducted for micturition, urgency, urinary incontinence, dry mouth, constipation, blurred vision and frequency of incontinence for the general OAB population, but the manufacturer deemed that there were insufficient data available to conduct MTC analyses for the subgroups (including sex) identified in the final NICE scope. For each population, fixed and random effects models were used with a non-informative prior distribution. Quality of fit was assessed through the Bayesian deviance information criterion, with the model with the lowest deviance information criterion selected.

3.18 The results of the manufacturer's MTC for the outcome of number of micturitions per 24 hours indicated that the effect of mirabegron 50 mg did not differ significantly from any other treatments, except for solifenacin succinate 10 mg, which was more effective than mirabegron (odds ratio [OR] −0.583 to 95% credible interval [CrI] −0.8324 to −0.3326) and tolterodine tartrate 4 mg, which was less effective than mirabegron (OR 0.157, 95% CrI −0.0002 to 0.3154). For

the outcome of number of incontinence episodes per 24 hours, the results indicate that there was no statistically significant difference between mirabegron and any of the comparators.

3.19 The manufacturer's MTC results for the adverse effects of dry mouth, constipation and blurred vision indicated that the mirabegron group had probabilities similar to the placebo group for all effects. All antimuscarinic drugs had a significantly higher risk of dry mouth compared with mirabegron 50 mg. The odds ratios for constipation for antimuscarinic drugs compared with mirabegron 50 mg were not statistically significantly different, except for solifenacin succinate 5 mg (OR 2.501, 95% CrI 1.41 to 4.127) and 10 mg (OR 4.369, 95% CrI 2.54 to 7.071), fesoterodine fumarate 8 mg (OR 1.926, 95% CrI 1.142 to 3.059) and trospium chloride 60 mg (OR 7.604, 95% CrI 2.08 to 22.59). These were associated with higher risks of constipation compared with mirabegron 50 mg. No differences in risk between mirabegron 50 mg and other treatments were found, with wide credible intervals around the odds ratios for blurred vision due to the rarity of this adverse event.

Quality of life

3.20 Health-related quality of life and treatment satisfaction were assessed using generic scales (EQ-5D, EQ-5D VAS, TS-VAS and WPAI:SHP) and disease specific scales (OABq and PPBC) in SCORPIO, ARIES and CAPRICORN. Data from SCORPIO, ARIES and CAPRICORN were pooled for a post-hoc analysis of EQ-5D results in the modified intention-to-treat set and no data from individual trials were presented in the manufacturer's submission. Adjusting for baseline confounders (the manufacturer's submission did not provide details of which confounders), mirabegron 50 mg had greater mean change from baseline to 12-week utility scores than tolterodine tartrate MR 4 mg in the pooled analysis of ARIES, CAPRICORN and SCORPIO (0.045 and 0.026 respectively, $p \leq 0.05$). The change between baseline and 12-week utility scores was not statistically significantly different between mirabegron 50 mg and placebo (placebo utility change 0.038, p=0.30 for difference).

3.21 SCORPIO, ARIES and CAPRICORN all showed that there was a greater improvement in quality of life in the mirabegron group than in the placebo group

as measured by the OAB-q, which reached statistical significance in SCORPIO and ARIES (SCORPIO estimated mean difference 2.3, 95% CI 0.2 to 4.5; ARIES mean difference 4.1, 95% CI 1.6 to 6.6; CAPRICORN mean difference 1.2, 95% CI −1.0 to 3.4). The mirabegron, placebo and tolterodine tartrate groups achieved a clinically meaningful improvement of 10 points above baseline.

ERG critique of clinical-effectiveness evidence

3.22 The ERG noted key strengths and weaknesses in the evidence submitted by the manufacturer. The ERG considered ARIES, CAPRICORN and SCORPIO to be well-designed trials, and that the results for the effectiveness of mirabegron were consistent across the trials. The ERG's clinical expert noted that it was recommended in NHS clinical practice that pharmaceutical treatments for OAB are assessed after 3 months. The ERG therefore considered the duration of treatment and follow-up of the trials included in the manufacturer's submission to be sufficient to assess the efficacy and safety of treatment with mirabegron.

3.23 The ERG questioned the omission of the data from DRAGON, 178-CL-045 and 178-CL-048, as well as TAURUS, from the primary analyses. The ERG also noted that no direct comparison between mirabegron and tolterodine tartrate was drawn, even though SCORPIO, DRAGON, TAURUS and 178-CL-048 used tolterodine tartrate as an active control. The ERG acknowledged that these trials were not powered to evaluate the superiority or non-inferiority of mirabegron versus tolterodine tartrate, but that exclusion of data from the tolterodine tartrate group in SCORPIO limited the evidence available that was relevant for the decision problem. The ERG requested more detailed information on these trials during the clarification phase, and included it in its report. Although one of the manufacturer's exclusion criteria for 178-CL-045 and 178-CL-048 was that they were exclusively conducted in Japan, the ERG's clinical expert stated that ethnicity is unlikely to influence the development of symptoms of OAB and therefore trials from any country and any population involving patients with OAB were likely to be representative of patients with OAB in England and Wales.

3.24 The ERG considered the use of the full analysis set population appropriate, as was using the last-observation-carried-forward methodology for missing data (in SCORPIO, ARIES, CAPRICORN and TAURUS). The ERG noted that the intention-

to-treat population was not reported across all trials for comparators. The ERG considered the multiplicity adjustments used by the manufacturer in SCORPIO, ARIES and CAPRICORN to be reasonable, in order to account for the multiple outcomes and the resulting increased probability of type I errors. The ERG noted that no statistical assessment of heterogeneity was performed on the pooled analysis.

3.25 For the comparison of mirabegron with tolterodine tartrate, the ERG performed an additional meta-analysis on the data from the 3 randomised controlled trials that had an active control of tolterodine tartrate (SCORPIO, DRAGON and 178-CL-048) for the outcomes of relevance to the cost-effectiveness analysis, but did not include TAURUS in this meta-analysis because the patients were mainly recruited from SCORPIO and ARIES, and this could have led to an 'enriched' dataset that was biased. The results showed that treatment with mirabegron 50 mg led to statistically significantly fewer micturitions per 24 hours compared with treatment with tolterodine tartrate MR 4 mg (mean difference −0.27, 95% CI −0.48 to −0.06, p=0.01). Conversely, data from TAURUS favoured tolterodine tartrate MR 4 mg, although the difference was not statistically significant (mean difference 0.12, 95% CI −0.11 to 0.35, p value not given). For incontinence episodes per 24 hours, the meta-analysis of the 3 trials showed that treatment with mirabegron 50 mg was statistically significantly more effective than treatment with tolterodine tartrate MR 4 mg (mean difference −0.21, 95% CI −0.41 to −0.01, p=0.04). However, the data from TAURUS showed that mirabegron was associated with statistically significantly more episodes per 24 hours (mean difference 0.25, 95% CI 0.01 to 0.49, p=0.04).

3.26 The ERG noted concerns with the inclusion and exclusion criteria for the manufacturer's MTC, and considered that the results should be interpreted cautiously. The ERG was concerned about potential clinical and methodological heterogeneity in the included studies, the inconsistency identified in 1 or more treatment comparisons for multiple outcomes, and the number of iterations used for sampling the posterior distributions (which may be an indicator of poor mixing of data within the model). The ERG noted that, for the random effects models used, there were no estimates of the between pairwise comparisons of heterogeneity given by the manufacturer.

3.27 The ERG re-ran the MTC with different inclusion and exclusion criteria on the

same 40 studies identified by the manufacturer to perform an analysis on a more homogeneous dataset. The ERG excluded trials that included patients other than those with OAB; that were carried out in a single sex population; that reported on outcomes available at a time point other than 12 weeks; or that were deemed to be of poor methodological quality based on the manufacturer's summary (less than 4 'yes' responses in the first 4 categories assessed). The ERG included only outcomes, treatment formulations and doses used in the economic model supplied by the manufacturer. This decreased the number of studies to 22 and led to a greater degree of concordance and consequently more reliable results.

3.28 For the outcome of micturition episodes per 24 hours, the ERG found no significant difference between mirabegron 50 mg and any of the other active treatments assessed in their MTC. The manufacturer's analyses indicated that the only significant difference was that solifenacin succinate 10 mg was statistically significantly more effective than mirabegron at reducing the number of micturition episodes (mean difference −0.583, 95% CrI −0.832 to −0.333).

3.29 For the outcome of incontinence episodes per 24 hours, the results of the ERG's MTC concurred with the manufacturer's MTC results, with the exception that mirabegron 50 mg was statistically significantly less effective in reducing the frequency of incontinence episodes than solifenacin succinate 5 and 10 mg (solifenacin succinate 5 mg mean difference −0.386, 95% CrI −0.717 to −0.055, solifenacin succinate 10 mg mean difference −0.380, 95% CrI −0.694 to −0.067). The manufacturer's analyses also indicated that solifenacin succinate was numerically more effective than mirabegron, but this result was not statistically significant.

3.30 The ERG also analysed adverse events in its revised MTC analysis. The ERG found that mirabegron was statistically significantly less likely to be associated with constipation than fesoterodine fumarate 8 mg (OR 2.12, 95% CI 1.13 to 3.64), solifenacin succinate 5 mg (OR 2.11, 95% CI 1.16 to 3.59) and 10 mg (OR 4.52, 95% CI 2.60 to 7.47), and trospium chloride MR 60 mg (OR 7.63, 95% CI 2.12 to 22.95). Mirabegron was also found to be associated with a statistically significantly lower risk of dry mouth compared with all other antimuscarinic drugs assessed. Only oxybutynin hydrochloride 15 mg had a statistically significantly higher rate of discontinuation than mirabegron.

Cost effectiveness

3.31 The manufacturer's cost-effectiveness evidence consisted of a systematic review of relevant literature and a de novo Markov model. None of the studies identified in the systematic review assessed the cost effectiveness of mirabegron and so the manufacturer developed a Markov model to analyse the cost effectiveness of 50 mg mirabegron against the final scope comparators (with the exception of non-oral preparations). The model was designed to simulate the therapeutic management, the course of the condition, and complications in hypothetical cohorts of patients with OAB to estimate costs and quality-adjusted life years (QALYs) over 5 years. The population modelled was the general OAB population (that is, the licensed population) and the model had a 5-year time horizon with a 1-month cycle length and no half-cycle correction.

Model overview

3.32 In the manufacturer's model, simulated patients are either allocated mirabegron or treatment A (a single scope comparator). At the end of each monthly cycle patients can remain on the same medication, switch medication or stop all medication. The next line of therapy is considered to have cost, efficacy and safety equivalent to solifenacin succinate 5 mg. Once 2 drugs have failed, or 1 drug has failed followed by a cycle off any drug, botulinum toxin is available as a treatment option (see section 3.36).

3.33 The manufacturer's model simultaneously simulated 2 key symptoms: frequency of micturition and incontinence. Each symptom was categorised into 5 severity levels, resulting in 25 possible combinations of micturition and incontinence. At the end of each month, a person's symptoms could stay the same, improve or deteriorate. The transitions between symptom severity states were determined by multinomial logistic regression using patient-level data from the SCORPIO trial and defined as a function of treatment, symptom severity in previous month, age and sex. For each symptom (micturition and incontinence), 3 transmission probability matrices were produced: i) transition between baseline and month 1, ii) transition between month 1 and month 2, and iii) transition between month 2 and month 3. For patients remaining on treatment beyond 3 months, the third matrix was applied until discontinuation. To develop transition matrices for

antimuscarinic drugs not studied in the mirabegron clinical study programme, a calibration approach was adopted to determine the beta coefficients for use in the multinomial logistic regression model.

3.34 The only adverse events incorporated into the model were dry mouth and constipation. The manufacturer stated that expert opinion suggested that these 2 were the most likely to occur with antimuscarinic drugs. Monthly probabilities of adverse events were obtained from SCORPIO for mirabegron and tolterodine tartrate MR 4 mg and from the MTC for the other antimuscarinic drugs. It was assumed that people who were on no treatment experienced no adverse events.

3.35 Discontinuation of treatment was incorporated into the model as a combination of background persistence with OAB medication and the occurrence of adverse events. The background persistence rate for the base case was taken from a published study (Wagg 2012) and a sensitivity analysis was performed on the estimate. The discontinuation rate used in the base-case model was 72%, and was based on that observed with tolterodine tartrate MR 4 mg. The manufacturer estimated that 54.7% of patients without an adverse event would discontinue treatment by 12 months. Discontinuation due to adverse events was based on expert opinion and set at 90%. The manufacturer did not identify any literature on treatment re-initiation rates after treatment discontinuation. The manufacturer assumed that 50% of patients who had stopped treatment with mirabegron or tolterodine tartrate (in the base-case model) would restart treatment annually (5.6% per month) without immediately switching to another drug. Of these, a third would go back to their previous drug, a third would receive next line A, and a third would receive next line B.

3.36 No data were available to the manufacturer on the probability of moving to botulinum toxin. The model assumed that 1% of people who had discontinued 2 therapies or discontinued 1 and gone to no treatment would receive botulinum toxin. The probability of success of botulinum toxin was taken from a previously published cost-effectiveness analysis. The model assumed that people in whom botulinum toxin was successful moved to the lowest level of symptoms for micturition and incontinence. For those in whom botulinum toxin failed, pre-botulinum toxin symptom severity levels were assumed.

3.37 Utility values assigned to the different symptom severities used in the base case

were derived from EQ-5D index scores, based on health-related quality-of-life data, which were collected in SCORPIO. A linear regression model was used to estimate utilities for each of the 25 combinations of symptoms, with adjustment for age, sex and country (as random effect). No interaction between micturition frequency and incontinence was assumed, despite borderline statistical significance (p=0.0566). The regression model was based on all treatment arms of SCORPIO, and predicted utility values ranging from 0.85 (for people with micturition frequency and incontinence severity levels of 1) to 0.73 (for people with micturition frequency and incontinence severity levels of 5). Patients experiencing an adverse event had an associated disutility of 0.0357 (if they remained on treatment). Additionally, a sensitivity analysis was performed estimating utilities based on OAB-q and EQ-5D collected in the SCORPIO, ARIES and CAPRICORN trials.

3.38 Costs included in the model were the acquisition prices of the drugs, cost of treatment with botulinum toxin, GP visits, specialist visits and cost of incontinence pads. It was assumed that GP consultations would be 1 visit at the start and then at every treatment switch, and that specialist consultations would occur at every switch and on average 1.5 specialist consultations at the start of treatment. Incontinence pad costs were included in the model and the number of pads was determined by the level of incontinence obtained from SCORPIO. There were no costs associated with managing adverse events except specialist referral in case of a switch in treatment.

3.39 The manufacturer performed deterministic and probabilistic sensitivity analyses on assumptions and parameter estimates in the model. It also performed subgroup analyses of the base case for men and women, and treatment-naive and previous treatment groups.

Model results

3.40 The manufacturer's base-case result comparing mirabegron with tolterodine tartrate MR 4 mg based on the SCORPIO trial gave an incremental cost-effectiveness ratio (ICER) of £4,386 per QALY gained. The manufacturer's probabilistic ICER was £4,886 per QALY gained. The results of the secondary analysis using the effectiveness results from the MTC gave ICERs of £340 per

QALY gained for solifenacin succinate 10 mg versus mirabegron, £3,607 per QALY gained for fesoterodine fumarate versus mirabegron, £3,715 per QALY gained for tolterodine tartrate MR 4 mg versus mirabegron, £3,878 per QALY gained for oxybutynin hydrochloride MR 10 mg versus mirabegron, £8,881 per QALY gained for trospium chloride MR 60 mg versus mirabegron, £12,493 per QALY gained for solifenacin succinate 5 mg versus mirabegron, and £14,234 per QALY gained for oxybutynin hydrochloride 10 mg versus mirabegron.

3.41 The manufacturer performed a fully incremental analysis assuming mirabegron persistence is equivalent to solifenacin succinate. Treatments are dominated when an alternative treatment is less expensive and has greater QALY gains, and a treatment is extendedly dominated if its ICER is higher than the next, more effective, alternative. When the dominated and extendedly dominated options are excluded, the incremental analysis shows that solifenacin succinate 5 mg has an ICER of £10,814 per QALY gained compared with oxybutynin hydrochloride 10 mg, and mirabegron has an ICER of £12,493 per QALY gained when compared with solifenacin succinate 5 mg.

3.42 Results from the manufacturer's base-case 1-way deterministic sensitivity analyses indicated that the primary base-case results were relatively insensitive to variation in parameter estimates, the transition probabilities between symptom severities having the highest impact. Uncertainty was explored by sensitivity analyses on the model time horizon, impact of OAB-related comorbidities (depression, fractures, urinary tract infections and skin infections) and the use of disease-specific health-related quality-of-life measures. The results of the sensitivity analyses in the primary and secondary base cases were similar. The effects of 1-way sensitivity analyses on the primary base-case parameters that the model results were most sensitive to were: the transition probabilities between symptom levels for incontinence and micturition for tolterodine tartrate; incontinence severity distribution across levels at baseline; the monthly probability of having botulinum toxin injections; and the transition probability between symptom levels for micturition for mirabegron.

3.43 The manufacturer submitted primary base-case ICERs (mirabegron versus tolterodine tartrate MR 4 mg) for subgroups by treatment status and by sex. The primary base-case ICERs were £3,836 per QALY gained for the previously treated patient subgroup and £5,315 per QALY gained for the treatment-naive subgroup.

The primary base-case ICERs for the subgroups by sex were £38,708 per QALY gained for the male subgroup and £3,091 per QALY gained for the female subgroup. The ICER fell to £2,266 per QALY gained in the female subgroup but rose to £65,968 per QALY gained in the male subgroup if utilities derived from the OAB-q were used, rather than those from the EQ-5D.

ERG critique of the manufacturer's model

3.44 The ERG commented that it thought the manufacturer's model was well constructed, transparent and accurate. The ERG noted that the manufacturer's primary base-case cost-effectiveness analysis was generally robust. The ERG considered that the use of deterministic rather than probabilistic results was appropriate, given the high level of consistency between the deterministic and probabilistic results. The ERG noted that the manufacturer's 1-way sensitivity analyses were thorough, and that the primary base-case result was relatively robust and insensitive to individual parameter estimate changes.

3.45 The ERG identified several areas of inaccuracy or uncertainty. These included:

- uncertainty resulting from heterogeneity associated with estimates from the manufacturer's MTC
- the assumption of variable other-cause discontinuation for mirabegron patients
- the assumption that immediate (that is, within the same cycle) discontinuation as a result of an adverse event would be equivalent to the rate of other-cause discontinuation
- the possibility of infinite treatment discontinuation and re-initiation, a factor of the 'lack of memory' associated with the Markov model
- the use of adverse event rates from SCORPIO rather than the manufacturer's safety study TAURUS
- the cost associated with botulinum toxin injections
- the use of NHS payment-by-results tariffs rather than reference costs to

inform the cost of outpatient specialist visits

- the exclusion of correlation from the probabilistic sensitivity analysis.

3.46 The ERG noted that the manufacturer considered the Pearson's correlation coefficient to assess any potential relationship between the frequency of micturition and incontinence. There was a small positive correlation ($r=0.19094$, $p<0.0001$) detected. Within the model, the manufacturer assumed that the frequency of micturition was independent of the frequency of incontinence, which the ERG considers may have compromised the accuracy of the model in the respect of the distribution of patients across different symptom levels. The ERG also noted that the correlation between these outcomes is unlikely to be affected by treatment and therefore may not result in model bias either towards or against mirabegron. The ERG accepted that dry mouth and constipation were likely to be the main drivers of adverse event-related discontinuation, and therefore considered that it was unlikely that exclusion of other adverse events would bias the model either towards or against mirabegron. The ERG noted that most of the parameters were based on clinical opinion that was estimated through open discussion, rather than generated through the use of elicitation techniques, which would lead to greater parameter uncertainty.

3.47 The ERG's clinical expert indicated that a 90% discontinuation rate with adverse events would be likely to be too high, but acknowledged that the manufacturer included a sensitivity analysis that assumed a 50% adverse event-related discontinuation rate, which had a limited effect on the ICER (£4,585 per QALY gained compared with the base-case ICER of £4,386 per QALY gained). The ERG noted that there were issues with the disaggregated discontinuation rate (rates for adverse event-related discontinuation, and for discontinuation due to other causes). The probability of other-cause discontinuation was assumed to be treatment specific and, in the manufacturer's base cases (primary and secondary), was derived from the published literature to exclude adverse event-related discontinuation. The ERG considered the application of the adverse event-related discontinuation rate inappropriate to other-cause discontinuation rates.

3.48 The ERG agreed with the manufacturer that the use of regression analysis to estimate transition probabilities in the model was appropriate, so that the

potentially confounding factors of age and sex could be taken account of, and could minimise the risk of overestimating the utility benefit of mirabegron. The ERG also noted that the manufacturer stated that the interaction between the numbers of micturition and incontinence episodes was tested (Wald test: p=0.0566) and found not to be significant. The ERG commented that covariate selection was neither systematic nor rigorous and that expert clinical advice was not sought in the formulation of the linear regression models, but that in comparison with published literature the ERG considered the manufacturer's utility values generated by the regression model reasonable. The ERG also considered the selection of the covariates in the manufacturer's repeated regression model reasonable. The ERG noted that utility values from SCORPIO were comparable to those in the published literature, and considered the use of trial-based data to be appropriate. The ERG thought that the SCORPIO utility data would be likely to be biased against the more effective treatment, as would the use of EQ-5D rather than OAB-q health-related quality-of-life data.

3.49 The ERG commented that the subgroup analyses indicated that the manufacturer's primary base-case ICER was robust with respect to the subgroups considered, except for the male subgroup. The ERG noted that the proportion of men recruited for the trial was lower, therefore reducing statistical power to detect differences in efficacy. The manufacturer and the ERG also noted that male patients displayed lower baseline severity levels of OAB, and experienced a higher placebo response.

3.50 The ERG considered that the manufacturer's assumption of long-term use, based on the TAURUS study, was reasonable. The ERG noted that the relative difference between mirabegron and tolterodine tartrate in adverse event rates was higher in SCORPIO than in TAURUS, which was longer term. The primary base-case ICER decreased by £72 (from £4,386 to £4,314 per QALY gained) when using adverse event data from TAURUS rather than SCORPIO.

3.51 The ERG's additional sensitivity analyses (described in 3.47 to 3.50) cumulatively increased the primary base-case ICER from £4,386 to £5,272 per QALY gained. However, the impact on the secondary base case had greater effects. The secondary fully incremental analysis of the ERG's cumulative sensitivity analyses included the assumptions that the persistence rate with mirabegron was 28% and the probability of re-initiating original therapy was set to 0, as well as using the

adverse event rates from TAURUS and NHS reference costs for botulinum toxin injections and outpatient specialist visits. The results of the analyses were largely consistent with the manufacturer's analyses (the ICER for trospium chloride MR 60 mg compared with oxybutynin hydrochloride increased by £586, and the ICER for solifenacin succinate 5 mg compared with trospium chloride MR 60 mg increased by £899). The largest change was for the ICER of mirabegron 50 mg compared with solifenacin succinate 5 mg, which changed from £12,493 to £32,712 per QALY gained, an increase of £20,219. The impact of the sensitivity analyses on the ICERs for mirabegron versus solifenacin succinate 10 mg ranged from £573 to mirabegron being dominated by solifenacin succinate 10 mg.

3.52 The ERG was unable to quantify the impact of using alternative assumptions or parameters for all the uncertainties it identified, including the difference between the manufacturer's MTC (with no statistically significant difference between mirabegron and solifenacin succinate in reducing incontinence episodes) and the ERG's MTC (in which solifenacin succinate 5 mg was statistically significantly more effective at reducing incontinence episodes than mirabegron). The ERG considered that its ICER was likely to be conservative, and that using the ERG's MTC data was likely to result in a higher ICER than £32,712 per QALY gained for mirabegron versus solifenacin succinate 5 mg.

3.53 Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of mirabegron, having considered evidence on the nature of overactive bladder (OAB) and the value placed on the benefits of mirabegron by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee considered the treatment pathway for OAB and where mirabegron might be positioned. It understood that NICE's guideline CG40 on urinary incontinence in women (now replaced by NICE's guideline on urinary incontinence and pelvic organ prolapse in women) and NICE's guideline on lower urinary tract symptoms in men recommend that bladder training and lifestyle advice should be offered as first-line treatments for OAB, and that an antimuscarinic drug should be offered as a second-line treatment. The Committee heard from clinical specialists that there are currently no pharmacological treatments available other than antimuscarinic drugs, and if these failed the only options were invasive procedures (for example, botulinum toxin injections). The Committee heard from clinical specialists and patient experts that there was variation in service provision across the country both for the holistic care and support of people with OAB and incontinence, and the provision of botulinum toxin for OAB. The Committee concluded that mirabegron would be positioned in a complex treatment pathway that varied geographically but potentially offered an additional pharmacological treatment before invasive treatment options were considered.

4.3 The Committee discussed the effect of OAB on people. It heard from clinical specialists and patient experts that OAB is a broad spectrum condition, and some people develop individual coping strategies (for example, toilet mapping). It noted comments from patient experts about how debilitating the condition can be, with some people finding work and normal social activities difficult, or even becoming so anxious about their bladder symptoms that they do not leave home. The Committee was aware that individual circumstances mean that the effect of OAB is different for different people. The Committee noted comments from clinical specialists that, in frail older people, OAB was associated with increased risk of falls, fractures and urinary tract infections.

4.4 The Committee discussed the use of antimuscarinic drugs for OAB in clinical practice. The patient experts and clinical specialists discussed the need for pharmacological treatment of OAB within a holistic context, including bladder training, psychological support and lifestyle adjustment. They highlighted the importance of the need to explain treatments for OAB as part of a pathway, rather than pharmacological agents providing a 'quick fix'. The Committee noted that antimuscarinic drugs are known to have side effects, notably dry mouth and constipation. One patient expert explained that pharmacological agents do not necessarily lead to a satisfactory psychosocial outcome, particularly if the side effects are perceived as negative by the patient, but that if the side effects were explained as evidence that the treatment is working, they may be more acceptable and better tolerated. They also indicated that, although the average benefit of these agents seemed modest in clinical trials, some patients may gain significant benefit from them. The Committee heard from patient experts and clinical specialists that a disadvantage of immediate-release oxybutynin hydrochloride is the need for a 2 to 3-times-daily dosage, which may be inconvenient and which also left 6 hours in 24 when no effective drug may be circulating. It also heard from clinical specialists that oxybutynin hydrochloride is rarely prescribed in secondary care because most people will have tried 1 antimuscarinic before referral to a specialist. The Committee also noted that some antimuscarinic drugs may not be suitable for older people with comorbidities. The Committee concluded that an effective agent that was not an antimuscarinic could provide a valuable additional treatment option for people with OAB.

4.5 The Committee discussed the low persistence rates seen with antimuscarinic drugs. The patient experts indicated that people may stop treatment because of side effects and/or lack of clinical benefit, both of which contribute to the high discontinuation rates. However, the Committee heard from a clinical expert that some people stop treatment because they learn to manage their condition, or it improves. The Committee noted that the side-effect profile of mirabegron differed from that of the antimuscarinic drugs but it was not possible to predict whether this would have an effect on persistence rates. The Committee concluded that there was no clear evidence that persistence rates with mirabegron would differ from current pharmacological treatments.

Clinical effectiveness

4.6 The Committee discussed the available evidence from the manufacturer and the Evidence Review Group (ERG): the individual trial results, the manufacturer's pooled analysis of SCORPIO, ARIES and CAPRICORN, the ERG's meta-analysis comparing mirabegron with tolterodine tartrate based on results from SCORPIO, DRAGON and 178-CL-048, the manufacturer's mixed treatment comparison (MTC) and the ERG's revised MTC. The Committee noted that the safety trial TAURUS was not incorporated into the ERG's meta-analysis comparing mirabegron with tolterodine tartrate, and that there was a paucity of evidence comparing mirabegron directly with the NICE final scope comparators other than tolterodine tartrate modified release (MR). The Committee concluded that the evidence for a comparison of mirabegron with tolterodine tartrate using direct trial data was more robust than that from the 2 MTCs.

4.7 The Committee considered the generalisability of the trials to the UK population. It noted that there were no biologically plausible reasons for differences in OAB between different ethnic groups, and that SCORPIO and CAPRICORN were largely conducted in Europe, and ARIES was conducted in North America. There was some disagreement among the patient experts and clinical specialists on the average age of the population with OAB in the UK. The patient experts thought that there was a high incidence in people in their mid-40s and older, whereas the clinical specialists thought that the prevalence was higher in older populations, particularly above the age of 60. The Committee noted the differences of opinion, but concluded that this may reflect the differing demographics of those who accessed various services, such as self-referral continence services compared with secondary care. The Committee concluded that the trials were generalisable to the UK population.

4.8 The Committee discussed which outcomes are important and relevant when treating OAB. The patient experts and clinical specialists discussed the range of attitudes of people towards their OAB, from it being a mild inconvenience to very debilitating. The patient experts and clinical specialists also commented that the definition of satisfactory treatment outcomes was broad and varied from person to person, with some people feeling that being completely 'dry' was the only important outcome, whereas others felt that being in control of the symptoms or having fewer micturition episodes was a satisfactory response to treatment. The

Committee considered the primary and secondary outcomes reported in the trials. The Committee noted that in the draft update to that NICE's guideline CG40 on urinary incontinence in women, only wet OAB was addressed, and treatment efficacy was assessed using a binary continent/incontinent outcome. However, this guideline was still in development and could be subject to change. The Committee noted that frequency of micturition and incontinence episodes were used as the primary outcomes in this appraisal. It agreed that these outcomes captured the main benefits for people with OAB, and included the benefits both for those who had incontinence and those who did not. The Committee concluded that frequency of micturitions and incontinence episodes were the most relevant outcomes for this appraisal.

4.9 The Committee discussed the results for micturition frequency and incontinence for mirabegron. It noted that there were modest changes in frequency compared with placebo (see section 3.11). It noted the results of the manufacturer's pooled analysis showing a statistically significant improvement in mean difference from baseline in incontinence and frequency of micturition compared with placebo. It noted comments from a patient expert that the people on placebo could have experienced benefits because they changed their lifestyle as part of the treatment, which they considered showed that medication was more effective when embedded in a holistic programme. The Committee concluded that mirabegron was clinically effective compared with placebo.

4.10 The Committee explored the evidence of mirabegron compared with tolterodine tartrate. The manufacturer explained that it did not provide a direct analysis of mirabegron against tolterodine tartrate despite it being a comparator arm in SCORPIO because tolterodine tartrate was designated an active control and the trial was not powered to make such comparisons. The Committee was not convinced that this was a good reason for not presenting a comparison, and noted that the manufacturer provided an indirect analysis for mirabegron compared with tolterodine tartrate through its MTC (see section 3.18). Additionally, it was aware that the ERG had performed a meta-analysis of mirabegron compared with tolterodine tartrate, using data from the 3 trials that had tolterodine tartrate as an active comparator (SCORPIO, DRAGON and 178-CL-048; see section 3.25). The Committee noted that the results of the ERG's meta-analysis showed that mirabegron was statistically significantly more effective at reducing frequency of micturition and reducing incontinence than

tolterodine tartrate. The Committee also noted that in TAURUS, a safety trial, there were no statistically significant differences between mirabegron and tolterodine tartrate for number of micturition episodes per day, but that tolterodine tartrate was statistically significantly more effective at reducing incontinence. The Committee noted the ERG's comments that the participants in TAURUS were recruited from SCORPIO and ARIES and so may be a selected rather than representative OAB population. On balance, despite some concerns about the data from TAURUS, the Committee concluded that the evidence for a comparison between mirabegron and tolterodine tartrate was satisfactory, and that mirabegron was likely to be as clinically effective as tolterodine tartrate.

4.11 The Committee discussed the manufacturer's MTC comparing mirabegron with the other drugs listed in the scope. The Committee noted that, in the manufacturer's MTC, which included 40 trials, there were very small gains or differences in the primary clinical outcomes for all the agents (see section 3.18). The Committee noted the ERG's comments that the manufacturer's MTC contained heterogeneous trials in terms of trial quality and populations. The Committee considered the ERG's MTC using fewer, more homogeneous trials. The Committee noted the ERG's MTC produced similar results to the manufacturer's MTC with the exception of solifenacin succinate 5 mg and 10 mg, which were statistically significantly more effective at reducing incontinence episodes than mirabegron. The ERG, like the manufacturer, generally found very small differences in effect between the comparators. The Committee heard different opinions from the clinical specialists as to whether, in clinical practice, the efficacy of all antimuscarinic drugs was similar to that of tolterodine tartrate. One clinical specialist indicated that solifenacin succinate was regarded as being more effective than other antimuscarinic drugs by some clinicians, particularly tolterodine tartrate. Another clinical specialist disagreed, indicating that solifenacin succinate may be perceived to be more effective, but this is because it is frequently used at a higher dose than is available for the other antimuscarinic agents. The Committee concluded that the MTCs indicated that mirabegron, like antimuscarinic drugs, offers modest improvements compared with placebo, but it was more uncertain whether it had equivalent efficacy to all antimuscarinics.

4.12 The Committee was aware that the rate of adverse events was no different between the mirabegron and tolterodine tartrate 4 mg arms in TAURUS (see section 3.16), but that the nature of the adverse events experienced differed. In

TAURUS and SCORPIO, dry mouth was more common in the tolterodine tartrate arm than in the mirabegron arm, in which the incidence was similar to that in the placebo arm. The Committee understood from the patient experts that dry mouth was the most bothersome side effect of antimuscarinic drugs and contributed to discontinuation with treatment. The Committee acknowledged that the rate of dry mouth was statistically significantly lower for mirabegron than for tolterodine tartrate, and the other antimuscarinic drugs (2.8% versus 8.6% in TAURUS, and for all antimuscarinic drugs in the MTC [see sections 3.16 and 3.19]). The Committee concluded that the different side effects of mirabegron compared with antimuscarinic drugs could be of benefit for those who cannot tolerate the specific side effects of antimuscarinic drugs, particularly dry mouth. The Committee concluded that, for people who cannot tolerate antimuscarinic drugs, mirabegron may be a suitable alternative treatment.

4.13 The Committee discussed whether there were any differences in the clinical effectiveness of mirabegron in men and women. It noted that sex was a pre-specified subgroup in the pooled analysis of the SCORPIO, ARIES and CAPRICORN trials. Additionally, it noted that, in the manufacturer's pooled analysis, mirabegron 50 mg was numerically more effective in women than men for micturition frequency and incontinence. However, the Committee noted that the trials contained a minority (approximately 30%) of male participants. Additionally, it was aware that the rate of incontinence was lower in male than in female trial participants, so the number of men with incontinence symptoms was low. The Committee also heard from 1 clinical specialist that, in older men, incontinence may be related to bladder outflow obstruction rather than OAB and that bladder outflow obstruction may have been present in some of the male participants in the trials. The clinical specialists explained that incontinence secondary to bladder outflow obstruction would not be expected to respond to either antimuscarinic drugs or mirabegron, and could therefore confound the results. The clinical specialists indicated that they knew of no biologically plausible reasons why mirabegron would be less effective in men than in women. The Committee concluded that the lower efficacy in men demonstrated in the trials might be explained by the trial design and recruitment, and it did not pursue this further.

4.14 The Committee discussed the subgroup analyses comparing the clinical effectiveness of mirabegron in treatment-naive and pre-treated populations. The

Committee noted there were no statistically significant differences between the effects of mirabegron in these 2 subgroups, and concluded there was no pharmacological reason why the effects of mirabegron would differ between these groups. In addition, the Committee heard from the manufacturer that trials using mirabegron in combination with antimuscarinic drugs were ongoing because it is thought that the different mechanisms of action may enhance the effects of the individual drugs.

4.15 The Committee considered the need for alternatives to current treatments for OAB. It heard from clinical specialists that, for those who had contraindications to antimuscarinic drugs, had not gained clinical benefit, or who had unacceptable side effects, there was an unmet need for alternative pharmacological treatments. This could avoid invasive treatments such as botulinum toxin, which may have significant side effects (for example, urinary retention needing catheterisation). The Committee heard that, in line with existing NICE guidelines, antimuscarinic drugs are routinely used as the first pharmacological treatment for OAB, and there is long-term evidence that people benefit from them. There is also considerable clinical experience in the use of antimuscarinic drugs and the management of their side effects. However, the Committee concluded that there was a need for pharmacological alternatives to antimuscarinic drugs for people in whom these are contraindicated, or for whom they are ineffective or associated with unacceptable side effects.

Cost effectiveness

4.16 The Committee considered the available cost-effectiveness evidence. It discussed the manufacturer's base-case incremental cost-effectiveness ratio ICER of £4,400 per quality-adjusted life years (QALY) gained for mirabegron 50 mg compared with tolterodine tartrate MR 4 mg. The Committee noted the ERG's comment that the manufacturer's model was accurate and transparent but also its concerns related to some of the costs in the model and assumptions of discontinuation (see section 3.52). The Committee noted the small QALY gains seen in both the manufacturer's and ERG's analyses (see section 3.41). The Committee acknowledged that the ERG's cumulative sensitivity analyses resulted in a similar ICER to the manufacturer's (£4,400 per QALY gained in the manufacturer's base case, and £5,272 per QALY gained in the ERG's cumulative

sensitivity analyses). The Committee concluded that the base-case analyses were similar for the manufacturer and the ERG, and were likely to be robust. The Committee concluded that mirabegron was therefore likely to be cost effective when compared with tolterodine tartrate MR 4 mg.

4.17 The Committee explored the results from the manufacturer's secondary base case and incremental analysis comparing mirabegron with the other antimuscarinic drugs defined in the scope. It observed that this analysis relied on the effectiveness results from the manufacturer's MTC and that, for technical reasons, it had not been possible for the results from the ERG's MTC to be incorporated into the ERG's economic analyses, leading to some uncertainty about the results. The Committee noted that most of the ERG's sensitivity analyses had a small effect on the resulting ICERs for mirabegron compared with comparators, except for solifenacin succinate 5 mg. In this case, when the assumption of persistence of treatment was set to 28% (as opposed to equal to that of the comparator, 35%) the ICER compared with solifenacin succinate 5 mg rose from £12,500 to £32,700 per QALY gained. The Committee acknowledged there were no data on persistence with mirabegron other than from the clinical trials, and that data from the trials were unlikely to be representative of the persistence rates in clinical practice because, in the trials, patients were actively encouraged to continue taking the drug for the entire trial duration. The Committee concluded that the ERG's analysis using a lower persistence rate for mirabegron than solifenacin succinate resulted in mirabegron being cost ineffective compared with solifenacin succinate 5 mg, and that, if the ERG's MTC had been incorporated into the model, the ICER could have been higher. However, because of the small differences in QALY gains, and the lack of evidence on persistence rates in practice for mirabegron, this was subject to significant uncertainty.

4.18 The Committee discussed the incorporation of adverse events in the economic analyses. It noted that the only adverse events incorporated into the modelling were dry mouth and constipation, and that dry mouth was a particular side effect of antimuscarinic drugs (see section 3.30). The Committee expressed concern that no side effects that may be more common with mirabegron were included in the model. It questioned whether this might be favourable to mirabegron because it took no account of the similar rate of withdrawal due to adverse events in the mirabegron and tolterodine tartrate arms of TAURUS (5.9% for mirabegron and

5.7% for tolterodine tartrate). As a result, the ICER for mirabegron compared with tolterodine tartrate could be underestimated. The Committee concluded that the specific adverse events incorporated in the model were likely to favour mirabegron over all the antimuscarinic drugs.

4.19 The Committee discussed the most plausible ICERs for mirabegron. It remained concerned about the fact that it had not been possible to assess the impact of incorporating the ERG's MTC into the economic analysis, which might have given different ICERs. However, the Committee noted that it had more robust evidence comparing mirabegron with tolterodine tartrate 4 mg and was satisfied that it was no less clinically effective than tolterodine tartrate 4 mg. The Committee questioned whether tolterodine tartrate was likely to be representative of the effectiveness of antimuscarinic drugs as a class, or whether the results from the manufacturer's MTC against the other agents were robust. The Committee noted that the ICERs were relatively unstable, and varied with small fluctuations in the QALY calculations. However, the differences between the QALYs calculated were consistently small in both the manufacturer's and ERG's analyses. The Committee accepted that mirabegron has a different mechanism of action than that of antimuscarinic drugs. It also has a different side-effect profile, but the same rate of discontinuation due to adverse events as tolterodine tartrate. It took into consideration that the calculated ICERs were based on small and uncertain differences of clinical efficacy between mirabegron and a range of available antimuscarinic drugs, which may or may not have similar efficacy as a class. Therefore the cost effectiveness compared with antimuscarinic drugs as a class was uncertain. However, the Committee concluded that mirabegron was likely to be a cost-effective treatment for people with OAB for whom antimuscarinic drugs are contraindicated, not effective, or produce unacceptable side effects.

4.20 The Committee considered a comment the manufacturer submitted in response to the appraisal consultation document, in which the manufacturer requested that the Committee consider how the guidance should be interpreted for more vulnerable groups of patients, for example, older patients or those who already have a high anticholinergic burden due to other prescribed medications. The Committee noted that withdrawal rates due to adverse events did not differ in the mirabegron and tolterodine tartrate arms of the TAURUS trial and the manufacturer did not provide additional evidence of mirabegron having a lower rate of adverse events in older patients. The Committee concluded that there

was no evidence to support a different recommendation for older people. With respect to people who had a high anticholinergic burden from other medications, the Committee concluded that normal prescribing practice would involve an assessment of existing medications and potential drug interactions, and it was not necessary to specify this in the guidance.

4.21 The Committee considered whether NICE's duties under the equalities legislation required it to alter or to add to its recommendations. The only potential equality issue identified was whether incontinence disproportionately affects people on a low income, due to the need to purchase incontinence pads and other auxiliary goods. However, the Committee noted that this was not a group protected under equalities legislation, and that the use of mirabegron would be unlikely to affect this group disproportionately.

4.22 The Committee discussed whether mirabegron should be considered an innovative technology, or if there were any significant and substantial health benefits that were not included in the economic model. The Committee considered the potentially innovative nature of mirabegron in that it targeted different receptors from those targeted by antimuscarinic drugs. The Committee accepted mirabegron's different and innovative mechanism of action, but concluded that all the benefits would be adequately captured in the QALY calculation.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has overactive bladder and the healthcare professional responsible for their care thinks that mirabegron is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members, guideline representatives and NICE project team

6.1 Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)
Department of Diagnostic Radiology, St George's Hospital, London

Professor Iain Squire (Vice-Chair)
Consultant Physician, University Hospitals of Leicester

Professor Thanos Athanasiou
Professor of Cardiovascular Sciences and Cardiac Surgery, Imperial College London; Consultant Cardiothoracic Surgeon, Imperial College Healthcare NHS Trust

Dr Jeremy Braybrooke
Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Gerardine Bryant
GP, Swadlincote, Derbyshire

Dr Fiona Duncan
Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital

Mr Andrew England
Lecturer in Medical Imaging, NIHR Fellow, University of Liverpool

Professor Jonathan Grigg
Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

Dr Brian Hawkins
Chief Pharmacist, Cwm Taf Health Board, South Wales

Dr Peter Heywood
Consultant Neurologist, Frenchay Hospital, Bristol

Dr Sharon Saint Lamont
Head of Quality and Innovation, North East Strategic Health Authority

Dr Ian Lewin
Consultant Endocrinologist, North Devon District Hospital

Dr Anne McCune
Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray
Professor of Medical Cardiology, University of Glasgow

Dr Mohit Misra
GP, Queen Elizabeth Hospital, London

Ms Sarah Parry
CNS Paediatric Pain Management, Bristol Royal Hospital for Children

Ms Pamela Rees

Lay Member

Dr Ann Richardson
Lay Member

Dr Paul Robinson
Medical Director, Merck Sharp & Dohme

Ms Ellen Rule
Programme Director, NHS Bristol

Mr Stephen Sharp
Senior Statistician, MRC Epidemiology Unit

Dr Peter Sims
GP, Devon

Dr Eldon Spackman
Research Fellow, Centre for Health Economics, University of York

Mr David Thomson
Lay Member

Dr John Watkins
Clinical Senior Lecturer, Cardiff University; Consultant in Public Health Medicine, National Public Health Service Wales

Dr Olivia Wu
Reader in Health Economics, University of Glasgow

6.2 Guideline representatives

The following individuals, representing the Guideline Development Group responsible for developing NICE's guideline related to this topic, were invited to attend the meeting to observe and to contribute as advisers to the Committee.

Dr Anthony RB Smith
Consultant Gynaecologist (urinary incontinence guideline development group Chair)

6.3 NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Dr Grace Jennings
Technical Lead

Dr Kay Nolan (until March 2013)
Technical Adviser

Bijal Joshi
Project Manager

7 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by BMJ Technology Assessment Group (BMJ-TAG):

- Edwards SJ, Karner C, Trevor N et al. Mirabegron for the treatment of symptoms associated with overactive bladder. (January 2013)

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Manufacturers or sponsors were also invited to make written submissions. Professional or specialist and patient or carer groups, and other consultees, had the opportunity to give their expert views. Manufacturers or sponsors, professional or specialist and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Manufacturer or sponsor:

- Astellas Pharma (mirabegron)

Professional or specialist and patient or carer groups:

- Association for Continence Advice
- Bladder and Bowel Foundation
- British Association of Urological Surgeons
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

Other consultees:

- Department of Health

- Welsh Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- BMJ Technology Assessment Group (BMJ-TAG)
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Health Care Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- National Clinical Guidelines Centre
- National Institute for Health Research Health Technology Assessment Programme
- Pfizer (fesoterodine fumarate, oxybutynin hydrochloride, tolterodine tartrate)

The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on mirabegron by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Mrs Cath Williams, ACA Executive Committee/Clinical and Operational Lead, Bladder and Bowel Service, nominated by organisation representing Association for Continence Advice – clinical specialist
- Mrs Suzie Venn, Consultant Urological Surgeon, nominated by organisation representing British Association of Urological Surgeons – clinical specialist
- Mrs Debbie Stuart, Clinical Manager, nominated by organisation representing Bladder and Bowel Foundation – patient expert
- Mrs June Rogers, PromoCon Team Director, nominated by organisation representing National Clinical Guidelines Centre – patient expert

Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Astellas Pharma

ISBN 978-1-4731-0198-2