NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Mirabegron for the treatment of symptoms associated with overactive bladder

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness for overactive bladder

- Where should mirabegron be placed in the treatment pathway?
- How generalisable are the trial populations to the UK OAB population? Should DRAGON, 178-CL-045 and 178-CL-048 have been included in the manufacturer's analyses?
- What are the most clinically relevant outcomes for OAB?
- Is the full analysis set (FAS) the appropriate data set for determining clinical effectiveness?
- How valid is the manufacturers mixed treatment comparison (e.g. in terms of study heterogeneity)? What reference should be given to the ERGs MTC, even though it did not form part of the ICER calculations?
- Is mirabegron equally effective in men and women?

Cost effectiveness

- Does the model adequately capture:
  - Clinical pathway for treatment of OAB in England? The relevant costs associated with OAB e.g. should incontinence pads be costed in the model?
  - The correct outcomes (urinary and incontinence frequency)?
  - The appropriate adverse events (dry mouth and constipation) associated with mirabegron and antimuscarinics?
- Have appropriate assumptions been made on modelling discontinuation, does it accurately capture the likely use of mirabegron in clinical practice?
- Is it reasonable to assume that the persistence rate on mirabegron should vary according to the comparison being made?
- What is the Committee's view on the clinical relevance of the health-related quality of life data (EuroQOL and OAB-q data) and how it has been used to derive utility values for each of the 25 combinations of symptoms?
- Are the subgroup analyses (male/female and prior treatment/treatment naïve) robust? Are they likely to be clinically plausible? What impact do the subgroups have on clinical and cost effectiveness?
- What is the plausible ICER for mirabegron against each scope comparator?

1 Background: clinical need and practice

1.1 Overactive bladder (OAB) typically results from spasms of the muscles of the bladder that produce a compelling urge to urinate, even though the bladder may only contain a small amount of urine. It is defined as urgency that occurs with or without urge urinary incontinence and usually with frequency and nocturia (urination at night). Causes of overactive bladder are often unclear but the condition has been linked to urinary tract infections, some types of drugs, benign prostatic hyperplasia and certain conditions that

affect nerves, including Parkinson's disease, multiple sclerosis and stroke.

1.2 OAB affects approximately 17% of men and women aged 40 years and over, and prevalence increases with age. The prevalence of OAB in men and women is similar, with women more likely to have OAB with incontinence and men more likely to have OAB without incontinence. In England and Wales an estimated 4.8 million people have symptoms of OAB, of whom around 60% have seen a doctor, and approximately one quarter have ever received treatment.

1.3 Approximately two thirds of people with OAB indicate that the condition impacts on their daily lives. Symptoms may cause significant social, psychological, physical and sexual problems, including lowered work productivity, increased rates of erectile dysfunction and lower sexual satisfaction, disrupted sleep patterns due to nocturia, leading to lower levels of health and decreased health-related quality of life. OAB is also associated with a variety of co-morbidities such as increased risk of falls and fractures, depression, urinary tract infections and skin infections.

1.4 NICE clinical guideline 40 'Urinary incontinence: the management of urinary incontinence in women' and NICE clinical guideline 97 'Lower urinary tract symptoms in men' recommend that bladder training and lifestyle advice should be offered as first-line treatments for OAB. An antimuscarinic drug should be offered second line. NICE clinical guideline 40 specifies that non-proprietary oxybutynin should be the first line antimuscarinic. If this is not effective, alternatives are darifenacin, solifenacin, tolterodine, trospium, or different oxybutynin formulations. Continuation with

OAB medication is low (approximately 28% at one year) due to perceived lack of effectiveness and adverse events.

2 The technology

2.1 Mirabegron (Betmiga, Astellas Pharma) has 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 β3-adrenoceptor agonist, which activates β3-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 25mg and 50mg tablets, with the recommended dose being 50mg once per day, and 25mg if there is renal or hepatic impairment.

2.2 The draft summary of product characteristics lists the following adverse reactions for mirabegron: urinary tract infection, tachycardia, vaginal infection, cystitis, palpitation, atrial fibrillation, dyspepsia, gastritis, urticarial, rash, rash macular, rash popular, pruritus, joint swelling, vulvovaginal pruritis, blood pressure increased, gamma-glytamyl transpeptidase increased, aspartate aminotransferase increased, alanine aminotransferase increased, eyelid oedema, lip oedema, leukocytoclastic vasculitis, 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 50mg or 25mg tablet, or an average cost of £29.40 for one month (assuming one tablet per day). Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of mirabegron within its licensed indication for the treatment of symptoms associated with overactive bladder

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Adults with symptoms of overactive bladder	As per NICE scope
	Final scope issued by NICE	**Decision problem addressed in the submission**
Intervention	Mirabegron	As per NICE scope
	Final scope issued by NICE	**Decision problem addressed in the submission**
Comparators	Antimuscarinic drugs including: oxybutynin (including modified-release preparations) tolterodine fesoterodine solifenacin trospium	As per NICE scope, and additionally: placebo

The ERG noted that the manufacturer's submission primarily compared the effects of mirabegron with placebo, which was not a comparator listed in the scope. The ERG also noted that the manufacturer excluded non-oral preparations of interventions, which was a deviation from the scope, which included modified-release formulations of oxybutynin (available as a transdermal patch) as a comparator. The manufacturer justified this on the basis that only 1.4% of prescriptions are for antimuscarinic transdermal patches.

	Final scope issued by NICE	Decision problem addressed in the submission
Outcomes	The outcome measures to be considered include: symptoms of urgency urinary frequency (micturition) frequency of urge urinary incontinence nocturia adverse effects of treatment health-related quality of life	As per NICE scope, and additionally: number of incontinence episodes volume voided during micturition

The manufacturer reported 2 additional outcomes. The ERG noted that one of these, the number of incontinence episodes, was an important element in the cost effectiveness model. The ERG's clinical expert noted that frequency of urgency urinary incontinence is analogous to number of incontinence episodes as incontinence is typically preceded by urgency.

	Final scope issued by NICE	Decision problem addressed in the submission
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per NICE scope Analyses of male and female and previously treated and treatment-naïve subgroups were presented by the manufacturer.

3.2 Mirabegron is being considered as a treatment for adults with overactive bladder, that is after bladder training, lifestyle and behavioural advice.

4 Clinical-effectiveness evidence

4.1 The manufacturer conducted 2 systematic reviews to identify published RCT and non-RCT evidence on the efficacy and safety of mirabegron in adults with symptoms of OAB. The clinical evidence submitted by the manufacturer consisted of 3 trials they identified as pivotal and 4 identified as supporting trials. Additionally a mixed treatment comparison was performed of mirabegron against placebo, tolterodine, oxybutynin, solifenacin, fesoterodine and trospium (see table 1).

Table 1: Summary of the mirabegron trials

Study	Intervention	Trial design	Patient population	No randomised patients	Trial length (wks)
DRAGON	Mirabegron 25 mg Mirabegron 50 mg Mirabegron 100 mg Mirabegron 200 mg Tolterodine ER 4 mg Placebo	Phase IIb, RCT, double-blind, double dummy, multicentre (Europe)	OAB, ≥ 18 years	928	12
SCORPIO	Mirabegron 50 mg Mirabegron 100 mg Tolterodine ER 4 mg Placebo	Phase III, RCT, double-blind, multicentre (Europe, Australia)	OAB, ≥ 18 years	1987	12
ARIES	Mirabegron 50 mg Mirabegron 100 mg Placebo	Phase III, RCT, double-blind, double dummy, multicentre (US and Canada)	OAB, ≥ 18 years	1329	12
CAPRICORN	Mirabegron 25 mg Mirabegron 50 mg Placebo	Phase III, RCT, double-blind, double dummy, multicentre (Europe, US, Canada)	OAB, ≥ 18 years	1306	12
178-CL-045	Mirabegron 25 mg Mirabegron 50 mg Mirabegron 100 mg Placebo	Phase II, RCT, double-blind, multicentre (Japan)	OAB, 20–80 years	842	12
178-CL-048	Mirabegron 50 mg Tolterodine 4 mg Placebo	RCT, double-blind, multicentre (Japan)	OAB , ≥ 20 years	1139	12

Study	Intervention	Trial design	Patient population	No randomised patients	Trial length (wks)
TAURUS	Mirabegron 50mg Mirabegron 100mg	Phase III, randomised, double-blind, parallel group, active-controlled study (Global – Europe, N America, Australia, South Africa)	OAB, ≥ 18 years	2452	2 weeks run-in, 52 on treatment

4.2 The clinical evidence presented by the manufacturer came from three Phase III randomised control trials, SCORPIO, ARIES and CAPRICORN. These trials compared mirabegron with placebo at varying dosages and tolterodine (as an active control in SCORPIO only). The supporting studies included TAURUS, a long-term safety study comparing mirabegron versus tolterodine (no placebo control), which examined adverse events over 52 weeks, and recruited patients mainly from SCORPIO and ARIES; DRAGON a phase II RCT of 12 weeks duration comparing mirabegron with placebo and tolterodine; and 2 RCTs (178-CL-045 and 178-CL-048) performed in Japan. 178-CL-045 examined mirabegron against placebo and 178-CL-048 examined mirabegron against tolterodine and placebo. The manufacturer presented individual results for the 3 main studies and a pooled analysis of the 3 main trials.

4.3 SCORPIO was a 12 week trial comparing mirabegron (50mg and 100mg once daily) and placebo, with 4mg tolterodine slow-release (tolterodine SR) as an active control in adults with symptomatic OAB. The trial population was 72% female and 63% of the

participants were aged less than 65. 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 50mg (n=497), mirabegron 100mg (n=498), tolterodine 4mg SR (n=495), and placebo (n=497) in a 1:1:1:1 ratio. Assessments were conducted at visits at week 4, 8, and 12.

4.4 ARIES was a 12 week trial that compared mirabegron (50mg and 100mg) and placebo in adults with symptomatic OAB. The trial had 74.8% female participants, and 60.3% of trial participants were aged less than 65. The trial was conducted in 132 sites in the US and Canada. There were 1329 participants, with patients randomised to mirabegron 50mg (n=442), mirabegron 100mg (n=433), and placebo control (n=454) in a 1:1:1 ratio. Assessments were conducted at visits at week 4, 8, and 12.

4.5 CAPRICORN was a 12 week trial that compared mirabegron (25mg and 50mg) and placebo in adults with symptomatic OAB. The trial had 68.5% female participants, and 62.8% of trial participants were aged less than 65. 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 25mg (n=433), mirabegron 50mg (n=440), and placebo (n=433) in a 1:1:1 ratio. Assessments were conducted at visits at week 4, 8, and 12.

4.6 TAURUS was a safety trial that compared mirabegron (50mg and 100mg) with tolterodine extended release (ER) as an active control in adults with symptomatic 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 50mg (n=815), mirabegron 100mg (n=824), and active control tolterodine 4mg (n=813) in a 1:1:1 ratio. Assessments were conducted at visits at screening, baseline, and in months 1, 3, 6, 9, and 12.

4.7 DRAGON was a phase II trial which compared mirabegron in 25mg, 50mg, 100mg, and 200mg doses with placebo, with tolterodine SR as an active control in adults with OAB over 12 weeks, in 14 European countries, including the UK. 178-CL-045 was a phase II trial carried out in Japan which compared 25mg, 50mg and 100mg mirabegron with placebo in adults with OAB over 12 weeks. 178-CL-048 was a phase III trial carried out in Japan which compared 50mg mirabegron with placebo or 4mg tolterodine ER as an active control in adults with OAB over 12 weeks.

4.8 The two primary outcomes of SCORPIO, ARIES and CAPRICORN were change from baseline to endpoint 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) (Grade 3 urgency is severe urgency (I could not postpone voiding, but had to rush to the toilet in order not to wet myself) and Grade 4 urgency is urge incontinence (I leaked before arriving to the toilet) per 24 hours, 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.

4.9 For the three trials (SCORPIO, ARIES and CAPRICORN) results were reported for several analyses: i) full analysis set (FAS)

(Patients who had at least one post dose assessment), ii) intention to treat (ITT) (all patients randomised to receive treatment), iii) modified ITT set for HRQoL (patients who were randomised, received at least one dose of double-blind study medication and completed the EQ-5D questionnaire at baseline and at least once post-baseline excluding any patients who presented serious deviations from the protocol or for whom the EQ-5D questionnaire data was not available at 12 weeks), iv) incontinence FAS (FAS-I) (same as FAS but only included patients with incontinence and used for incontinence outcomes) and v) safety analysis set (SAS) (all randomised patients who took ≥ 1 dose of double-blind study drug).

4.10 The doses of mirabegron used in the trials ranged from 25mg to 200mg. The manufacturer focused its submission on mirabegron 50mg as the anticipated licensed dose.

4.11 The manufacturer performed a pre-specified pooled analysis of the three main studies (SCORPIO, ARIES and CAPRICORN). Multiplicity adjustments were made during the analysis of all outcomes; no statistical assessment of heterogeneity of the three studies was performed.

4.12 At the clarification stage the ERG requested information on the primary and secondary outcomes from DRAGON, 178-CL-045 and 178-CL-048 studies. These are presented below alongside the results for the 3 trials originally presented by the manufacturer.

Primary outcomes

4.13 Urinary frequency was measured as change from baseline in mean number of micturitions in 24 hours (measured by micturition diary). The results from the FAS 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 to placebo (see table 2). In the DRAGON and 178-CL-048 trials, there was no statistically significant difference between mirabegron and tolterodine. In the 178-CL-045 trial significant improvements were seen with mirabegron compared to placebo. The results of the manufacturer's pooled analysis of the 3 trials (ARIES, CAPRICORN and SCORPIO) showed a statistically significant difference between mirabegron 50mg and placebo (mean difference -0.55, 95%CI –0.75 to –0.36, p<0.001).

Table 2: Urinary frequency (Change from baseline to final visit in mean number of micturitions per 24 hours) in 3 mirabegron trials

Study	Mirabegron 50 mg vs tolterodine		Mirabegron 50 mg vs placebo	
	MD	95% CI	MD	95% CI
SCORPIO	NR	NR	–0.60	–0.90 to –0.29
ARIES	N/A	N/A	–0.61	–0.98 to –0.24
CAPRICORN	N/A	N/A	–0.42	–0.76 to –0.08
Manufacturer's pooled analysis			–0.55	–0.75 to –0.36
			Mirabegron 50 mg, N=1,324 Placebo, N=1,328	
DRAGON	–0.14	–0.80 to 0.53	–0.64	–1.19 to –0.10
178-CL-045	N/A	N/A	–0.74	–1.12 to –0.36
178-CL-048	–0.25	–0.55 to 0.04	–0.86	–1.16 to –0.57

Abbreviations used in table: CI, confidence interval; MD, mean difference; mg, milligram; NA, not applicable; NR, not reported.

4.14 Frequency of incontinence was measured as the mean number of incontinence episodes per 24 hours and assessed in the manufacturers submission by the full analysis set – incontinence (FAS-I) population. The results from the SCORPIO, ARIES and CAPRICORN indicate statistically significant improvements in change from baseline to week 12 in mean number of incontinence episodes per 24 hours versus placebo (table 3). In the DRAGON and 178-CL-048 trials, there was no statistically significant difference between mirabegron and tolterodine. In the 178-CL-045 trial significant improvements were seen with mirabegron compared to placebo at both mirabegron doses. The results of the manufacturer's pooled analysis for the 3 trials showed a statistically significant difference between mirabegron 50mg and placebo (mean difference -0.40, 95% CI -0.58 to -0.21 p<0.001).

Table 3. Change from baseline to final visit in mean number of incontinence episodes per 24 hours

Study	Mirabegron 50 mg vs tolterodine		Mirabegron 50 mg vs placebo	
	MD	**95% CI**	**MD**	**95% CI**
178-CL-046 (SCORPIO)	NR	NR	–0.41	–0.72 to –0.09
178-CL-047 (ARIES)	N/A	N/A	–0.34	–0.66 to –0.03
178-CL-074 (CAPRICORN)	N/A	N/A	–0.42	–0.76 to –0.08
Manufacturer's pooled analysis			–0.40	–0.58 to –0.21
			Mirabegron 50 mg, N=862 Placebo, N=878	
178-CL-044 (DRAGON)	–0.34	–1.06 to 0.39	–0.62	–1.22 to –0.02
178-CL-045	N/A	N/A	–0.40	–0.67 to –0.13
178-CL-048	–0.10	-0.36 to 0.15	-0.42	-0.67 to -0.17

Abbreviations used in table: CI, confidence interval; MD, mean difference; mg, milligram; NA, not applicable; NR, not reported.

Secondary outcomes

4.15 The results for the FAS populations for SCORPIO, ARIES and CAPRICORN for the change from baseline to week 12 in mean volume voided per micturition were statistically significantly different between the mirabegron and placebo (table 4) indicating an improvement with mirabegron. The pooled analysis of SCORPIO, ARIES and CAPRICORN also showed a statistically significant difference (mean difference 11.9, 95% CI 8.3 to 15.5, p<0.001). In DRAGON and 178-CL-048, there was no statistically significant difference between mirabegron 50mg and tolterodine 4mg.

Table 4. Mean volume voided per micturition

Study	Mirabegron 50 mg vs tolterodine		Mirabegron 50 mg vs placebo	
	MD	95% CI	MD	95% CI
178-CL-046 (SCORPIO)	NR	NR	11.9	6.3 to 17.4
178-CL-047 (ARIES)	N/A	N/A	11.1	4.4 to 17.9
178-CL-074 (CAPRICORN)	N/A	N/A	12.4	6.3 to 18.6
Manufacturer's pooled analysis			11.9	8.3 to 15.5
			Mirabegron 50 mg, N=1,324 Placebo, N=1,328	
178-CL-044 (DRAGON)	–16.81	–-28.5 to -5.09	N/A	N/A
178-CL-045	N/A	N/A	16.204	8.635 to 23.774
178-CL-048	-4.274	-9.066 to 0.519	14.775	9.974 to 19.576
Abbreviations used in table: CI, confidence interval; MD, mean difference; mg, milligram; NA, not applicable; NR, not reported.				

4.16 Frequency of urge urinary incontinence was assessed in the FAS-I population. All 6 trials found a statistically significant decrease in frequency of urge incontinence episodes in the mirabegron 50mg group compared with placebo. This was also demonstrated in the

manufacturer's pooled analysis of SCORPIO, ARIES and CAPRICORN (mean difference -0.40, 95% CI -0.57 to -0.23, p<0.001) (see table 5). In DRAGON and 178-CL-048, the difference between mirabegron 50mg and tolterodine 4mg was not statistically significant.

Table 5. Change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours

Study	Mirabegron 50 mg vs tolterodine		Mirabegron 50 mg vs placebo	
	MD	**95% CI**	**MD**	**95% CI**
178-CL-046 (SCORPIO)	NR	NR	–0.35	–0.65 to –0.05
178-CL-047 (ARIES)	N/A	N/A	–0.43	–0.72 to –0.15
178-CL-074 (CAPRICORN)	N/A	N/A	–0.39	–0.69 to –0.08
Manufacturer's pooled analysis			–0.40	–0.57 to –0.23
			Mirabegron 50 mg, N=862 Placebo, N=878	
178-CL-044 (DRAGON)	–0.37	–0.99 to 0.24	–0.69	–1.18 to –0.19
178-CL-045	N/A	N/A	–0.27	–0.53 to –0.01
178-CL-048	–0.04	–0.28 to 0.21	–0.36	–0.59 to –0.12
Abbreviations used in table: CI, confidence interval; MD, mean difference; mg, milligram; NA, not applicable; NR, not reported.				

4.17 Mean level of urgency was assessed in the FAS population of SCORPIO, ARIES, CAPRICORN and DRAGON. There was a

statistically significant difference between mirabegon 50mg and placebo in SCORPIO, ARIES and CAPRICORN, and in the pooled analysis of these three trials (mean difference -0.11, 95%CI -0.16 to -0.07, p value<0.001), although not in DRAGON (see table 6). There was no significant difference between mirabegron 50mg and tolterodine 4mg in either DRAGON or 178-CL-048.

Table 6. Change from baseline to final visit in mean level of urgency

Study	Mirabegron 50 mg vs tolterodine		Mirabegron 50 mg vs placebo	
	MD	**95% CI**	**MD**	**95% CI**
178-CL-046 (SCORPIO)	NR	NR	–0.09	–0.16 to –0.01
178-CL-047 (ARIES)	N/A	N/A	–0.11	–0.18 to –0.04
178-CL-074 (CAPRICORN)	N/A	N/A	–0.14	–0.22 to –0.06
Manufacturer's pooled analysis			–0.11	–0.16 to –0.07
			Mirabegron 50 mg, N=1,324 Placebo, N=1,328	
178-CL-044 (DRAGON)	–0.08	–0.22 to 0.05	–0.04	–0.20 to 0.13
Abbreviations used in table: CI, confidence interval; MD, mean difference; mg, milligram; N/A, not applicable; NR, not reported.				

4.18 For the FAS population, the number of urgency episodes (level 3 or 4) per 24 hours was lower in the mirabegron 50mg groups than in the placebo groups for all six trials (see table 7). In the manufacturer's pooled analysis of SCORPIO, ARIES and CAPRICORN, there was a statistically significant difference

between mirabegron 50mg and placebo (mean difference -0.64, 95% CI -0.89 to -0.39, p<0.001). There was no statistically significant difference between mirabegron 50mg and tolterodine 4mg in either DRAGON or 178-CL-048.

Table 7. Change from baseline to final visit in mean number of urgency episodes (Grade 3 or 4) per 24 hours

Study	Mirabegron 50 mg vs tolterodine		Mirabegron 50 mg vs placebo	
	MD	95% CI	MD	95% CI
178-CL-046 (SCORPIO)	NR	NR	–0.60	–1.02 to –0.18
178-CL-047 (ARIES)	N/A	N/A	–0.75	–1.20 to –0.30
178-CL-074 (CAPRICORN)	N/A	N/A	–0.59	–1.01 to –0.16
Manufacturer's pooled analysis			–0.64	–0.89 to –0.39
			Mirabegron 50 mg, N=1,324 Placebo, N=1,328	
178-CL-044 (DRAGON)	–0.22	–1.06 to 0.62	–0.60	–1.29 to 0.08
178-CL-045	N/A	N/A	–0.29	–0.77 to 0.19
178-CL-048	–0.13	–0.49 to 0.23	–0.54	–0.90 to –0.18
Abbreviations used in table: CI, confidence interval; MD, mean difference; mg, milligram; N/A, not applicable; NR, not reported.				

4.19 Nocturia episodes per 24 hours was lower in mirabegron 50mg groups in the FAS population than in the placebo groups, although the results were statistically significant in only three of the six trials for mirabegron 50mg (SCORPIO, ARIES and DRAGON) (see table 8). In the manufacturer's pooled analysis of SCORPIO, ARIES and CAPRICORN, there was a statistically significant difference

between mirabegron 50mg and placebo (mean difference -0.14, 95% CI -0.23 to -0.05, p=0.003). There were no statistically significant differences between mirabegron 50mg and tolterodine 4mg in DRAGON or 178-CL-048.

Table 8. Change from baseline to final visit in mean number of nocturia episodes per 24 hours

Study	Mirabegron 50 mg vs tolterodine		Mirabegron 50 mg vs placebo	
	MD	95% CI	MD	95% CI
178-CL-046 (SCORPIO)	NR	NR	–0.15	–0.28 to –0.02
178-CL-047 (ARIES)	N/A	N/A	–0.18	–0.36 to –0.01
178-CL-074 (CAPRICORN)	N/A	N/A	–0.04	–0.20 to 0.12
Manufacturer's pooled analysis			–0.14	–0.23 to –0.05
			Mirabegron 50 mg, N=1,324 Placebo, N=1,328	
DRAGON	–0.01	–0.27 to 0.25	–0.22	–0.44 to –0.01
178-CL-045	N/A	N/A	–0.16	–0.33 to 0.00
178-CL-048	–0.02	–0.15 to 0.11	–0.12	–0.25 to 0.01
Abbreviations used in table: CI, confidence interval; MD, mean difference; mg, milligram; N/A, not applicable; NR, not reported.				

4.20 Mirabegron 25mg is half the recommended dose for the general population with OAB, and is recommended for some patients with renal or hepatic impairment. For the change in number of micturitions per 24 hours, the result from CAPRICORN was statistically significant for mirabegron 25mg versus placebo (mean difference -0.47, 95% CI -0.76 to -0.08, p=0.015). The change in number of micturitions per 24 hours was not statistically significantly different in DRAGON. The difference between mirabegron 25mg and placebo for the change in number of

incontinence episodes was statistically significant in CAPRICORN (mean difference -0.34, 95% CI -0.67 to -0.01, p=0.015) and DRAGON (mean difference -0.84, 95% CI -1.45 to -0.23, p value not given). For the secondary outcomes, the only outcomes that reached statistically significance in the mirabegron 25mg groups compared to placebo were: the mean number of urgency episodes (mean difference -0.70, 95% CI -1.38 to -0.01, p value not given) and mean number of urge incontinence episodes (mean difference -0.86, 95% CI -1.38 to -0.35, p value not given) in DRAGON, and for the mean number of urge incontinence episodes in CAPRICORN (mean difference -0.36, 95% CI -0.67 to -0.05, p=0.004).

Subgroup analyses

4.21 The manufacturer performed pooled subgroup analyses (from SCORPIO, ARIES and CAPRICORN) for male versus female, and treatment naive versus previously treated populations for the 2 primary outcomes. Mirabegron 50mg 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 (FAS-I) in the male mirabegron 50mg treatment group was -0.07 (95% CI -0.50, 0.36), which is not statistically significant. The change in the adjusted mean difference versus placebo for incontinence episodes per 24 hours FAS-I) in the female mirabegron 50mg treatment group was -0.47 (95%CI -0.67, -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, -0.01) in the male mirabegron 50mg treatment group, which was statistically significant. The

adjusted mean difference versus placebo in the mean number of micturitions per 24 hours female mirabegron 50mg treatment group was -0.62 (95%CI -0.85, -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 males and females.

4.22 In the pooled subgroup analyses comparing previously treated and treatment naïve groups, mirabegron 50mg 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 (FAS-I) in the previously treated mirabegron 50mg treatment group was -1.49 (95% CI -1.66, -1.32) and the adjusted mean difference versus placebo was -0.57 (95% CI -0.81, -0.33). The change in the mean number of incontinence episodes per 24 hours between baseline and final visit (FAS-I) in the treatment-naïve mirabegron 50mg treatment group was -1.50 (95% CI -1.71, -1.29) and the adjusted mean difference versus placebo was -0.15 (95%CI -0.44, 0.14). The change in the mean number of micturitions per 24 hours between baseline and final visit (FAS) in the previously treated mirabegron 50mg treatment group was -1.67 (95% CI -1.86, -1.48) and the adjusted mean difference versus placebo was -0.74 (95% CI -1.01, -0.47). The change in the mean number of micturitions per 24 hours between baseline and final visit (FAS) in the treatment-naïve mirabegron 50mg treatment group was -1.84 (95% CI -2.04, -1.64) and the adjusted mean difference versus placebo was -0.33 (95%CI -0.62, -0.05). Mirabegron 50mg 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-naïve 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 mean number of micturitions).

Safety outcomes

4.23 Data on adverse events presented in the manufacturer's submission was largely derived from the 52 week study TAURUS (mirabegron versus tolterodine). Additionally information was available from SCORPIO, ARIES and CAPRICORN trials. Treatment-emergent adverse events (TEAEs) were adverse events that occurred after treatment, while treatment-related AEs were directly linked to treatment. The incidence of treatment-related AEs was similar in the three groups, with 26.2% in the mirabegron 50mg group and 27.6% in the tolterodine group in TAURUS. In TAURUS, the overall incidence of TEAEs was similar across the mirabegron 50mg (59.7%) and tolterodine (62.6%) groups in TAURUS (SAS analysis). Most TEAEs were mild or moderate in all treatment groups. The overall incidence of treatment-emergent severe adverse events was 5.2% in the mirabegron 50mg group and 5.4% in the tolterodine group in TAURUS (SAS). For TEAEs leading to permanent discontinuation of the study drug, the rates were 5.9% in the mirabegron 50mg group and 5.7% in the tolterodine group in TAURUS (SAS). In SCORPIO, ARIES and CAPRICORN, the incidence of TEAEs were similar across all the treatment groups (SAS population) (see table 9).

Table 9. Overview of safety data from randomised controlled trials evaluating mirabegron with a treatment duration of 3 months

Study	Mirabegron 50 mg	Tolterodine ER 4 mg	Placebo
Adverse events			
178-CL-046 (SCORPIO)	211 (42.8)	231 (46.7)	214 (43.3)
178-CL-047 (ARIES)	228 (51.6)	N/A	227 (50.1)
178-CL-074 (CAPRICORN)	208 (47.3)	N/A	217 (50.1)
178-CL-044 (DRAGON)	74 (43.8)	41 (48.2)	73 (43.2)
178-CL-045	171 (82.2)	N/A	157 (74.1)
178-CL-048	281 (74.1)	305 (81.3)	292 (77.0)
Treatment-related adverse event			
178-CL-046 (SCORPIO)	100 (20.3)	131 (26.5)	89 (18.0)
178-CL-047 (ARIES)	80 (18.1)	N/A	66 (14.6)
178-CL-074 (CAPRICORN)	76 (17.3)	N/A	77 (17.8)
178-CL-044 (DRAGON)	38 (22.5)	13 (15.3)	26 (15.4)
178-CL-045	51 (24.5)	N/A	40 (18.9)
178-CL-048	93 (24.5)	131 (34.9)	91 (24.0)
SAE			
178-CL-046 (SCORPIO)	14 (2.8)	11 (2.2)	8 (1.6)
178-CL-047 (ARIES)	11 (2.5)	N/A	9 (2.0)
178-CL-074 (CAPRICORN)	4 (0.9)	N/A	12 (2.8)
178-CL-044 (DRAGON)	1 (0.6)	1 (1.2)	1 (0.6)
178-CL-045	1 (0.5)	N/A	4 (1.9)
178-CL-048	3 (0.8)	4 (1.1)	4 (1.1)
Discontinuations due to adverse event			
178-CL-046 (SCORPIO)	24 (4.9)	22 (4.4)	13 (2.6)
178-CL-047 (ARIES)	18 (4.1)	N/A	17 (3.8)
178-CL-074 (CAPRICORN)	11 (2.5)	N/A	16 (3.7)
178-CL-044 (DRAGON)	4 (2.4)	1 (1.2)	5 (3.0)
178-CL-045	7 (3.4)	N/A	4 (1.9)
178-CL-048	12 (3.2)	12 (3.2)	8 (2.1)
Abbreviations used in table: ER, extended release; mg, milligram; N/A, not applicable; SAE, serious adverse event.			

4.24 The adverse events that were designated a priori of interest due to their association with antimuscarinics were dry mouth and

constipation. Table 10 details the rates of constipation and dry mouth by treatment group for TAURUS and SCORPIO; the rates were not given for ARIES and CAPRICORN.

Table 10. Rates of key adverse events in TAURUS and SCORPIO trials

	TAURUS		SCORPIO		
Adverse event	**Mirabegron**	**Tolterodine ER 4 mg**	**Mirabegron**	**Placebo**	**Tolterodine**
Dry mouth	2.8%	8.6%	1.8%	1.8%	9.5%
Constipation	2.8%	2.7%	NR	NR	NR

Mixed treatment comparison

4.25 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 (5 and 10mg), fesoterodine (4 and 8mg), trospium, tolterodine, solifenacin (5 and 10mg) and placebo. This was done through a network analysis, using direct comparisons where available, or indirect comparison via placebo where available, or through another comparator if necessary. Oxybutynin and tolterodine have both extended release (ER) and intermittent release (IR) 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.

4.26 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 (DIC), with the model with the lowest DIC selected. Mean changes and associated standard errors were used for continuous variables. Where the mean change was not available, it was calculated as the difference between the mean at baseline and at 12 weeks. Where the standard error was not available, it was derived from standard deviation of change, variance or confidence intervals around the mean. For dichotomous safety data, the data were extracted from the studies, or calculated from the observed proportion and total number of patients in the study where specific adverse event data were not available.

4.27 The results of the manufacturer's MTC for all outcomes are detailed in table 11. For the outcome of number of micturitions per 24 hours indicated that the effect of mirabegron 50mg did not differ significantly from other treatments, except for solifenacin 10mg which was more effective than mirabegron) and tolterodine 4mg, which was less effective than mirabegron. For the outcome of number of incontinence episodes per 24 hours, the results indicate that there was no significant difference for any of the comparators for this outcome. The effect of mirabegron 50mg was numerically greater than for tolterodine 4mg, oxybutynin 10mg, fesoterodine 4 and 8mg. Mirabegron was numerically not as effective as solifenacin 5 and 10mg. For the outcome of number of urge incontinence episodes per 24 hours, the effect of mirabegron 50mg did not differ significantly from antimuscarinics, except for solifenacin 10mg which was more effective than mirabegron.

Table 11. Results of the mixed treatment comparison for all outcomes

Outcome	Mean difference vs mirabegron 50 mg (odds ratio)	95% Credible Interval
Micturition episodes per 24 hours		
Tolterodine 4 mg	0.157	-0.0002; 0.3154
Fesoterodine 4 mg	0.137	-0.1613; 0.4345
Fesoterodine 8 mg	-0.048	-0.2489; 0.1524
Oxybutynin 10 mg	0.139	-0.5290; 0.8058
Placebo	0.696	0.5544; 0.8378
Solifenacin 10 mg	-0.583	-0.8324; -0.3326
Solifenacin 5 mg	-0.240	-0.4921; 0.0132
Trospium 60mg	-0.124	-0.5767; 0.3261
Incontinence episodes per 24 hours		
Tolterodine 4 mg	0.082	-0.0649; 0.2286
Fesoterodine 4 mg	0.107	-0.3911; 0.6033
Fesoterodine 8 mg	0.226	-0.2770; 0.7299
Oxybutynin 10 mg	0.137	-0.3986; 0.6752
Placebo	0.497	0.3724; 0.6225
Solifenacin 10 mg	-0.240	-0.4875; 0.0066
Solifenacin 5 mg	-0.237	-0.4824; 0.0073
Urge incontinence episodes per 24 hours		
Tolterodine 4 mg	0.095	-0.1226; 0.3071
Fesoterodine 4 mg	-0.034	-0.3841; 0.3033
Fesoterodine 8 mg	-0.225	-0.5348; 0.0475
Oxybutynin 10 mg	-0.279	-0.9464; 0.3847
Placebo	0.437	0.2553; 0.6244
Solifenacin 10 mg	-0.420	-0.7860; -0.05629
Solifenacin 5 mg	-0.288	-0.6416; 0.0711
Trospium 60mg	-0.112	-0.7071; 0.4853
Dry mouth (change from baseline)		
Tolterodine ER 4 mg	4.168	2.733; 6.117
Fesoterodine 4mg	4.436	2.693; 6.974
Fesoterodine 8mg	9.7	6.109; 14.686
Oxybutynin ER 10 mg	6.795	3.894; 11.25
Oxybutynin ER 15 mg	7.864	2.912; 17.48
Oxybutynin ER 5 mg	4.13	1.559; 9.024
Oxybutynin IR 10 mg	14.069	6.565; 26.4
Oxybutynin IR 15 mg	39.208	14.98; 85.64

Outcome	Mean difference vs mirabegron 50 mg (odds ratio)	95% Credible Interval
Oxybutynin IR 9 mg	10.778	5.592; 18.92
Placebo	1.303	0.859; 1.916
Solifenacin 10 mg	10.078	6.027; 15.97
Solifenacin 5 mg	4.229	2.484; 6.825
Tolterodine IR 4 mg	7.042	4.311; 11.03
Trospium 40 mg	5.672	2.955; 9.981
Trospium 60 mg	4.481	1.598; 10.46
Constipation (change from baseline)		
Tolterodine ER 4 mg	1.109	0.716; 1.647
Fesoterodine 4mg	1.066	0.576; 1.808
Fesoterodine 8mg	1.926	1.142; 3.059
Oxybutynin ER 10 mg	1.021	0.527; 1.793
Oxybutynin ER 15 mg	2.158	0.27; 8.276
Oxybutynin ER 5 mg	2.459	0.421; 8.71
Oxybutynin IR 15 mg	1.614	0.416; 4.375
Oxybutynin IR 9 mg	0.989	0.412; 1.992
Placebo	0.732	0.483; 1.066
Solifenacin 10 mg	4.369	2.54; 7.071
Solifenacin 5 mg	2.501	1.41; 4.127
Tolterodine IR 4 mg	1.034	0.594; 1.673
Trospium 40 mg	1.692	0.883; 2.979
Trospium 60 mg	7.604	2.08; 22.59
Blurred vision (change from baseline)		
Tolterodine ER 4 mg	1.44	0.559; 3.128
Fesoterodine 4mg	0.8	0.041; 3.705
Fesoterodine 8mg	0.727	0.038; 3.402
Oxybutynin ER 10 mg	2.612	0.206; 12.12
Oxybutynin ER 15 mg	7.071	0.021; 41.747
Oxybutynin ER 5 mg	5.117	0.05; 28.873
Oxybutynin IR 15 mg	2.454	0.071; 13.72
Oxybutynin IR 9 mg	0.403	0; 2.577
Placebo	5.271	0.902; 18.47
Solifenacin 10 mg	0.792	0.305; 1.714
Solifenacin 5 mg	1.936	0.669; 4.499
Tolterodine IR 4 mg	1.147	0.382; 2.71
Trospium 40 mg	0.752	0.237; 1.83
Trospium 60 mg	2.437	0.147; 11.93

4.28 For the adverse effects of dry mouth, constipation and blurred vision, mirabegron had probabilities similar to placebo. All anti-muscarinics had a significantly higher risk of dry mouth compared with mirabegron 50mg. The odds ratios for constipation for antimuscarinics compared to mirabegron 50mg were not statistically significantly different, except for solifenacin 5 and10mg, fesoterodine 8mg and trospium 60mg. These were associated with higher risks of constipation compared with mirabegron 50mg. No differences in risk between mirabegron 50mg 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

4.29 HRQoL 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 m-ITT set and no data from individual trials were presented in the manufacturer's submission. Adjusting for baseline confounders (manufacturer's submission did not provide details of which confounders), mirabegron 50mg had greater change from baseline to 12 week utility scores than tolterodine 4mg 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 were not statistically significantly different between mirabegron 50mg and placebo (placebo utility change 0.038, $p=0.30$ for difference).

4.30 Treatment satisfaction was assessed using the treatment satisfaction visual analogue scale (TS VAS). In SCORPIO, ARIES and CAPRICORN, mirabegron 50mg and tolterodine 4mg

demonstrated statistically significant differences in the change from baseline to final visit compared with placebo, in favour of the active treatments. In TAURUS, treatments (mirabegron or tolterodine) were numerically effective at improving health related quality of life (no figures given for statistical significance between baseline and final visit).

4.31 SCORPIO, ARIES and CAPRICORN 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 (see table 12), which reached statistical significance in SCORPIO and ARIES. The mirabegrongroup, the placebo group, and the tolterodine group achieved a clinically meaningful improvement of 10 points above baseline.

Table 12. OAB-q HRQoL total score for SCORPIO, ARIES, and CAPRICORN

Study	Mirabegron 50 mg vs tolterodine ER 4 mg		Mirabegron 50 mg vs placebo	
	MD	95% CI	MD	95% CI
178-CL-046 (SCORPIO)	NR	NR	2.3	0.2 to 4.5[a]
178-CL-047 (ARIES)	N/A	N/A	4.1	1.6 to 6.6[b]
178-CL-074 (CAPRICORN)	N/A	N/A	1.2	–1.0 to 3.4[c]

[a] Adjusted mean CFB to final visit in OAB-q: 16.1 in the mirabegron 50 mg group versus 13.7 in the placebo group.

[b] Adjusted mean CFB to final visit in OAB-q: 14.8 in the mirabegron 50 mg group versus 10.7 in the placebo group.

[c] Adjusted mean CFB to final visit in OAB-q: 14.3 in the mirabegron 50 mg group versus 13.0 in the placebo group.

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Abbreviations used in table: CI, confidence interval; ER, extended release; HRQoL, health-related quality of life; MD, mean difference; mg, milligram; NA, not applicable; NR, not reported; OAB-q, overactive bladder questionnaire.

ERG critique of clinical effectiveness evidence

4.32 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 within 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.

4.33 The ERG questioned the omission of the data from DRAGON, 178-CL-045, 178-CL-048, as well as TAURUS, from the primary analyses. The ERG also noted that no direct comparison between mirabegron and tolterodine was drawn, even though SCORPIO, DRAGON, TAURUS and 178-CL-048 used tolterodine as an active control. The ERG acknowledged that these trials were not powered to evaluate the superiority or non-inferiority of mirabegron versus tolterodine, but that exclusion of data from the tolterodine 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 their 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.

4.34 The ERG considered the use of the FAS 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 ITT population was not reported across all trials for comparators. The ERG considered the multiplicity adjustment 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.

4.35 For the comparison of mirabegron with tolterodine, the ERG performed an additional meta-analysis on the data from the 3 RCTs that had an active control of tolterodine (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. This meta-analysis of the 3 trials showed that treatment with mirabegron 50mg led to significantly fewer micturitions per 24 hours compared with treatment with tolterodine 4mg (mean difference -0.27, 95% CI -0.48 to -0.06, p=0.01). Conversely data from TAURUS favoured tolterodine 4mg, 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 50mg was statistically significantly more effective than with tolterodine 4mg (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). The results from the meta-analysis and TAURUS were not entirely concordant.

4.36 For the comparison with all other comparators, the ERG also 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 one 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 heterogeneity given by the manufacturer.

4.37 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 homogenous dataset. The ERG excluded trials that included patients other than those with OAB, that were carried out in a single gender population, or 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 four yeses in the first four categories assessed). The ERG only included 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.

4.38 Table 13 presents the ERGs results for the outcome of micturition episodes per 24 hours. The ERG found no significant difference between mirabegron 50mg and any of the other active treatment assessed. The only significant difference found was by the manufacturer for solifenacin 10mg, which was found to significantly

reduce the number of episodes compared with mirabegron (mean difference -0.583, 95% CrI -–0.832 to –0.333).

Table 13. Results of the manufacturer's MTC for micturition compared with the ERG's revised MTC using mirabegron 50 mg as the baseline treatment

Micturition	Manufacturer's MTC		ERG's MTC	
	MD	95% CrI	MD	95% CrI
Fesoterodine 4 mg	0.137	–0.161 to 0.435	0.381	–0.398 to 1.154
Fesoterodine 8 mg	–0.048	–0.249 to 0.152	0.138	–0.636 to 0.913
Oxybutynin 10 mg	0.139	–0.529 to 0.806	–0.536	–1.849 to 0.782
Placebo	0.696	0.554 to 0.838	0.700	0.254 to 1.141
Solifenacin 5 mg	–0.240	–0.492 to 0.013	–0.193	–1.066 to 0.672
Solifenacin 10 mg	–0.583	–0.832 to –0.333	–0.560	–1.346 to 0.225
Tolterodine 4 mg	0.157	–0.0002 to 0.315	0.087	–0.421 to 0.591
Trospium 60 mg	–0.124	–0.577 to 0.326	–0.121	–1.351 to 1.091
Abbreviations used in table: CrI, credible interval; ERG, Evidence Review Group; MD, mean difference; mg, milligram; MTC, mixed treatment comparison.				

4.39 For the outcome of incontinence episodes per 24 hours, the results of the ERG's analyses concurred with the manufacturer's MTC results, with the exception that mirabegron 50mg was significantly less effective in reducing the frequency of incontinence episodes than solifenacin 5 and 10mg (see table 14). The manufacturer's analyses also indicated that solifenacin was numerically more effective than mirabegron, but this result was not statistically significant.

Table 14. Results of the manufacturer's MTC for incontinence compared with the ERG's MTC using mirabegron 50 mg as the baseline treatment

Comparator	Manufacturer's MTC		ERG's MTC	
	MD	95% CrI	MD	95% CrI
Fesoterodine 4 mg	0.107	–0.391 to 0.603	0.108	–0.383 to 0.597
Fesoterodine 8 mg	0.226	–0.277 to 0.730	0.231	–0.277 to 0.731
Oxybutynin 10 mg	0.137	–0.399 to 0.675	–0.476	–1.011 to 0.054
Placebo	0.497	0.372 to 0.623	0.499	0.370 to 0.627
Solifenacin 5 mg	–0.237	–0.482 to 0.007	–0.386	–0.717 to –0.055
Solifenacin 10 mg	–0.240	–0.488 to 0.007	–0.380	–0.694 to –0.067
Tolterodine 4 mg	0.082	–0.065 to 0.2296	0.066	–0.089 to 0.221
Abbreviations used in table: CrI, credible interval; ERG, Evidence Review Group; MD, mean difference; mg, milligram; MTC, mixed treatment comparison; OR, odds ratio.				

4.40 The ERG also analysed AEs in their revised MTC analysis. The ERG found that mirabegron was found to be statistically significantly less likely to be associated with constipation than fesoterodine 8mg (OR 2.12, 95% CI 1.13 to 3.64), solifenacin 5mg (OR 2.11, 95% CI 1.16 to 3.59) and 10mg (OR 4.52, 95% CI 2.60 to 7.47), and trospium 60mg (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 muscarinics assessed. Only oxybutynin IR 15mg had a statistically significantly higher rate of discontinuation than mirabegron.

5 Comments from other consultees

5.1 A professional group stated that the only class of medication currently available for OAB was anticholinergics, which have significant side effects. They noted that the trial populations for mirabegron may have had milder symptoms than those in trials for anticholinergics, which may have led to lower efficacy results. The

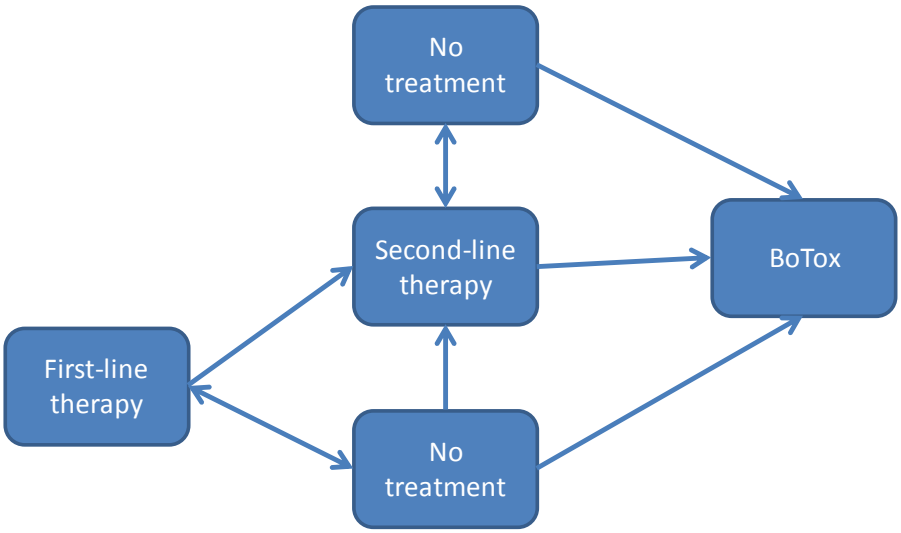
professional group pointed out that the adverse event profile for mirabegron is different to that for anticholinergics, with incidence of dry mouth, constipation and heartburn at the same level as in the placebo group. The group noted that it has been licensed and marketed in Japan for a year. Long term efficacy and safety studies have been conducted in Japan and Europe, although these are unpublished. The professional group noted the possibility of combining mirabegron with anticholinergics, although stressed there is no data for this practice. The professional groups said the lack of published data precluded specialist recommendations. The professional group felt that mirabegron would be prescribed in primary and secondary care, and education would need to be provided from specialists to general practitioners, once evidence was made available. There were no comments from patient groups or NHS organisations.

6 Cost-effectiveness evidence

6.1 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 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 QALYs over 5 years. The population modelled was the general OAB population (i.e. the licensed population) and the model had a 5 year time horizon with a 1 month cycle length and no half cycle correction.

6.2 Figure 1 presents a schematic representation of the clinical pathway in the manufacturer's model. People in the model 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 the cost, efficacy and safety equivalent to solifenacin 5mg. Once patients have failed on 2 drugs or failed on one drug and had a cycle off any drug, botulinum toxin is available as a treatment option.

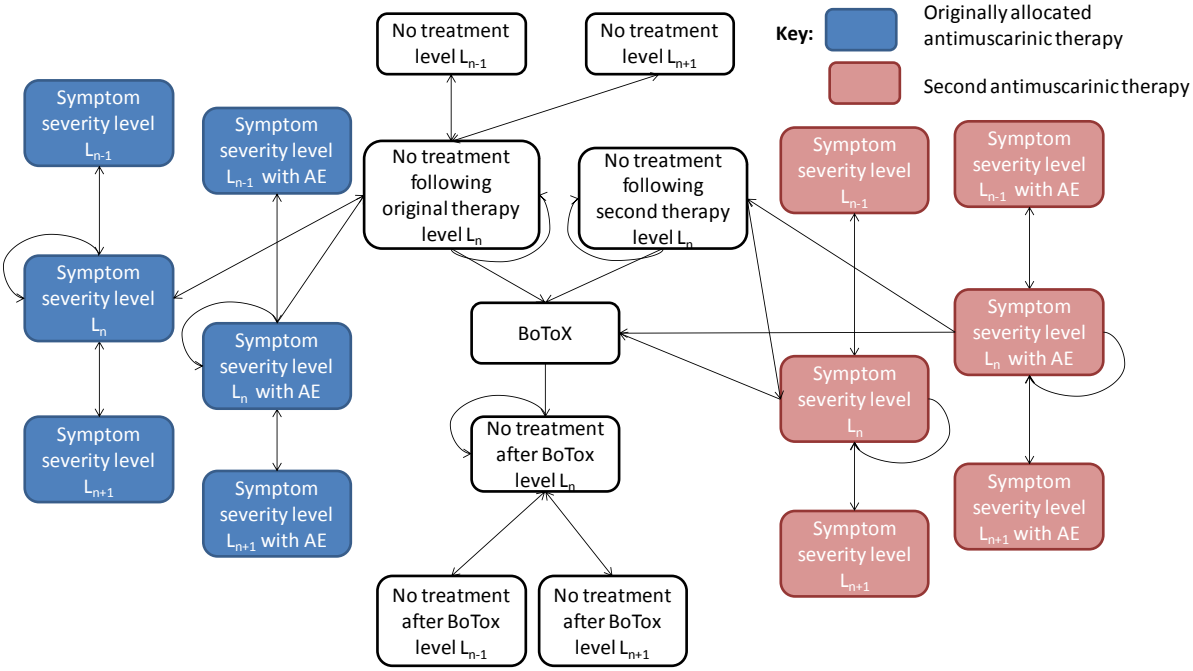
Figure 1. Model structure of treatment pathway in manufacturers model



6.3 The manufacturer's model simultaneously simulates 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 time step, individual'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 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 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 (see figure 2). To develop transition matrices for antimuscarinics not studied in the mirabegron clinical study programme a calibration approach was adopted to determine the beta coefficients for use in a logistic regression.

Figure 2. Schematic representation of the manufacturer's model structure



6.4 The only AEs incorporated into the model were dry mouth and constipation, the manufacturer stated that expert opinion suggested that these 2 were the most bothersome to patients and likely. Monthly probabilities of AEs were obtained from SCORPIO for mirabegron and tolterodine 4mg and from the MTC for the other antimuscarinics. It was assumed that people who were on no treatment experienced no AEs.

6.5 Discontinuation of treatment was incorporated into the model as a combination of background persistence with OAB medication and the occurrence of adverse events (AE). The background persistence rate for the base case was taken from a published study (Wagg 2012) and a sensitivity analyses performed on the estimate. The discontinuation rate used in the model was 78%, and was based on that observed with tolterodine. The manufacturer estimated that 54.7% of patients without an AE would discontinue treatment by 12 months. Discontinuation due to AE was based on expert opinion and set at 90%. The manufacturer did not identify any literature on treatment reinitiation rates after treatment discontinuation. The manufacturer assumed that 50% of patients would restart treatment annually (5.6% per month), who had stopped treatment with mirabegron or tolterodine (in the base case model) without immediately switching to another drug. Of these, one third would go back to their previous drug, one third would receive next line A, and one third would receive next line B.

6.6 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 one 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 which botulinum toxin failed pre- botulinum toxin symptom severity levels were assumed.

6.7 Utility values assigned to the different symptom severities used in the base case were derived from EQ-5D index scores, based on HRQoL data, which were collected in SCORPIO. A linear

regression model was estimated, with adjustment on age, gender and country (as random effect). The regression model was based on all treatment arms of SCORPIO (see table 15). Patients experiencing an AE had a standardised 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.

Table 15. EQ-5D utility values by disease severity profile

Incontinence frequency level	**Micturitions frequency level**				
	1	**2**	**3**	**4**	**5**
1	0.85	0.83	0.81	0.80	0.79
2	0.83	0.81	0.79	0.78	0.77
3	0.82	0.80	0.78	0.77	0.76
4	0.80	0.78	0.76	0.75	0.74
5	0.79	0.77	0.75	0.74	0.73

6.8 Costs included in the model are detailed in tables 16 and 17. It was assumed that GP consultations would be 1 visit at the start and then at every treatment switch and specialist consultations would occur at every switch and on average 1.5 at the start of treatment. Incontinence pads 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 AEs except specialist referral in case of a switch in treatment.

Table 16. Intervention costs used in the manufacturer's model

OAB medication	Cost per pack (£)	No. of tablets per pack	Cost per day (£)	Cost per month[a] (£)	Source
Antimuscarinics					
Mirabegron 50 mg	29.00	30	0.97	29.40	Astellas
Tolterodine ER 4 mg	25.78	28	0.92	28.01	BNF63
Solifenacin 5mg	27.62	30	0.92	28.00	
Solifenacin 10 mg	35.91	30	1.20	36.41	
Trospium chloride MR 60 mg	23.05	28	0.82	25.04	
Fesoterodine 4 or 8 mg	25.78	28	0.92	28.01	
Oxybutynin ER 10 mg	27.54	30	0.92	27.92	
Oxybutynin IR 10 mg (cost of 5mg)	11.60	84	0.14	8.40	
Injection	**Cost of injection (£)**	**Visits per year[b]**	**Visits per month**	**Cost per month (£)**	**Source**
Botulinum toxin injection					
Initial	1,158	–		1,158	Nottingham Urology Group
Reinjections	964	2	0.17	163.88	

[a] Considering (365/12) days per month.

[b] Based on clinical expert opinion.

Abbreviations used in table: BNF, British National Formulary; ER, extended-release; IR, immediate-release; mg, milligram; MR, modified-release.

Table 17. Model inputs: unit costs of health care resources

Parameter	Base case value	Sources
GP consultation	£36	PSSRU 2011
Specialist visit: Follow-up visit	£96	NHS Payment 2010-2011
Botulinum toxin injection: Initial / Reinjections	£1158/£964	Nottingham Urology Group
Incontinence pad (per pad)	£0.16	AgeUK incontinence

Abbreviations: GP, general practitioner.

6.9 The manufacturer performed deterministic and probabilistic sensitivity analyses on assumptions and parameter estimates in the

model. Additional the manufacturer performed subgroup analyses of the base case for males and females and treatment naïve and previous treatment groups.

6.10 The base case result comparing mirabegron with tolterodine 4mg based on SCORPIO trial indicated mirabegron was cost effective at a £20,000 QALY threshold with an ICER of £4,386 per QALY gained. The manufacturer's probabilistic ICER was £4886.The results of the secondary analysis using the MTC are detailed in table 18 again suggesting that mirabegron is cost effective when compared to available antimuscarinics.

Table 1. Base case results, general OAB population, mirabegron versus antimuscarinics, based on MTC results

Treatment	Total			Incremental			ICER (£) versus mirabegron
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Solifenacin 10 mg	£1,647.60	4.666	3.762	£3.53	0	0.0104	£340
Fesoterodine 4 mg	£1,601.40	4.666	3.758	£38.09	0	0.0106	£3,607
Tolterodine 4 mg	£1,601.64	4.666	3.759	£37.85	0	0.0102	£3,715
Oxybutynin 10mg ER	£1,587.06	4.666	3.755	£42.12	0	0.0109	£3,878
Trospium chloride 60 mg MR	£1,551.86	4.666	3.759	£83.89	0	0.0094	£8,881
Solifenacin 5 mg	£1,592.94	4.666	3.768	£58.19	0	0.0047	£12,493
Oxybutynin 10 mg IR	£1,421.00	4.666	3.7516	£208.18	0	0.0146	£14,234

6.11 The manufacturer performed a fully incremental analysis assuming mirabegron persistence is equivalent to solifencin persistence (see table 19). The incremental analysis indicates that oxybutynin ER 10mg is weakly dominated by treatment with trospium chloride MR 60mg, fesoterodine 4mg is strictly dominated by treatment with

solifenacin 5mg; tolterodine ER 4mg and solifenacin 10mg are extendedly dominated by mirabegron 50mg, and mirabegron has an ICER of £12,493.21/QALY when compared to solifenacin 5mg.

Table 19. Base case results, general OAB population, mirabegron versus antimuscarinics, incremental analysis using persistence with solifenacine or tolterodine

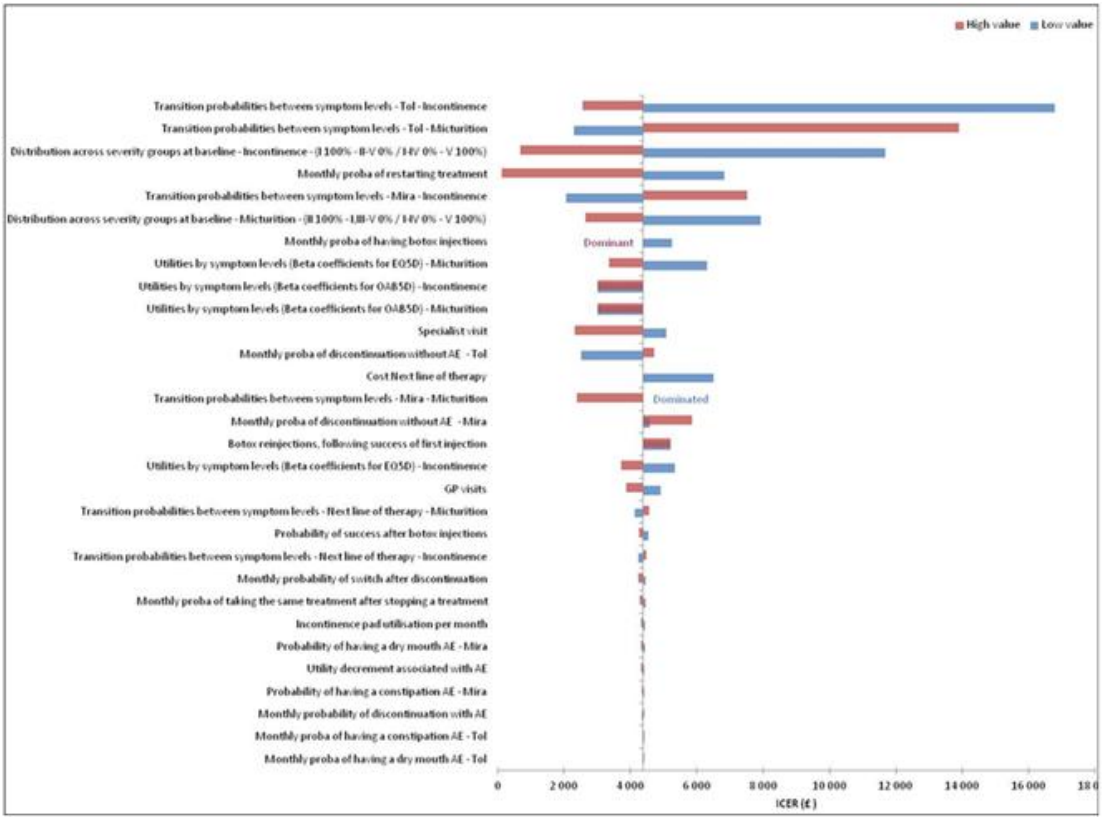
Intervention	Total cost	Total QALYs	Cost	QALYs	ICER (£/QALY) next best
Oxybutynin 10 mg IR	1421.00	3.7516	-	-	-
Trospium chloride 60 mg MR	1551.86	3.7586	Weakly dominated		
Oxybutinin 10mg ER	1587.06	3.7554	Dominated		
Solifenacin 5 mg	1592.94	3.7675	171.94	0.0159	10,813.84
Fesoterodine 4 mg	1601.40	3.7585	Dominated		
Tolterodine 4 mg	1601.64	3.7589	Dominated		
Solifenacin 10 mg	1647.60	3.7618	Dominated		
Mirabegron 50 mg	1651.14	3.7722	58.20	0.0047	12,382.98

Abbreviations: ER, extended-release; ICER, incremental cost-effectiveness ratio; IR, immediate-release; MR, modified-release; QALY, quality adjusted life year.

6.12 Results from the manufacturer's base case one 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. Assessment of structural uncertainty was explored by sensitivity analyses on the model time horizon, impact of OAB related co-morbidities (depression, fractures, UTIs and skin infections) and the use of disease specific HRQoL. The results of the sensitivity analyses in the primary and secondary base cases were similar. Figure 3 shows the effects of one way sensitivity analyses on the primary base case the parameters that the model results were most sensitive to were the transition probabilities between symptom levels for incontinence and micturition for tolterodine, 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.

Figure 3. Results of manufacturer's one-way sensitivity analysis on primary (mirabegron 50 mg versus tolterodine ER 4 mg) base case cost-effectiveness results (reproduced from MS; Figure 48; pg 237)



6.13 The manufacturer submitted primary base case ICERs (mirabegron vs tolterodine 4mg) for subgroups by treatment status and by sex. The primary base case ICERs were £3836 for the previously treated patient subgroup and £5315 for the treatment-naïve subgroup. The primary base case ICERs for the subgroups by sex were £38,708 for the male subgroup and £3091 for the female subgroup. The ICER fell to £2266 in the female subgroup but rose to £65,968 in the male subgroup if utilities derived from the OAB-q were used, rather than those from EQ-5D.

6.14 The ERG commented that they 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 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 one-way sensitivity analyses were thorough, and that the primary base case result was relatively robust and insensitive to individual parameter estimate changes.

6.15 The ERG identified several areas of inaccuracy or uncertainty; these included:

- ◊ Uncertainty resulting from heterogeneity associated with estimates from the manufacturers MTC
- ◊ the assumption of variable other cause discontinuation for mirabegron patients
- ◊ the assumption that immediate (i.e. within the same cycle) discontinuation as a result of an AE 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 AE rates from SCORPIO rather than the manufacturer's safety study TAURUS
- ◊ the cost associated with botulinum toxin injections
- ◊ the use of NHS pbR tariffs rather than reference costs to inform the cost of outpatient specialist visits
- ◊ the exclusion of correlation from the PSA

6.16 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 toward 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 AEs would bias the model either towards or against mirabegron. The ERG noted that a majority of parameters were based on clinical opinion that were estimated through open discussion, rather than generated through the use of elicitation techniques, which would lead to greater parameter uncertainty.

6.17 The ERG's clinical expert indicated that a 90% discontinuation rate with AEs would be likely to be too high, but acknowledged that the manufacturer included a sensitivity analysis that assumed a 50% AE-related discontinuation rate, which had a limited effect on the ICER (£4,585 compared with the base case ICER of £4,386). The ERG noted that there were issues with the disaggregated discontinuation rate (rates for AE-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), were derived from the published literature to exclude AE-related discontinuation. The ERG considered the application of the AE-

related discontinuation rate inappropriate to other-cause discontinuation rates.

6.18 The ERG agreed with the manufacturer that the use of regression analysis was appropriate so that the potentially confounding factors of age and gender could be taken account of, and could minimize 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 noted 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 utilities 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 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 HRQoL data.

6.19 The ERG commented that the subgroup analyses indicate 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 males 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.

6.20 The ERG considered 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 in AE rates was higher in SCORPIO than in TAURUS which was longer term. The primary base case ICER decreased by £72 (from £4386 to £4314) when using AE data from TAURUS rather than SCORPIO.

6.21 The ERG conducted a sensitivity analysis for the discontinuation rates, using the 28% persistence rate used by the manufacturer (based on the tolterodine rate from Wagg et al), resulting in a £3 decrease in the primary base case ICER. The ERG considered that the 28% persistence rate (equal to that of tolterodine) would be likely to be favourable to mirabegron.

6.22 The ERG's additional sensitivity analyses cumulatively increased the primary base case ICER from £4386 to £5272. However the impact on the secondary base case had greater effects. The impact on the secondary fully incremental analysis of the ERGs cumulative sensitivity analyses is shown in table 20, which included the assumptions that the persistence rate with mirabegron was 28%, the probability of reinitiating original therapy was set to 0, the use of AE rates from TAURUS, the use of NHS reference costs for botulinum toxin injections, and the use of NHS reference costs for outpatient specialist visits.

Table 20. Combined impact of ERG's sensitivity analyses on manufacturer's incremental secondary base case cost-effectiveness results

Treatment	Manufacturer's base case ICER (£/QALY)	Total		Incremental (versus previous therapy)		ICER (£/QALY) versus oxybutynin IR 10 mg	Incremental ICER (£/QALY)
		Cost (£)	QALY	Cost (£)	QALY		
Oxybutynin IR 10 mg	–	1,329.37	3.753	–	–	–	–
Trospium chloride MR 60 mg	18,816.13[a]	1,437.46	3.759	108.09	0.006	19,401.56	19,401.56[a]
Oxybutynin 10mg ER	Strictly dominated[d]	1,467.09	3.756	29.63	–0.003	45,763.53	Strictly dominated[b]
Solifenacin 5 mg	4,591.75[c]	1,477.88	3.766	10.80	0.010	11,483.59	£5,491.22[c]
Fesoterodine 4 mg	Strictly dominated[d]	1,484.00	3.759	6.12	–0.007	27,923.18	Strictly dominated[d]
Tolterodine ER 4 mg	Extendedly dominated[e]	1,484.65	3.759	0.65	0.000	26,571.76	Strictly dominated[d]
Solifenacin 10 mg	Extendedly dominated[e]	1,512.41	3.761	27.77	0.002	22,478.28	Strictly dominated[d]
Mirabegron 50 mg	12,493.21[f]	1,524.29	3.768	11.88	0.006	13,582.07	32,711.50[f]

a versus Oxybutynin IR 10 mg.
b by trospium chloride 60 mg MR.
c versus trospium chloride 60 mg MR.
d by solifenacin 5 mg.
e by mirabegron 50 mg.
f versus solifenacin 5 mg.
Abbreviations used in table: ER, extended release; ICER, incremental cost-effectiveness ratio; IR, immediate release; MR, modified release; QALY, quality adjusted life year.

6.23 Tolterodine ER 4mg and solifenacin 10mg were no longer extendedly dominated by mirabegron 50mg, but were instead strictly dominated by solifenacin 5mg. The ICER of mirabegron 50mg vs solifenacin 5mg changed from £12,493 to £32,712, an increase of £20,219. The impact of the sensitivity analyses on the

ICERs for mirabegron vs solifenacin ranged from £573 to mirabegron being dominated by solifenacin 10mg.

6.24 The ERG was unable to quantify the impact of using alternative assumptions or parameters for all the uncertainties they identified, including the difference between the manufacturer's MTC (with no statistically significant difference between mirabegron and solifenacin in reducing incontinence episodes) and the ERG's MTC (where solifenacin 5mg was statistically significantly more effective at reducing incontinence episodes than mirabegron). The ERG considered that their 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 for mirabegron vs solifenacin 5mg.

7 Equalities issues

7.1 It was discussed at the scoping stage that people with OAB whose symptoms have not been controlled need to provide their own incontinence pads. Socioeconomic inequalities mean this may represent a disproportionate cost for people on low incomes. The perspective of NICE during a technology appraisal indicates that these costs should not be included unless they are reimbursed by the NHS/PSS. Additionally, socioeconomic status is not a protected characteristic, but is a factor which the Committee may wish to consider during the course of the appraisal.

8 Innovation

8.1 The manufacturer states that mirabegron represents a step change in the treatment of OAB, as it has a different mechanism of action than the standard antimuscarinic treatments. It has a different safety profile, with different adverse effects.

9 Authors

Dr Grace Jennings

Technical Lead

Dr Kay Nolan

Technical Adviser

with input from the Lead Team (Mr Stephen Sharp, Dr Geraldine Bryant, Dr Ann Richardson).

Appendix A: Supporting evidence

Related NICE guidance

Published

- Lower urinary tract symptoms: The management of lower urinary tract symptoms in men. NICE clinical guideline 97 (2010). Available from www.nice.org.uk/guidance/CG97
- Urinary incontinence: Urinary incontinence: the management of urinary incontinence in women. NICE clinical guideline 40 (2006). Available from www.nice.org.uk/guidance/CG97
- Percutaneous posterior tibial nerve stimulation for overactive bladder syndrome. NICE interventional procedure guidance 362 (2010). Available from www.nice.org.uk/guidance/IPG362
- Sacral nerve stimulation for urge incontinence and urgency-frequency. NICE interventional procedure guidance 64 (2004). Available from www.nice.org.uk/guidance/IPG64