

IQWiG Reports – Commission No. A14-19

Mirabegron – Benefit assessment according to §35a Social Code Book V¹

Extract

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³ Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CI	confidence interval
EQ-5D	European Quality of Life-5 Dimensions
ER	extended release
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KHQ	King's Health Questionnaire
OAB	overactive bladder
OAB-q	Overactive Bladder symptom and health-related quality of life questionnaire
OR	odds ratio
PPBC	Patient Perception of Bladder Condition
PT	preferred term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug mirabegron. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as “the company”). The dossier was sent to IQWiG on 2 June 2014.

Research question

The aim of the present report is to assess the added benefit of mirabegron compared with the appropriate comparator therapy (ACT) in symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

The G-BA specified treatment with one of the following drugs as ACT for this therapeutic indication: darifenacin, fesoterodine, flavoxate, propiverine, solifenacin, tolterodine and trospium chloride.

Following the G-BA’s specification, the company chose tolterodine as the ACT. However, it limited its choice to extended-release formulations of tolterodine, although immediate-release formulations of tolterodine are also approved for the therapeutic indication. According to the G-BA’s specification at drug level, all formulations of tolterodine are to be considered. The company’s limitation had no consequence, however, because it did not change the study pool for direct comparative studies.

The dossier assessment was conducted in comparison with the ACT tolterodine.

The assessment was based on patient-relevant outcomes. Only direct comparative randomized controlled trials (RCTs) were included in the assessment.

Results

One long-term study (049) and 4 short-term studies (044, 046, 048 and 090) were included in the assessment. The company rated the 049 long-term study as having a high risk of bias and did not use it for the derivation of an added benefit. Deviating from the company’s approach, however, the 049 long-term study was rated as having a low risk of bias and was used for the assessment. As therapy of the OAB syndrome is a long-term treatment, the 049 study, which lasted 12 months, provided the key data for the present assessment. The results of the 4 short-term studies (044, 046, 048 and 090) after 12 weeks were used as additional information.

The 049 long-term study was a phase 3 study. In the relevant study arms, 815 patients were randomized to mirabegron, and 813 patients were randomized to tolterodine. The 4 short-term studies (044, 046, 048 and 090) also compared mirabegron with tolterodine.

The risk of bias was rated as low for all studies, but the risk of bias at outcome level was partially rated as high.

Mortality

All-cause mortality

Neither in the long-term study nor in the 4 short-term studies did the results differ statistically significantly between the treatment groups. An added benefit of mirabegron compared with tolterodine for overall survival is therefore not proven.

Morbidity – patient perception of symptoms

OAB symptoms (PPBC and OAB-q – Symptom Bother Score)

For both questionnaires, there was no statistically significant difference between the treatment groups in the 049 long-term study. The outcomes were not recorded in the 044, 048 and 090 short-term studies. In the 046 short-term study, there was no statistically significant difference between the treatment groups. Hence an added benefit of mirabegron in comparison with tolterodine is not proven for the outcome “OAB symptoms (Patient Perception of Bladder Condition [PPBC] and Overactive Bladder symptom and health-related quality of life questionnaire [OAB-q] – Symptom Bother Score)”.

OAB symptoms (KHQ – Symptom Severity Scale)

The outcome was not recorded in the 049 long-term study or in the 044, 046 and 048 short-term studies. In the 090 short-term study, there was no statistically significant difference between the treatment groups. Hence an added benefit of mirabegron in comparison with tolterodine is not proven for the outcome “OAB symptoms (King’s Health Questionnaire [KHQ] – Symptom Severity Scale)”.

Health status (EQ-5D VAS)

In the 049 long-term study, there was no statistically significant difference between the treatment arms for the outcome. The outcome was not recorded in the 044, 048 and 090 short-term studies. In the 046 short-term study, there was also no statistically significant difference between the treatment arms. Hence an added benefit of mirabegron in comparison with tolterodine is not proven for the outcome “European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS)”.

Morbidity – frequency of symptoms

Incontinence and urge incontinence

There were no evaluable data for the total populations of the studies for the outcomes “incontinence” and “urge incontinence” from the long-term study or from the short-term

studies. Hence an added benefit of mirabegron in comparison with tolterodine is not proven for the outcomes “incontinence” and “urge incontinence”.

Micturition frequency

There was no statistically significant difference between the treatment groups in the 049 long-term study. In the meta-analysis of the 044, 046, 048 and 090 short-term studies, there was a statistically significant effect in favour of mirabegron. However, the 95% confidence interval [CI] of Hedges' g was not fully below the irrelevance threshold of -0.2. Hence an advantage of mirabegron in comparison with tolterodine is not proven for the outcome “micturition frequency”.

Urgency

There was no statistically significant difference between the treatment groups for the outcome in the analysis of the change in the course of the study in the 049 long-term study or in the meta-analysis of the 044, 046, 048 and 090 short-term studies. In addition, responder analyses were available for the 044, 048 and 090 short-term studies, but not for the 049 long-term study and the 046 short-term study. The meta-analysis of the 044, 048 and 090 short-term studies showed no statistically significant difference between the treatment groups for the responder analyses. Hence an advantage of mirabegron in comparison with tolterodine is not proven for the outcome “urgency”.

Nocturia

The analysis of the change in the course of the study in the 049 long-term study showed no statistically significant difference between the treatment groups. In the meta-analysis of the 044, 046, 048 and 090 short-term studies, there was a statistically significant effect in favour of mirabegron. However, the 95% CI of Hedges' g was not fully below the irrelevance threshold of -0.2. In addition, responder analyses were available for the 044, 048 and 090 short-term studies, but not for the 049 long-term study and the 046 short-term study. The meta-analysis of the 044, 048 and 090 short-term studies showed no statistically significant difference between the treatment groups for the responder analyses. Hence an advantage of mirabegron in comparison with tolterodine is not proven for the outcome “nocturia”.

Summary: morbidity

In summary, there was no advantage of mirabegron for the patient-reported outcomes, which reflect the burden of the patients from OAB symptoms as perceived by the patients, or for the outcomes that represent only the frequency of the symptoms. Hence no added benefit of mirabegron can be derived in the overall assessment of morbidity outcomes. Moreover, there were no data on the outcomes “incontinence” and “urge incontinence” for the total population. Hence relevant data for the assessment of the added benefit of mirabegron versus the ACT are missing.

Health-related quality of life***Overactive Bladder Questionnaire***

There was no statistically significant difference between the treatment groups in the 049 long-term study. The OAB-q was not recorded in the 044, 048 and 090 short-term studies. In the 046 short-term study, there was no statistically significant difference between the treatment groups. Hence an added benefit of mirabegron in comparison with tolterodine is not proven for the outcome “OAB-q”.

King’s Health Questionnaire

The outcome “KHQ” was not recorded in the 049 long-term study and in the 044 and 046 short-term studies. There was no statistically significant difference between the treatment groups in the meta-analysis of the 048 and 090 short-term studies. Hence an added benefit of mirabegron in comparison with tolterodine is not proven for the outcome “KHQ”.

Adverse events***Serious adverse events and discontinuation due to adverse events***

There was no statistically significant difference between the treatment groups for the outcomes “serious adverse events (SAEs)” and “discontinuation due to adverse events (AEs)” in the 049 long-term study or in the meta-analysis of the 044, 046, 048 and 090 short-term studies. Hence greater/lesser harm from mirabegron compared with tolterodine for the outcomes “SAEs” and “treatment discontinuation due to AEs” is not proven.

Dry mouth

There was a statistically significant difference in favour of mirabegron in the 049 long-term study. In the meta-analysis of the 044, 046, 048 und 090 short-term studies, there was considerable heterogeneity between the studies ($p < 0.2$) so that no common estimate was calculated. However, there was an effect modification by the characteristic “age” in the short-term studies. The meta-analysis of the subgroups in the short-term studies showed a statistically significant effect in favour of mirabegron both in the age group of patients under the age of 65 years and in the group of patients over the age of 65 years. In summary, there is proof of lesser harm from mirabegron for the outcome “dry mouth”.

Discontinuation due to dry mouth

There was no statistically significant difference between the treatment groups for the outcome in the 049 long-term study. In the meta-analysis of the 044, 046, 048 and 090 short-term studies, there was no statistically significant difference between the treatment groups. Hence greater/lesser harm from mirabegron for the outcome “discontinuation due to dry mouth” is not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

On the basis of the results presented, the extent and probability of the added benefit of the drug mirabegron compared with the ACT is assessed as follows:

Overall, a positive effect remains in the category “non-serious/non-severe AEs” with the probability “proof” and the extent “considerable”. However, as analyses for the total population are missing for the patient-relevant outcomes “incontinence” and “urge incontinence”, no conclusive balancing of the added benefit can be conducted for the total population.

In summary, an added benefit of mirabegron versus the ACT tolterodine is not proven for patients with OAB symptoms.

Table 2 presents a summary of the extent and probability of the added benefit of mirabegron.

Table 2: Mirabegron – extent and probability of added benefit

Therapeutic indication	ACT ^a	Extent and probability of added benefit
Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder syndrome	Darifenacin, fesoterodine, flavoxate, propiverine, solifenacin, tolterodine and trospium chloride	Added benefit not proven
<p>a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. In the present case, the company limited the ACT to extended-release formulations of tolterodine. This limitation was not followed.</p> <p>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee</p>		

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

⁴ On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

2.2 Research question

The aim of the present report is to assess the added benefit of mirabegron compared with the ACT in symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with OAB syndrome.

The G-BA specified treatment with one of the following drugs as ACT for this therapeutic indication: darifenacin, fesoterodine, flavoxate, propiverine, solifenacin, tolterodine and trospium chloride.

Following the G-BA's specification, the company chose tolterodine as the ACT. However, it limited its choice to extended-release formulations of tolterodine, although immediate-release formulations of tolterodine are also approved for the therapeutic indication. According to the G-BA's specification at drug level, all formulations of tolterodine are to be considered. The company's limitation had no consequence, however, because it did not change the study pool for direct comparative studies.

The dossier assessment was conducted in comparison with the ACT tolterodine.

The assessment was based on patient-relevant outcomes. Only direct comparative RCTs were included in the assessment.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on mirabegron (studies completed up to 3 March 2014)
- bibliographical literature search on mirabegron (last search on 2 March 2014)
- search in trial registries for studies on mirabegron (last search on 3 March 2014)

To check the completeness of the study pool:

- search in trial registries for studies on mirabegron (last search on 16 June 2014)

No additional relevant study was identified from the check.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

The studies listed in the following Table 3 were included in the benefit assessment.

Table 3: Study pool – RCT, direct comparison: mirabegron vs. tolterodine

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study ^a (yes/no)	Third-party study (yes/no)
178-CL-049 (TAURUS)	Yes	Yes	No
178-CL-044 (DRAGON)	Yes	Yes	No
178-CL-046 (SCORPIO)	Yes	Yes	No
178-CL-048	Yes	Yes	No
178-CL-090	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

The study pool concurred with the one of the company. It included the studies 178-CL-049 (TAURUS), 178-CL-044 (DRAGON), 178-CL-046 (SCORPIO), 178-CL-048 and 178-CL-090. Hereinafter, the studies are referred to as “049”, “044”, “046”, “048” and “090”. In all 5 studies, mirabegron was directly compared with the G-BA’s ACT (tolterodine).

Section 2.6 contains a reference list for the studies included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Study characteristics

Table 4 and Table 5 describe the studies used for the benefit assessment.

Table 4: Characteristics of the studies included – RCT, direct comparison: mirabegron vs. tolterodine

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
049	RCT, double-blind, double-dummy, parallel, active-controlled	Adult patients with overactive bladder symptoms (≥ 3 months)	1) MIR 50 mg (N = 815) 2) MIR 100 mg (N = 824) 3) TOL 4 mg (N = 813) relevant study arms thereof: 1) MIR 50 mg (N = 815) 2) TOL 4 mg (N = 813)	Placebo run-in: 2 weeks double-blind treatment: 12 months	306 centres worldwide: 181 in Europe, 97 in the United States, 18 in Canada, 6 in South Africa, 4 in Australia/New Zealand 4/2008 – 5/2010	<i>Primary:</i> safety and tolerability of long-term treatment with mirabegron <i>Secondary:</i> patient perception of symptoms, incontinence, urge incontinence, micturition frequency, urgency, nocturia, health-related quality of life, mortality, adverse events
044	RCT, double-blind, double-dummy, parallel, placebo-controlled, active-controlled	Adult patients with overactive bladder symptoms (≥ 3 months)	1) MIR 25 mg (N = 169) 2) MIR 50 mg (N = 169) 3) MIR 100 mg (N = 169) 4) MIR 200 mg (N = 167) 5) TOL 4 mg (N = 85) 6) placebo (N = 169) relevant study arms thereof: 1) MIR 50 mg (N = 169) 2) TOL 4 mg (N = 85)	Placebo run-in: 2 weeks double-blind treatment: 12 weeks	Europe: 97 centres in 14 countries 4/2006 – 3/2007	<i>Primary:</i> micturition frequency <i>Secondary:</i> patient perception of symptoms, incontinence, urge incontinence, urgency, nocturia, mortality, adverse events

(continued)

Table 4: Characteristics of the studies included – RCT, direct comparison: mirabegron vs. tolterodine (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
046	RCT, double-blind, double-dummy, parallel, placebo-controlled, active-controlled	Adult patients with overactive bladder symptoms (≥ 3 months)	1) MIR 50 mg (N = 497) 2) MIR 100 mg (N = 498) 3) TOL 4 mg (N = 495) 4) placebo (N = 497) relevant study arms thereof: 1) MIR 50 mg (N = 497) 2) TOL 4 mg (N = 495)	Placebo run-in: 2 weeks double-blind treatment: 12 weeks follow-up: 30 days	Europe and Australia: 189 centres in 27 countries 4/2008 – 3/2009	<i>Primary:</i> micturition frequency <i>Secondary:</i> patient perception of symptoms, incontinence, urge incontinence, urgency, nocturia, health-related quality of life, mortality, adverse events
048	RCT, double-blind, double-dummy, parallel, placebo-controlled, active-controlled	Adult patients with overactive bladder symptoms (≥ 6 months)	1) MIR 50 mg (N = 380) 2) TOL 4 mg (N = 378) 3) placebo (N = 381) relevant study arms thereof: 1) MIR 50 mg (N = 380) 2) TOL 4 mg (N = 378)	Placebo run-in: 2 weeks double-blind treatment: 12 weeks follow-up: 2 weeks	Japan: 93 centres 7/2009 – 2/2010	<i>Primary:</i> micturition frequency <i>Secondary:</i> patient perception of symptoms, incontinence, urge incontinence, urgency, nocturia, health-related quality of life, mortality, adverse events
090	RCT, double-blind, double-dummy, parallel, placebo-controlled, active-controlled	Adult patients with overactive bladder symptoms (≥ 3 months)	1) MIR 50 mg (N = 372) 2) TOL 4 mg (N = 377) 3) placebo (N = 377) relevant study arms thereof: 1) MIR 50 mg (N = 372) 2) TOL 4 mg (N = 377)	Placebo run-in: 2 weeks double-blind treatment: 12 weeks follow-up: 2 weeks	Asia: 67 centres in China, India, Korea and Taiwan 12/2009 – 9/2011	<i>Primary:</i> micturition frequency <i>Secondary:</i> patient perception of symptoms, incontinence, urge incontinence, urgency, nocturia, health-related quality of life, mortality, adverse events
a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment. MIR: mirabegron; N: number of randomized patients; n: relevant subpopulation; RCT: randomized controlled trial; TOL: tolterodine; vs.: versus						

Table 5: Characteristics of the interventions – RCT, direct comparison: mirabegron vs. tolterodine

Study	Intervention ^a	Comparison	Concomitant medication
049	Mirabegron 50 mg once daily + placebo to tolterodine once daily	Tolterodine ER 4 mg once daily + placebo to mirabegron once daily	▪ Non-permitted medication: anticholinergics/antispasmodics, CYP2D6 substrates with narrow therapeutic indices, strong CYP3A4 inhibitors
044	Mirabegron 50 mg once daily + placebo to tolterodine once daily	Tolterodine ER 4 mg once daily + placebo to mirabegron once daily	▪ Non-permitted medication, particularly: anticholinergics/antispasmodics, Parkinson drugs, tricyclic antidepressants, CYP3A4 inducing drugs, CYP2D6 and CYP3A4 substrates with narrow therapeutic indices and CYP3A4 and CYP2D6 inhibitors, peripheral alpha adrenoceptor agonists, drugs causing sinus tachycardia, alpha antagonists, (oral) beta adrenoceptor agonists
046	Mirabegron 50 mg once daily + placebo to tolterodine once daily	Tolterodine ER 4 mg once daily + placebo to mirabegron once daily	▪ Non-permitted medication, particularly: anticholinergics/antispasmodics, CYP2D6 substrates with narrow therapeutic indices, strong CYP3A4 inhibitors
048	Mirabegron 50 mg once daily + placebo to tolterodine once daily	Tolterodine ER 4 mg once daily + placebo to mirabegron once daily	▪ Non-permitted medication, particularly: anticholinergics and beta-2 receptor antagonists, antidepressants, antihistamines, Parkinson drugs, parasympatholytic drugs and parasympathetic blockers, 3A4 inducers, CYP2D6 and substrates with narrow therapeutic indices and CYP3A4 inhibitors
090	Mirabegron 50 mg once daily + placebo to tolterodine once daily	Tolterodine ER 4 mg once daily + placebo to mirabegron once daily	▪ Non-permitted medication, particularly: anticholinergics/antispasmodics, beta-2 adrenoceptor agonists, other OAB treatments, loop diuretics, cytochrome P450 (CYP) 3A4-inducers, CYP2D6 substrates with narrow therapeutic indices, strong CYP3A4 inhibitors
a: Depending on the number of study arms, patients received up to 3 placebo tablets. The presentation of the intervention and of the comparison in the present table is limited to the study arms relevant for the assessment. ER: extended release; OAB: overactive bladder; RCT: randomized controlled trial; vs.: versus			

The company's study pool consisted of one long-term study (049) and 4 short-term studies (044, 046, 048 and 090). The long-term study (049) was primarily used for the benefit assessment.

The 049 long-term study was a multicentre study conducted in Europe, North America, South Africa and Australia. The study duration was 12 months. Adult patients with OAB symptoms were enrolled in the study. More than 80% of these patients had already participated in one of the previous studies on mirabegron conducted by the company. This was either the 046 study or the 178-CL-047 study. Because of this, the company rated the 049 long-term study as having a high risk of bias, only reported its results separately, and also did not use the study

for the derivation of an added benefit. However, deviating from the company's approach, the 049 study was used (for reasons, see Section 2.7.2.4.1 of the full dossier assessment) and provided the key data for the present assessment because of its 12-month duration.

The 049 long-term study was a blinded, randomized, active-controlled phase 3 study. Mirabegron was administered in the 2 study arms at a dose of 50 mg or 100 mg daily. Only the patients from the study arm with approval-compliant treatment with 50 mg mirabegron (N = 815) daily were included in the present assessment. The patients in the comparator arm (N = 813) received tolterodine extended release (ER) 4 mg once daily.

The 044, 046, 048 and 090 short-term studies were blinded, randomized, active-controlled and placebo-controlled studies. The 044 study was a phase-2b study, whereas the 046, 048 and 090 studies were phase-3 studies. All studies included patients with OAB symptoms. The study duration of all the studies was 12 weeks. Mirabegron 50 mg daily versus tolterodine 4 mg was investigated in all the studies. In addition, each of the studies had study arms, in which placebo or mirabegron dosages that did not comply with the approval were administered. Only study arms in which mirabegron was administered at the approval-compliant dose of 50 mg daily were included in the present assessment (study 044 [N = 169], study 046 [N = 497], study 048 [N = 380], study 090 [N = 372]) and the study arms in which tolterodine was administered at 4 mg daily (study 044 [N = 85], study 046 [N = 495], study 048 [N = 378], study 090 [N = 377]). The 044 study was only conducted in Europe, and the 046 study in Europe and Australia. In contrast, the 048 study was conducted in Japan, and the 090 study in various countries in Asia.

Table 6 and Table 7 show the characteristics of the patients in the studies included.

Table 6: Characteristics of the study populations – (demography) – RCT, direct comparison: mirabegron vs. tolterodine

<i>Time point</i> study group	N	Age [years] mean (SD)	Age groups [years] (%)	Sex [F/M] %	Ethnicity [white/Asian/ others/missing] (%)	Treatment dis- continuations n (%)
<i>52 weeks</i>						
049			[< 75/≥ 75]			
mirabegron	815	59 (13)	91/9	74/26	95.7/1.0/3.3/-	186 (22.8)
tolterodine	813	60 (12)	90/10	74/26	96.2/0.6/3.2/-	192 (23.6)
<i>12 weeks</i>						
044			[>75]			
mirabegron	169	57 (13)	5	89/11	97.0/0/1.8/1.2	16 (9.5)
tolterodine	85	57 (13)	6	81/19	95.3/2.4/1.2/1.2	3 (3.5)
046			[< 75/≥ 75]			
mirabegron	497	59 (12)	91/9	72/28	98.9/0.4/0.6/-	57 (11.5)
tolterodine	495	59 (13)	93/7	73/27	99.4/0.2/0.4/-	50 (10.1)
048			[≥ 70]			
mirabegron	380	58 (14)	25	84/16	ND	31 (8.2)
tolterodine	378	58 (14)	23	83/17	only conducted in Japan	23 (6.1)
090			[≥ 70]			
mirabegron	372	54 (15)	14	68/32	0/100/0/-	61 (16.4)
tolterodine	377	54 (14)	14	65/35	0/100/0/-	67 (17.8)
F: female; M: male; N: number of randomized patients; n: number of patients with event; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus						

Table 7: Characteristics of the study populations (disease characteristics) – RCT, direct comparison: mirabegron vs. tolterodine

Time point study group	N	Type of incontinence [urge/mixed^a/no incontinence] (%)	Symptom duration [months] (median [min, max])	Medical pretreatment of OAB^b [yes/no] (%)
<i>52 weeks</i>				
049				
mirabegron	815	36/29/35	56.4 [3, 653]	55/45
tolterodine	813	39/26/35	55.7 [3, 642]	55/45
<i>12 weeks</i>				
044				
mirabegron	169	40/28/32	31.0 [6, 343]	46/54
tolterodine	85	45/28/27	43.0 [3, 230]	41/59
046				
mirabegron	497	41/23/37	49.9 [3, 637]	51/49
tolterodine	495	39/22/39	47.2 [3, 711]	49/51
048				
mirabegron	380	62/29/8	49.0 [6, 486]	ND
tolterodine	378	64/26/11	54.0 [6, 608]	ND
090				
mirabegron	372	36/20/44	38.0 [3, 610]	52/48 ^c
tolterodine	377	40/17/43	37.0 [3, 493]	51/49 ^c
a: Patients with urge and stress incontinence. b: 044: ≤ 1 year before the start of the study; 046 and 049: without limitation of time; 090: ≤ 4 weeks before the start of the study; 049: actual proportion with OAB medication might be underestimated because drugs that were only administered within the framework of a previous study participation were not considered in this analysis. c: There was contradictory information on the results in Module 4 from the additional analyses versus the clinical study report. max: maximum; min: minimum; N: number of randomized patients; ND: no data; OAB: overactive bladder; RCT: randomized controlled trial; vs.: versus				

In the 049 long-term study, there were no important differences between the treatment arms regarding age, sex, ethnicity and with respect to disease characteristics. The proportion of women was considerably larger in the study.

In the 044, 046, 048 and 090 short-term studies, there were no important differences between the treatment arms regarding age, sex, ethnicity and with respect to disease characteristics within the studies. The proportion of women was considerably larger in all studies. In the 048 study, nearly one quarter of the patients were older than 70 years. There were relevant differences between the studies with regard to ethnicity: In the 044 and 046 studies, the vast majority of participants were white. No information on ethnicity was provided for the 048 study. However, it was assumed that, as in the 090 study, mainly Asians were enrolled in the

study because it was conducted in Japan. The number of treatment discontinuations in the 044 study was higher in the mirabegron arm (9.5%) than in the tolterodine arm (3.5%). In the 048 study, the proportion of patients without incontinence at baseline was, with 8% in the mirabegron arm and 11% in the tolterodine arm, far lower than in the other studies. This is hard to comprehend because, also for this study, the proportion of patients who were included in the incontinence analyses was below 70% (see Section 2.4.3 and Section 2.7.2.4.3 of the full dossier assessment). Moreover, for the 048 study, there was no information on the number of patients who had already received medical pretreatment of OAB.

Table 8 shows the risk of bias at study level.

Table 8: Risk of bias at study level – RCT, direct comparison: mirabegron vs. tolterodine

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
049	Yes	Yes	Yes	Yes	Yes	Yes	Low
044	Yes	Yes	Yes	Yes	Yes	Yes	Low
046	Yes	Yes	Yes	Yes	Yes	Yes	Low
048	Yes	Yes	Yes	Yes	Yes	Yes	Low
090	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for all studies. This contradicts the company's assessment, which rated the risk of bias for the 049 study as high (see Section 2.7.2.4.2 of the full dossier assessment for reasons for the deviating assessment).

Further information on study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and in Appendix 4-F of the dossier, and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
 - all-cause mortality
- Morbidity
 - OAB symptoms (PPBC)
 - OAB symptoms (OAB-q)
 - OAB symptoms (KHQ)
 - health status (EQ-5D VAS)
 - incontinence
 - urge incontinence
 - micturition frequency
 - urgency
 - nocturia
- Health-related quality of life
 - health-related quality of life (OAB-q)
 - health-related quality of life (KHQ)
- Adverse events
 - SAEs
 - treatment discontinuation due to AEs
 - dry mouth [preferred term (PT)]
 - Discontinuation due to dry mouth (PT)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.7.2.4.3 of the full dossier assessment).

Further information on the choice of outcomes can be found in Module 4, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Section 2.7.2.4.3 of the full dossier assessment.

Table 9 shows for which outcomes data were available in the studies included.

Table 9: Matrix of outcomes – RCT, direct comparison: mirabegron vs. tolterodine

Study	Outcomes																		
	All-cause mortality	OAB symptoms (PPBC)	OAB symptoms (OAB-q ^a)	OAB symptoms (KHQ ^b)	Health status (EQ-5D VAS)	Incontinence	Incontinence (responders)	Urge incontinence	Micturition frequency	Urgency	Urgency (responders)	Nocturia	Nocturia (responders)	Health-related quality of life (OAB-q ^c)	Health-related quality of life (KHQ ^d)	SAEs	Discontinuation due to AEs	AE “dry mouth”	Discontinuation due to AE “dry mouth”
049	Y	Y	Y	– ^e	Y	N ^f	N ^f	N ^f	Y	Y	– ^e	Y	– ^e	Y	– ^e	Y	Y	Y	Y
044	Y	– ^e	– ^e	– ^e	– ^e	Y ^g	N ^f	Y ^g	Y	Y	Y	Y	Y	– ^e	– ^e	Y	Y	Y	Y
046	Y	Y	Y	– ^e	Y	N ^f	N ^f	N ^f	Y	Y	– ^e	Y	– ^e	Y	– ^e	Y	Y	Y	Y
048	Y	– ^e	– ^e	– ^e	– ^e	N ^f	N ^f	N ^f	Y	Y	Y	Y	Y	– ^e	Y	Y	Y	Y	Y
090	Y	– ^e	– ^e	Y	– ^e	N ^f	N ^f	N ^f	Y	Y	Y	Y	Y	– ^e	Y	Y	Y	Y	Y
<p>a: OAB-q symptom scale (Symptom Bother Score). b: KHQ symptom scale (Symptom Severity Scale). c: OAB-q quality of life scale. d: KHQ quality of life scale. e: Outcome not recorded in the study. f: No evaluable data (for reasons, see Section 2.7.2.4.3 of the full dossier assessment). g: For the 044 study, data of the total population would be available in Module 5. Because relevant amounts of data are missing – no evaluable data for the total population in the long-term study as well as in the remaining short-term studies – the data of the study were not used for this outcome, however. AE: adverse event; EQ-5D: European Quality of Life-5 Dimensions; KHQ: King’s Health Questionnaire; N: no; OAB: overactive bladder; OAB-q: Overactive Bladder symptom and health-related quality of life questionnaire; PPBC: Patient Perception of Bladder Condition; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus; Y: yes</p>																			

2.4.2 Risk of bias

Table 10 shows the risk of bias for these outcomes.

Table 10: Risk of bias at study and outcome level – RCT, direct comparison: mirabegron vs. tolterodine

Study	Study level	Outcomes																		
		All-cause mortality	OAB symptoms (PPBC)	OAB symptoms (OAB-q ^a)	OAB symptoms (KHQ ^b)	Health status (EQ-5D VAS)	Incontinence	Incontinence (responders)	Urge incontinence	Micturition frequency	Urgency	Urgency (responders)	Nocturia	Nocturia (responders)	Health-related quality of life (OAB-q ^c)	Health-related quality of life (KHQ ^d)	SAEs	Discontinuation due to AEs	AE “dry mouth”	Discontinuation due to AE “dry mouth”
049	L	L	H ^{e,f}	H ^e	— ^g	H ^e	— ^h	— ^h	— ^h	H ^e	H ^e	— ^g	H ^{e,f}	— ^g	H ^e	— ^g	L	L	L	L
044	L	L	— ^g	— ^g	— ^g	— ^g	— ⁱ	— ^h	— ⁱ	H ^e	H ^e	H ^e	H ^{e,f}	H ^f	— ^g	— ^g	L	L	L	L
046	L	L	H ^{e,f}	H ^e	— ^g	H ^e	— ^h	— ^h	— ^h	H ^e	H ^e	— ^g	H ^{e,f}	— ^g	H ^e	— ^g	L	L	L	L
048	L	L	— ^g	— ^g	— ^g	— ^g	— ^h	— ^h	— ^h	H ^e	H ^e	H ^e	H ^{e,f}	H ^f	— ^g	N ^j	L	L	L	L
090	L	L	— ^g	— ^g	H ^f	— ^g	— ^h	— ^h	— ^h	H ^e	H ^e	H ^e	H ^{e,f}	H ^f	— ^g	H ^{f,k}	L	L	L	L
<p>a: OAB-q symptom scale. b: KHQ symptom scale. c: OAB-q quality of life scale. d: KHQ quality of life scale. e: No information on the proportion of missing values in the LOCF analysis. f: Proportion of patients not included in the analysis > 10%. g: Outcome not recorded in the study. h: No evaluable data (for reasons, see Section 2.7.2.4.3 of the full dossier assessment). i: For the 044 study, data of the total population would be available in Module 5. Because relevant amounts of data are missing – no data for the total population in the long-term study as well as in the remaining short-term studies – the data of the study were not used for this outcome, however. j: Proportion of patients not included in the analysis > 10% for domain “personal relationships”. k: Proportion of patients not included in the analysis > 30% for domain “personal relationships”. AE: adverse event; EQ-5D: European Quality of Life-5 Dimensions; H: high; KHQ: King’s Health Questionnaire; L: low; LOCF: last observation carried forward; OAB: overactive bladder; OAB-q: Overactive Bladder symptom and health-related quality of life questionnaire; PPBC: Patient Perception of Bladder Condition; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus</p>																				

The assessment of the risk of bias at outcome level deviates from that of the company.

Deviating from the company, the risk of bias for the following outcomes was rated as high: OAB symptoms (PPBC, OAB-q, EQ-5D) and health-related quality of life (OAB-q) in the 046 study, and OAB symptoms (KHQ) and health-related quality of life (KHQ) in the 090 study. Deviating from the company, the risk of bias for the outcomes “micturition frequency”, “urgency” and “nocturia ” in the 044, 046, 048 and 090 short-term studies was rated as high.

For the 049 study, the company rated the risk of bias for all outcomes on side effects as high because it rated the risk of bias of the study itself as high. The risk of bias for the outcomes on side effects and mortality were rated as low in the present dossier assessment just as the risk of bias for the study itself was rated as low. Detailed reasons for the assessment of the risk of bias can be found in Section 2.7.2.4.2 of the full dossier assessment.

Further information on the risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3, and in Appendix 4-F of the dossier and in Section 2.7.2.4.2 of the full dossier assessment.

2.4.3 Results

Table 11, Table 12, Table 13 and Table 14 summarize the results on the comparison of mirabegron and tolterodine in patients with OAB.

Where necessary, the data from the company’s dossier were supplemented by the Institute’s calculations. The Peto odds ratio (OR) offers a good approximation of the relative risk in some situations. Bradburn et al. [3] recommend the Peto OR method because of its simulation results for rare events ($\leq 1\%$), small or moderate effect estimates, and when sample size is similar in both groups in the majority of the studies. In these situations, the Peto OR was therefore used as estimate for the relative risk. When this kind of situations forms the majority in a meta-analysis, the meta-analysis is also performed using the Peto OR method.

If neither scale-specific irrelevance thresholds nor responder analyses are available for certain outcomes, a general statistical measure for evaluating relevance is drawn upon in the form of standardized mean differences (SMD expressed as Hedges’ g). An irrelevance threshold of -0.2 is then used: If the CI corresponding to the effect estimate lies completely below this irrelevance threshold, it is assumed that the effect size does not lie within a range that is certainly irrelevant. This is to ensure that the effect can be regarded at least as “small” with sufficient certainty [1].

Data on incontinence only for subpopulation

For the outcomes “incontinence” and “urge incontinence”, the company presented analyses in Module 4 in which only those patients were included who already had an event (incontinence, urge incontinence) at the start of the study. These are only between 38% and 69% of the total populations of the studies. Hence it described the results on incontinence and urge incontinence only for a subpopulation of the studies and also only for a subpopulation of the

patients who can be treated with mirabegron according to the approval. It is possible that, in the course of the study, these symptoms also occur in patients who had no incontinence or urge incontinence at the start of the study. However, the company presented no data for the subpopulation of patients without incontinence or urge incontinence at the start of the study. For this reason, no conclusion can be drawn for the total population from the data available in Module 4 of the dossier on the outcomes “incontinence” and “urge incontinence”.

With the exception of the 044 study, Module 5 also only contained analyses for the subpopulations with incontinence events at the start of the study. Because relevant amounts of data were missing – no data for the total population in the long-term study as well as in the remaining short-term studies – the data of the total population of the 044 study were not used for the outcome “incontinence”.

In principle, there would be the possibility to consider the subpopulations of patients with incontinence events at the start of the study separately from the ones without such events and to derive a separate assessment for these subpopulations. For an interpretation of the analyses of these subpopulations, analyses for both subpopulations on all outcomes of interest would be needed, which were incomplete (see Section 2.7.2.4.3 of the full dossier assessment).

Data of long-term study primarily relevant

The data of the 049 long-term study after 12 months and, as additional information, of the 4 short-term studies (044, 046, 048 and 090) after 12 weeks were primarily used in the benefit assessment. The figures of the meta-analyses of the short-term studies can be found in Appendix A of the full dossier assessment.

As the 049 long-term study had a low risk of bias, the derivation of indications is principally possible. If the results of the long-term study are supported by the ones of the short-term studies, the derivation of proof is also possible. This assessment concurs with that of the company, which also derived proof, but only on the basis of the short-term studies. Any possible weakening of the results by outcome-specific aspects will be noted separately for individual outcomes in the following presentation of the results.

Table 11: Results on mortality – RCT, direct comparison: mirabegron vs. tolterodine

Outcome time point study	Mirabegron		Tolterodine		Mirabegron vs. tolterodine
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value
All-cause mortality					
52 weeks					
049	812	3 (0.4)	812	2 (0.2)	1.49 [0.26; 8.64] ^a ; > 0.999 ^b
12 weeks					
044	169	0 (0)	85	0 (0)	NC
046	493	0 (0)	495	1 (0.2)	0.33 [0.01; 8.20] ^c ; 0.349 ^d
048	379	0 (0)	378 ^e	0 (0)	NC
090	369 ^e	0 (0)	372 ^e	0 (0)	NC
a: Institute's calculation; Peto OR. b: Institute's calculation, Fisher exact test. c: Institute's calculation, RR with correction of 0.5 in each cell. d: Institute's calculation, unconditional exact test (CSZ method according to [4]). e: There was contradictory information in Module 4 from the additional analyses versus the clinical study report. CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; NC: not calculable; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; vs.: versus					

Mortality

All-cause mortality

Only few deaths occurred. There was no statistically significant difference between the treatment groups in the 049 long-term study. No deaths occurred in the 044, 048 and 090 short-term studies. In the 046 short-term study, there was no statistically significant difference between the treatment groups. An added benefit of mirabegron compared with tolterodine for overall survival is therefore not proven.

This concurs with the company's assessment.

Table 12 shows the results on morbidity.

Table 12: Results on morbidity – RCT, direct comparison: mirabegron vs. tolterodine

Outcome category		Mirabegron			Tolterodine			Mirabegron vs. tolterodine
outcome	N	Values at start of study	Change at end of study		N	Values at start of study	Change at end of study	Mean difference
time point		mean (SE)	mean ^{a, b} (SE)			mean (SE)	mean ^{a, b} (SE)	[95% CI]; p-value
study								
Morbidity								
OAB symptoms (PPBC) ^c								
52 weeks								
049	655	3.85 (0.04)	-0.76 (0.04)		673	3.80 (0.04)	-0.83 (0.04)	0.07 [-0.05; 0.19]; 0.25
12 weeks								
044					Outcome not recorded			
046	416	4.13 (0.05)	-0.98 (0.06)		426	4.32 (0.05)	-1.01 (0.06)	0.02 [-0.13; 0.18]; 0.79
048					Outcome not recorded			
090					Outcome not recorded			
OAB symptoms (OAB-q – Symptom Bother Score) ^d								
52 weeks								
049	779	44.59 (0.75)	-13.07 (0.66)		781	44.17 (0.74)	-14.37 (0.66)	1.30 [-0.52; 3.12]; 0.16
12 weeks								
044					Outcome not recorded			
046	465	49.56 (0.93)	-19.61 (0.86)		469	50.31 (0.93)	-18.47 (0.86)	-1.15 [-3.53; 1.24]; 0.35
048					Outcome not recorded			
090					Outcome not recorded			
OAB symptoms (KHQ – Symptom Severity Scale) ^d								
52 weeks								
049					Outcome not recorded			
12 weeks								
044					Outcome not recorded			
046					Outcome not recorded			
048					Outcome not recorded			
090	313	31.71 (0.85)	-9.66 (0.75) ^e		311	31.68 (0.83)	-9.72 (0.75) ^e	0.06 [-2.01; 2.13]; 0.95
Health status (EQ-5D VAS) ^f								
52 weeks								
049	776	68.89 (0.75)	6.44 (0.54)		777	70.60 (0.72)	6.33 (0.54)	0.12 [-1.38; 1.62]; 0.88
12 weeks								
044					Outcome not recorded			
046	466	65.11 (0.90)	6.87 (0.76)		467	63.51 (0.91)	6.10 (0.76)	0.77 [-1.33; 2.87]; 0.47
048					Outcome not recorded			
090					Outcome not recorded			

(continued)

Table 12: Results on morbidity – RCT, direct comparison: mirabegron vs. tolterodine (continued)

Outcome <i>time point</i>	Mirabegron			Tolterodine			Mirabegron vs. tolterodine	
	study	N	Values at start of study mean (SE)	Change at end of study mean ^{a, b} (SE)	N	Values at start of study mean (SE)	Change at end of study mean ^{a, b} (SE)	Mean difference [95% CI]; p-value
Incontinence	No evaluable data for the total population							
Urge incontinence	No evaluable data for the total population							
Micturition frequency (number of micturitions/24 h)								
<i>52 weeks</i>								
049	789	11.13 (0.10)	-1.26 (0.08)	791	10.94 (0.09)	-1.38 (0.08)	0.13 [-0.11; 0.36]; 0.29	
<i>12 weeks</i>								
044	167	11.85 (0.26)	-2.15 (0.19)	85	12.31 (0.40)	-2.05 (0.27)		
046	473	11.65 (0.14)	-1.94 (0.11)	475	11.55 (0.13)	-1.60 (0.11)		
048	369	11.15 (0.14)	-1.68 (0.11)	368	11.10 (0.13)	-1.43 (0.11)		
090	360	12.05 (0.22)	-2.05 (0.16)	361	12.09 (0.19)	-1.50 (0.16)		
Total							-0.32 [-0.51; -0.14]; < 0.001 ^g Hedges' g -0.14 [-0.21; -0.06] ^h	
Urgency (number of urgency episodes/24 h)								
<i>52 weeks</i>								
049	788	5.67 (0.13)	-1.62 (0.11)	788	5.45 (0.12)	-1.62 (0.11)	-0.00 [-0.30; 0.30]; 0.98	
<i>12 weeks</i>								
044	166	5.94 (0.30)	-1.75 (0.28)	85	5.38 (0.40)	-1.65 (0.39)		
046	470	5.72 (0.17)	-2.22 (0.15)	472	5.79 (0.16)	-2.04 (0.15)		
048	369	4.27 (0.15)	-1.85 (0.13)	368	4.13 (0.15)	-1.71 (0.13)		
090	359	5.16 (0.24)	-2.27 (0.20)	359	5.41 (0.23)	-2.27 (0.20)		
Total							-0.12 [-0.36; 0.11]; 0.310 ^g	

(continued)

Table 12: Results on morbidity – RCT, direct comparison: mirabegron vs. tolterodine (continued)

Outcome <i>time point</i> study	Mirabegron		Tolterodine		Mirabegron vs. tolterodine		
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value		
Urgency (responders ⁱ)							
52 weeks							
049			Outcome not recorded				
12 weeks							
044	166	24 (14.5)	85	13 (15.3)			
046			Outcome not recorded				
048	369	84 (22.8)	368	73 (19.8)			
090	337	104 (30.9)	333	103 (30.9)			
Total					1.05 [0.88; 1.24]; 0.599 ^g		
Outcome <i>time point</i> study	N	Values at start of study mean (SE)	Change at end of study mean ^{a, b} (SE)	N	Values at start of study mean (SE)	Change at end of study mean ^{a, b} (SE)	Mean difference [95% CI]; p-value
Nocturia (number of nocturia episodes/24 h) ^j							
52 weeks							
049	693	2.08 (0.05)	-0.45 (0.04)	693	2.02 (0.05)	-0.42 (0.04)	-0.03 [-0.14; 0.08]; 0.58
12 weeks							
044	142	1.70 (0.09)	-0.58 (0.07)	72	1.78 (0.12)	-0.54 (0.10)	
046	423	2.09 (0.06)	-0.56 (0.05)	433	2.14 (0.06)	-0.45 (0.05)	
048	323	1.72 (0.06)	-0.45 (0.05)	332	1.71 (0.06)	-0.43 (0.05)	
090	337	2.30 (0.08)	-0.57 (0.07)	335	2.41 (0.10)	-0.40 (0.07)	
Total							-0.08 [-0.16; -0.00]; 0.039 ^g
							Hedges' g -0.09 [-0.17; -0.01] ^h

(continued)

Table 12: Results on morbidity – RCT, direct comparison: mirabegron vs. tolterodine (continued)

Outcome time point study	Mirabegron		Tolterodine		Mirabegron vs. tolterodine
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value
Nocturia (responders ^j)					
52 weeks					
049			Outcome not recorded		
12 weeks					
044	142	34 (23.9)	72	13 (18.1)	
046			Outcome not recorded		
048	323	55 (17.0)	332	57 (17.2)	
090	318	32 (10.1)	309	33 (10.7)	
Total					1.03 [0.81; 1.32]; 0.807 ^g
a: Unless stated otherwise, LOCF analysis. b: Adjusted for baseline values. c: Negative changes in comparison with start of study indicate improvement on a scale of 0 to 6. d: Negative changes in comparison with start of study indicate improvement on a scale of 0 to 100. e: No LOCF analysis. f: Positive changes in comparison with start of study indicate improvement. g: Institute's calculation from meta-analysis. h: Calculated from meta-analysis. i: Response criterion: no event at the end of treatment (measured in the 3 days before the last study visit). j: Only analyses on patients who already presented with nocturia events at the start of the study were available for this outcome. As the proportion of these patients was over 80% in all studies, these analyses could be used for the benefit assessment. CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; h: hours; KHQ: King's Health Questionnaire; LOCF: last observation carried forward; N: number of analysed patients; n: number of patients with event, OAB: overactive bladder; OAB-q: Overactive Bladder symptom and health-related quality of life questionnaire; PPBC: Patient Perception of Bladder Condition; RCT: randomized controlled trial; RR: relative risk; SE: standard error; VAS: visual analogue scale; vs.: versus.					

Morbidity – patient perception of symptoms

OAB symptoms (PPBC)

In the 049 long-term study, there was no statistically significant difference between the treatment groups for the outcome “OAB symptoms (PPBC)”. The outcome was not recorded in the 044, 048 and 090 short-term studies. In the 046 short-term study, there was no statistically significant difference between the treatment groups. Hence an added benefit of mirabegron in comparison with tolterodine is not proven for the outcome “OAB symptoms (PPBC)”.

This concurs with the company's assessment. However, the company presented the outcome “OAB symptoms (PPBC)” as quality of life outcome.

OAB symptoms (OAB-q – Symptom Bother Score)

In the 049 long-term study, there was no statistically significant difference between the treatment groups for the outcome “OAB symptoms (OAB-q – Symptom Bother Score)”. The outcome was not recorded in the 044, 048 and 090 short-term studies. In the 046 short-term study, there was no statistically significant difference between the treatment groups. Hence an added benefit of mirabegron in comparison with tolterodine is not proven for the outcome “OAB symptoms (OAB-q – Symptom Bother Score)”.

This concurs with the company’s assessment. However, the company presented the outcome “OAB symptoms (OAB-q – Symptom Bother Score)” as quality of life outcome.

OAB symptoms (KHQ – Symptom Severity Scale)

The outcome “OAB symptoms (KHQ – Symptom Severity Scale)” was not recorded in the 049 long-term study or in the 044, 046 and 048 short-term studies. In the 090 short-term study, there was no statistically significant difference between the treatment groups. Hence an added benefit of mirabegron in comparison with tolterodine is not proven for the outcome “OAB symptoms (KHQ – Symptom Severity Scale)”.

This concurs with the company’s assessment. However, the company presented the outcome “OAB symptoms (KHQ – Symptom Severity Scale)” as quality of life outcome.

Health status (EQ-5D VAS)

In the 049 long-term study, there was no statistically significant difference between the treatment arms for the outcome “health status (EQ-5D VAS)”. The outcome was not recorded in the 044, 048 and 090 short-term studies. In the 046 short-term study, there was also no statistically significant difference between the treatment arms. Hence an added benefit of mirabegron in comparison with tolterodine is not proven for the outcome.

This concurs with the company’s assessment. However, the company presented the outcome as quality of life outcome.

Morbidity – frequency of symptoms***Incontinence***

There were no evaluable data for the total populations of the studies for the outcome “incontinence” from the long-term study or from the short-term studies. Hence an added benefit of mirabegron in comparison with tolterodine is not proven for the outcome “incontinence”.

This concurs with the company’s assessment.

In Appendix C of the full dossier assessment, the results for the subpopulation of patients with incontinence events at the start of the study are presented as additional information.

Urge incontinence

There were no evaluable data for the total populations of the studies for the outcome “urge incontinence” from the long-term study or from the short-term studies. Hence an added benefit of mirabegron in comparison with tolterodine is not proven for the outcome “urge incontinence”.

This concurs with the company’s assessment.

In Appendix C of the full dossier assessment, the results for the subpopulation of patients with incontinence events at the start of the study are presented as additional information.

Micturition frequency

In the 049 long-term study, there was no statistically significant difference between the treatment groups for the outcome “micturition frequency”. In the meta-analysis of the 044, 046, 048 and 090 short-term studies, there was a statistically significant effect in favour of mirabegron. However, the 95% CI of Hedges’ g was not fully below the irrelevance threshold of -0.2. Hence an advantage of mirabegron in comparison with tolterodine is not proven for the outcome “micturition frequency”.

This contradicts the company’s assessment, which derived proof of added benefit of mirabegron for this outcome.

Urgency

There was no statistically significant difference between the treatment groups for the outcome “urgency” in the analysis of the change in the course of the study in the 049 long-term study or in the meta-analysis of the 044, 046, 048 and 090 short-term studies. In addition, responder analyses for the outcome “urgency” were available for the 044, 048 and 090 short-term studies, but not for the 049 long-term study and the 046 short-term study. The meta-analysis of the 044, 048 and 090 short-term studies showed no statistically significant difference between the treatment groups for the responder analyses. Hence an advantage of mirabegron in comparison with tolterodine is not proven for the outcome “urgency”.

This concurs with the company’s assessment.

Nocturia

For the outcome “nocturia”, the analysis of the change in the course of the study in the 049 long-term study showed no statistically significant difference between the treatment groups. In the meta-analysis of the 044, 046, 048 and 090 short-term studies, there was a statistically significant effect in favour of mirabegron. However, the 95% CI of Hedges’ g was not fully below the irrelevance threshold of -0.2. In addition, responder analyses for the outcome “nocturia” were available for the 044, 048 and 090 short-term studies, but not for the 049 long-term study and the 046 short-term study. The meta-analysis of the 044, 048 and 090 short-term studies showed no statistically significant difference between the treatment groups

for the responder analyses. Hence an advantage of mirabegron in comparison with tolterodine is not proven for the outcome “nocturia”.

This contradicts the company’s assessment, which derived proof of added benefit of mirabegron for this outcome.

Summary

In summary, there was no advantage of mirabegron for the patient-reported outcomes, which reflect the burden of the patients from OAB symptoms or for the outcomes that represent only the frequency of the symptoms. Hence no added benefit of mirabegron can be derived in the overall assessment of morbidity outcomes. Moreover, there were no data on the outcomes “incontinence” and “urge incontinence” for the total population. Hence relevant data for the assessment of the added benefit of mirabegron versus the ACT are missing.

Table 13 shows the results on health-related quality of life.

Table 13: Results on health-related quality of life – RCT, direct comparison: mirabegron vs. tolterodine

Instrument outcome	Mirabegron				Tolterodine			Mirabegron vs. tolterodine
time point study	N	Values at start of study mean (SE)	Change at end of study mean ^{a, b} (SE)	N	Values at start of study mean (SE)	Change at end of study mean ^{a, b} (SE)	Mean difference [95% CI]; p-value	
Overactive Bladder symptom and health-related quality of life questionnaire (OAB-q) ^c								
OAB-q – total score								
52 weeks								
049	779	66.56 (0.77)	10.53 (0.59)	783	67.31 (0.76)	11.42 (0.58)	-0.90 [-2.52; 0.73]; 0.28	
12 weeks								
044				Outcome not recorded				
046	468	62.02 (0.96)	16.04 (0.77)	470	61.04 (0.97)	14.80 (0.77)	1.24 [-0.91; 3.38]; 0.26	
048				Outcome not recorded				
090				Outcome not recorded				
OAB-q – coping								
52 weeks								
049	780	60.84 (0.93)	12.01 (0.70)	783	61.10 (0.93)	13.33 (0.70)	-1.32 [-3.26; 0.62]; 0.18	
12 weeks								
044				Outcome not recorded				
046	468	54.21 (1.13)	18.46 (0.94)	470	53.05 (1.15)	17.83 (0.94)	0.63 [-1.97; 3.23]; 0.64	
048				Outcome not recorded				
090				Outcome not recorded				
OAB-q – concern								
52 weeks								
049	781	65.93 (0.89)	11.58 (0.67)	784	66.72 (0.86)	12.42 (0.67)	-0.84 [-2.68; 1.01]; 0.38	
12 weeks								
044				Outcome not recorded				
046	469	61.39 (1.12)	18.31 (0.87)	470	60.13 (1.17)	16.16 (0.87)	2.15 [-0.27; 4.57]; 0.08	
048				Outcome not recorded				
090				Outcome not recorded				
OAB-q – sleep								
52 weeks								
049	781	62.13 (0.89)	10.63 (0.67)	784	62.98 (0.90)	11.24 (0.67)	-0.61 [-2.48; 1.26]; 0.52	
12 weeks								
044				Outcome not recorded				
046	469	59.10 (1.16)	15.11 (0.88)	470	58.44 (1.18)	13.94 (0.88)	1.17 [-1.26; 3.60]; 0.35	
048				Outcome not recorded				
090				Outcome not recorded				

(continued)

Table 13: Results on health-related quality of life – RCT, direct comparison: mirabegron vs. tolterodine (continued)

Instrument outcome	Mirabegron			Tolterodine			Mirabegron vs. tolterodine
time point study	N	Values at start of study mean (SE)	Change at end of study mean ^{a, b} (SE)	N	Values at start of study mean (SE)	Change at end of study mean ^{a, b} (SE)	Mean difference [95% CI]; p-value
OAB-q – social							
52 weeks							
049	780	81.04 (0.76)	6.42 (0.50)	785	82.42 (0.74)	7.16 (0.50)	-0.74 [-2.12; 0.64]; 0.29
12 weeks							
044				Outcome not recorded			
046	469	78.43 (0.99)	10.00 (0.68)	470	77.72 (1.02)	8.78 (0.68)	1.22 [-0.68; 3.11]; 0.21
048				Outcome not recorded			
090				Outcome not recorded			
King’s Health Questionnaire (KHQ) ^d							
KHQ – general health							
52 weeks							
049				Outcome not recorded			
12 weeks							
044				Outcome not recorded			
046				Outcome not recorded			
048	365	31.92 (0.93)	-2.67 (0.91) ^e	365	33.90 (0.94)	-1.42 (0.91) ^e	
090	313	45.21 (1.11)	-5.71 (1.05) ^e	311	45.50 (1.28)	-4.29 (1.06) ^e	
Total							-1.32 [-3.23; 0.58]; 0.174 ^f
KHQ – incontinence impact							
52 weeks							
049				Outcome not recorded			
12 weeks							
044				Outcome not recorded			
046				Outcome not recorded			
048	365	47.67 (1.40)	-14.52 (1.22) ^e	365	49.41 (1.38)	-10.55 (1.22) ^e	-3.97 [-7.35; -0.60]; 0.021
							Hedges’ g
							-0.17 [-0.32; -0.03]
090	313	68.48 (1.62)	-11.74 (1.53) ^e	311	71.38 (1.51)	-15.50 (1.54) ^e	3.76 [-0.49; 8.01]; 0.08
Total				Heterogeneity: Q = 7.82; p = 0.005; I ² = 87.2% ^f			

(continued)

Table 13: Results on health-related quality of life – RCT, direct comparison: mirabegron vs. tolterodine (continued)

Instrument outcome	Mirabegron			Tolterodine			Mirabegron vs. tolterodine
time point study	N	Values at start of study mean (SE)	Change at end of study mean ^{a, b} (SE)	N	Values at start of study mean (SE)	Change at end of study mean ^{a, b} (SE)	Mean difference [95% CI]; p-value
KHQ – limitation of daily life							
52 weeks							
049				Outcome not recorded			
12 weeks							
044				Outcome not recorded			
046				Outcome not recorded			
048	365	34.66 (1.24)	-11.38 (1.07) ^e	365	35.21 (1.21)	-8.74 (1.07) ^e	
090	311	52.20 (1.76)	-12.65 (1.43) ^e	311	52.89 (1.66)	-12.78 (1.43) ^e	
Total							-1.58 [-4.22; 1.07]; 0.242 ^f
KHQ – physical limitation							
52 weeks							
049				Outcome not recorded			
12 weeks							
044				Outcome not recorded			
046				Outcome not recorded			
048	365	37.08 (1.39)	-10.86 (1.09) ^e	365	38.58 (1.42)	-7.92 (1.09) ^e	
090	311	54.02 (1.74)	-11.75 (1.41) ^e	311	52.95 (1.71)	-11.52 (1.41) ^e	
Total							-1.88 [-4.47; 0.71]; 0.154 ^f
KHQ – social limitation							
52 weeks							
049				Outcome not recorded			
12 weeks							
044				Outcome not recorded			
046				Outcome not recorded			
048	365	19.38 (1.17)	-6.20 (0.91) ^e	365	19.63 (1.10)	-5.93 (0.91) ^e	
090	312	36.50 (1.71)	-9.74 (1.28) ^e	310	36.11 (1.68)	-8.36 (1.29) ^e	
Total							-0.64 [-2.71; 1.42]; 0.542 ^f

(continued)

Instrument outcome		Mirabegron		Tolterodine			Mirabegron vs. tolterodine
<i>time point</i> study	N	Values at start of study mean (SE)	Change at end of study mean ^{a, b} (SE)	N	Values at start of study mean (SE)	Change at end of study mean ^{a, b} (SE)	Mean difference [95% CI]; p-value
KHQ – personal relationships							
<i>52 weeks</i>							
049					Outcome not recorded		
<i>12 weeks</i>							
044					Outcome not recorded		
046					Outcome not recorded		
048	263	10.20 (1.16)	-2.87 (0.80) ^e	278	8.03 (0.93)	-3.27 (0.77) ^e	0.40 [-1.78; 2.58]; 0.72
090					No evaluable results ^g		
KHQ – emotions							
<i>52 weeks</i>							
049					Outcome not recorded		
<i>12 weeks</i>							
044					Outcome not recorded		
046					Outcome not recorded		
048	365	36.59 (1.32)	-10.39 (1.10) ^e	365	36.47 (1.33)	-9.26 (1.10) ^e	
090	313	43.56 (1.69)	-12.13 (1.34) ^e	311	45.09 (1.82)	-10.22 (1.34) ^e	
Total							-1.44 [-3.79; 0.91]; 0.229 ^f
KHQ – sleep/energy							
<i>52 weeks</i>							
049					Outcome not recorded		
<i>12 weeks</i>							
044					Outcome not recorded		
046					Outcome not recorded		
048	365	27.76 (1.22)	-9.57 (0.96) ^e	365	30.00 (1.24)	-7.70 (0.96) ^e	
090	313	45.53 (1.48)	-11.55 (1.19) ^e	311	43.30 (1.54)	-9.58 (1.20) ^e	
Total							-1.91 [-3.98; 0.16]; 0.071 ^f

(continued)

Table 13: Results on health-related quality of life – RCT, direct comparison: mirabegron vs. tolterodine (continued)

Instrument outcome	Mirabegron			Tolterodine			Mirabegron vs. tolterodine	
	time point study	N	Values at start of study mean (SE)	Change at end of study mean ^{a, b} (SE)	N	Values at start of study mean (SE)	Change at end of study mean ^{a, b} (SE)	Mean difference [95% CI]; p-value
KHQ – severity/social embarrassment								
52 weeks								
		049			Outcome not recorded			
12 weeks								
		044			Outcome not recorded			
		046			Outcome not recorded			
		048	365	30.50 (0.98)	-8.19 (0.75) ^e	365	30.16 (0.97)	-7.92 (0.75) ^e
		090	312	29.64 (1.36)	-6.56 (0.86) ^e	311	30.27 (1.36)	-7.30 (0.86) ^e
		Total						0.17 [-1.39; 1.73]; 0.833 ^f
a: Unless stated otherwise, LOCF analysis.								
b: Adjusted for values at the start of the study.								
c: OAB-q: The total score can be between 0 and 100, positive changes in comparison with the start of the study indicate improvement.								
d: KHQ: The scores of the individual domains can be between 0 and 100, negative changes in comparison with the start of the study indicate improvement.								
e: No LOCF analysis.								
f: Institute’s calculation from meta-analysis.								
g: More than 30% missing values in both arms: Due to the high proportion of patients who were not considered in the analyses, the results of the study are assessed as not valid. These results were therefore not included in the benefit assessment.								
CI: confidence interval; KHQ: King’s Health Questionnaire; LOCF: last observation carried forward; N: number of analysed patients; OAB-q: Overactive Bladder symptom and health-related quality of life questionnaire; RCT: randomized controlled trial; SE: standard error; vs.: versus								

Health-related quality of life

Overactive Bladder Questionnaire

In the 049 long-term study, there was no statistically significant difference between the treatment groups for the outcome “OAB-q” in the total score or in the individual domains. The OAB-q was not recorded in the 044, 048 and 090 short-term studies. In the 046 short-term study, there was no statistically significant difference between the treatment groups in the total score or in the individual domains. Hence an added benefit of mirabegron in comparison with tolterodine is not proven for the outcome “OAB-q”.

This concurs with the company's assessment.

King's Health Questionnaire

The outcome “KHQ” was not recorded in the 049 long-term study and in the 044 and 046 short-term studies. In 8 of 9 KHQ domains, there was no statistically significant difference between the treatment groups in the meta-analysis of the 048 and 090 short-term studies. For the domain “KHQ – incontinence impact”, there was considerable heterogeneity between the studies 048 and 090 ($p < 0.2$) so that no common estimate was calculated. In the 048 short-term study, there was a statistically significant effect in favour of mirabegron in the domain “incontinence impact”. However, the 95% CI of Hedges' g was not fully below the irrelevance threshold of -0.2. For the 090 short-term study, there was no statistically significant difference between the treatment groups for the domain “incontinence impact”. Hence an added benefit of mirabegron in comparison with tolterodine is not proven for the outcome “KHQ”.

This concurs with the company's assessment.

Table 14 shows the results on adverse events.

Table 14: Results on adverse events – RCT, direct comparison: mirabegron vs. tolterodine

Outcome category	Mirabegron		Tolterodine		Mirabegron vs. tolterodine
outcome <i>time point</i> study	N	Patients with at least one event n (%)	N	Patients with at least one event n (%)	RR [95% CI]; p-value
Adverse events					
AEs					
<i>52 weeks</i>					
049	812	485 (59.7)	812	508 (62.6)	
<i>12 weeks</i>					
044	169	74 (43.8)	85	41 (48.2)	
046	493	211 (42.8)	495	231 (46.7)	
048	379	281 (74.1)	378 ^a	305 (80.7)	
090	369 ^a	107 (29.0)	372 ^a	128 (34.4)	
SAEs					
<i>52 weeks</i>					
049	812	42 (5.2)	812	44 (5.4)	0.95 [0.63; 1.44]; 0.825
<i>12 weeks</i>					
044	169	1 (0.6)	85	1 (1.2)	
046	493	14 (2.8)	495	11 (2.2)	
048	379	3 (0.8)	378 ^a	4 (1.1)	
090	369 ^a	5 (1.4)	372 ^a	6 (1.6)	
total	1.02 [0.57; 1.83]; 0.948 ^b				
Discontinuation due to AEs					
<i>52 weeks</i>					
049	812	48 (5.9)	812	46 (5.7)	1.04 [0.70; 1.55]; 0.832
<i>12 weeks</i>					
044	169	4 (2.4) ^a	85	1 (1.2) ^a	
046	493	24 (4.9)	495	22 (4.4)	
048	379	12 (3.2)	378 ^a	12 (3.2)	
090	369 ^a	9 (2.4)	372 ^a	11 (3.0)	
total	1.03 [0.69; 1.53]; 0.895 ^c				

(continued)

Table 14: Results on adverse events – RCT, direct comparison: mirabegron vs. tolterodine (continued)

Outcome <i>time point study</i>	Mirabegron		Tolterodine		Mirabegron vs. tolterodine
	N	Patients with at least one event n (%)	N	Patients with at least one event n (%)	RR [95% CI]; p-value
AE “dry mouth”					
52 weeks					
049	812	23 (2.8)	812	70 (8.6)	0.33 [0.21; 0.52]; < 0.001
12 weeks					
044	169	3 (1.8)	85	3 (3.5)	0.50 [0.10; 2.44]; 0.394
046	493	14 (2.8)	495	50 (10.1)	0.28 [0.16; 0.50]; < 0.001
048	379	10 (2.6)	378 ^a	55 (14.6)	0.18 [0.09; 0.35]; < 0.001
090	369 ^a	18 (4.9)	372 ^a	30 (8.1)	0.60 [0.34; 1.07]; 0.082
total					Heterogeneity: Q = 7.98, p = 0.046, I ² = 62.4% ^c
Discontinuation due to AE “dry mouth”					
52 weeks					
049	812	3 (0.4)	812	4 (0.5)	0.75 [0.17; 3.31] ^d ; > 0.999 ^e
12 weeks					
044	169	0 (0)	85	0 (0)	
046	493	0 (0)	495	1 (0.2)	
048	379	0 (0)	375 ^a	3 (0.8)	
090	366 ^a	1 (0.3)	371 ^a	2 (0.5)	
total					0.31 [0.06; 1.56]; 0.157 ^c
a: There was contradictory information in Module 4 from the additional analyses versus the clinical study report. b: Calculated from meta-analysis. c: Institute’s calculation from meta-analysis. d: Institute’s calculation, Peto OR. e: Institute’s calculation, Fisher exact test. AE: adverse event; CI: confidence interval; N: number of analysed patients; n: number of patients with event; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus					

Adverse events

The AEs, SAEs and discontinuations due to AEs that most commonly occurred in the 049 long-term study are presented in Appendix B of the full dossier assessment.

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome “SAEs” in the 049 long-term study or in the meta-analysis of the 044, 046, 048 and 090 short-term studies. Hence greater/lesser harm from mirabegron in comparison with tolterodine is not proven for this outcome.

This concurs with the company's assessment.

Discontinuation due to AEs

There was no statistically significant difference between the treatment groups for the outcome “discontinuation due to AEs” in the 049 long-term study or in the meta-analysis of the 044, 046, 048 and 090 short-term studies. Hence greater/lesser harm from mirabegron in comparison with tolterodine is not proven for this outcome.

This concurs with the company's assessment.

Dry mouth

For the outcome “dry mouth”, there was a statistically significant difference in favour of mirabegron in the 049 long-term study. In the meta-analysis of the 044, 046, 048 und 090 short-term studies, there was considerable heterogeneity between the studies ($p < 0.2$) so that no common estimate was calculated. There was no statistically significant difference between the treatment groups in the 044 and 090 short-term studies. There was a statistically significant difference in favour of mirabegron in the 046 and 048 short-term studies. Subgroup analyses were additionally used to explain this heterogeneity, and age was identified to be an effect modifier ($</\geq 65$ years). There was a homogeneous situation with a statistically significant advantage of mirabegron in both age groups (see Figure 17 in Appendix A of the full dossier assessment). In the overall consideration of the long- and short-term studies it was therefore possible to derive the probability “proof” for this outcome. In summary, there is proof of lesser harm from mirabegron for the outcome “dry mouth”.

This concurs with the company's assessment.

Discontinuation due to dry mouth

In the 049 long-term study, there was no statistically significant difference between the treatment groups for the outcome “dry mouth”. In the meta-analysis of the 044, 046, 048 and 090 short-term studies, there was no statistically significant difference between the treatment groups. Hence greater/lesser harm from mirabegron in comparison with tolterodine is not proven for this outcome.

The company did not present the outcome “discontinuation due to dry mouth” in Module 4 of its dossier.

Further information on the outcome results can be found in Module 4, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Section 2.7.2.4.3 of the full dossier assessment.

2.4.4 Subgroups and other effect modifiers

Selected subgroups were investigated for the presence of heterogeneous treatment effects in order to identify possible effect modifications. The company presented the corresponding analyses for the characteristics “age ($</\geq 65$ years)” and “sex”. The subgroup characteristics

presented by the company and the cut-off values were specified a priori in the studies. The company presented no analyses for the characteristics “centre and country effects” also considered to be relevant.

The prerequisite for proof of different subgroup effects is a statistically significant interaction ($p < 0.05$). A p-value of ≥ 0.05 and < 0.2 provides an indication of an effect modification.

For the 049 long-term study, subgroup analyses were only available for the outcome “dry mouth”. These showed no indication or proof of an interaction between treatment effect and subgroup characteristic. The subgroup analyses of the 044, 046, 048 and 090 short-term studies for the present benefit assessment were only used for the outcomes in which the results were relevant for the assessment of the probability of the added benefit. In the short-term studies, there was proof of an effect modification by the characteristic “age” for the outcome “dry mouth” (see also Section 2.4.3 and Figure 17 of the full dossier assessment). No additional effect modifiers for mirabegron were identified.

This concurs with the company’s assessment.

Further information on the subgroup results can be found in Module 4, Sections 4.3.1.3.2 and 4.3.2.1.3.2 of the dossier, and in Section 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the General Methods of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

Based on the data presented in Section 2.4, there is no proof of added benefit of mirabegron in comparison with tolterodine for patients with OAB. However, there is proof of lesser harm from mirabegron in comparison with tolterodine for the outcome “dry mouth”.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 15). The derivation of the added benefit was primarily based on the results of the 049 long-term study. In cases where the results of the short-term studies were additionally used for the derivation of probability, there is a corresponding footnote in the table.

Table 15: Extent of added benefit at outcome level: mirabegron vs. tolterodine

Outcome category outcome	Mirabegron vs. tolterodine proportion of events or MD effect estimate [95% CI] p-value probability ^a	Derivation of extent ^b
Mortality		
All-cause mortality	0.4% vs. 0.2% Peto-OR: 1.49 [0.26; 8.64] ^c p > 0.999 ^d	Added benefit not proven
Morbidity		
OAB symptoms (PPBC)	-0.76 vs. -0.83 MD: 0.07 [-0.05; 0.19] p = 0.25	Added benefit not proven
OAB symptoms (OAB-q – Symptom Bother Score)	-13.07 vs. -14.37 MD: 1.30 [-0.52; 3.12] p = 0.16	Added benefit not proven
OAB symptoms (KHQ – Symptom Severity Scale)	Outcome not recorded in long-term study	Added benefit not proven
Health status EQ-5D VAS	6.44 vs. 6.33 MD: 0.12 [-1.38; 1.62] p = 0.88	Added benefit not proven
Incontinence	No evaluable data	Added benefit not proven
Urge incontinence	No evaluable data	Added benefit not proven
Micturition frequency	-1.26 vs. -1.38 ^e MD: 0.13 [-0.11; 0.36] p = 0.29	Added benefit not proven
Urgency	-1.62 vs. -1.62 ^e MD: -0.00 [-0.30; 0.30] p = 0.98	Added benefit not proven
Nocturia	-0.45 vs. -0.42 ^e MD: -0.03 [-0.14; 0.08] p = 0.58	Added benefit not proven
Health-related quality of life		
OAB-q – total score	10.53 vs. 11.42 MD: -0.90 [-2.52; 0.73] p = 0.28	Added benefit not proven
KHQ	Outcome not recorded in long-term study	Added benefit not proven

(continued)

Table 15: Extent of added benefit at outcome level: mirabegron vs. tolterodine (continued)

Outcome category outcome	Mirabegron vs. tolterodine proportion of events or MD effect estimate [95% CI] p-value probability ^a	Derivation of extent ^b
Adverse events		
SAEs	5.2% vs. 5.4% RR: 0.95 [0.63; 1.44] p = 0.825	Greater/lesser harm not proven
Discontinuation due to AEs	5.9% vs. 5.7% RR: 1.04 [0.70; 1.55] p = 0.832	Greater/lesser harm not proven
AE “dry mouth”	2.8% vs. 8.6% RR: 0.33 [0.21; 0.52] p < 0.001 probability: “proof” ^{ef}	Outcome category: non-serious/non-severe AEs CI _u < 0.80 lesser harm extent: “considerable”
Discontinuation due to AE “dry mouth”	0.4% vs. 0.5% Peto-OR: 0.75 [0.17; 3.31] ^c p > 0.999 ^d	Greater/lesser harm not proven
<p>a: Probability provided if statistically significant differences were present. b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u. c: Institute’s calculation, Peto OR. d: Institute’s calculation, Fisher exact test. e: Change in the number of events/24 h. f: Proof, derived from the additional consideration of the short-term studies.</p> <p>AE: adverse event; CI: confidence interval; CI_u: upper limit of the CI; EQ-5D: European Quality of Life-5 Dimensions; KHQ: King’s Health Questionnaire; LOCF: last observation carried forward; MD: mean difference; OAB: overactive bladder; OAB-q: Overactive Bladder symptom and health-related quality of life questionnaire; OR: odds ratio; PPBC: Patient Perception of Bladder Condition; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus</p>		

2.5.2 Overall conclusion on added benefit

Table 16 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of mirabegron compared with tolterodine

Positive effects	Negative effects
Proof of lesser harm – extent: “considerable” (non-serious/non-severe adverse events: dry mouth)	–
Due to the missing analyses for the outcomes “incontinence” and “urge incontinence”, no conclusive balancing on the added benefit is possible.	

Overall, a positive effect remains in the category “non-serious/non-severe AEs” with the probability “proof” and the extent “considerable”. However, as analyses for the total population are missing for the patient-relevant outcomes “incontinence” and “urge incontinence”, no conclusive balancing of the added benefit can be conducted for the total population. No conclusive balancing can be conducted for the subpopulation of patients with incontinence at the start of the study, either. Analyses on incontinence are available for this subpopulation, but there are no analyses for further outcomes such as patient-reported morbidity and health-related quality of life.

In summary, an added benefit of mirabegron versus the ACT tolterodine is not proven for patients with OAB symptoms.

The result of the assessment of the added benefit of mirabegron in comparison with the ACT is summarized in Table 17.

Table 17: Mirabegron – extent and probability of added benefit

Therapeutic indication	ACT ^a	Extent and probability of added benefit
Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder syndrome	Darifenacin, fesoterodine, flavoxate, propiverine, solifenacin, tolterodine and trospium chloride	Added benefit not proven
<p>a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. In the present case, the company limited the ACT to extended-release formulations of tolterodine. This limitation was not followed.</p> <p>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee</p>		

This deviates from the company's approach, which derived proof of a minor added benefit.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

Study 049

1. Astellas Pharma Global Development. Post hoc analysis; safety (subgroup and total analysis) [unpublished]. 2014.

2. Astellas Pharma Global Development. Post hoc analysis; efficacy and quality of life (subgroup and total analysis) [unpublished]. 2014.

3. Astellas Pharma Europe. A randomized, double-blind, parallel group, active controlled, multicenter long-term study to assess the safety and efficacy of the beta-3 agonist YM178 (50 mg qd and 100 mg qd) in subjects with symptoms of overactive bladder [online]. In: Pharmnet.Bund Klinische Prüfungen. [Accessed: 3 March 2014]. URL: <http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm>.
4. Astellas. A randomized, double-blind, parallel group, active controlled, multi-center long-term study to assess the safety and efficacy of the beta-3 agonist mirabegron (YM178) 50 mg qd and 100 mg qd in subjects with symptoms of overactive bladder: phase 3 long-term safety study; study 178-CL-049 (TAURUS); clinical study report [unpublished]. 2011.
5. Astellas Pharma Europe. A randomized, double-blind, parallel group, active controlled, multicenter long-term study to assess the safety and efficacy of the beta-3 agonist YM178 (50 mg qd and 100 mg qd) in subjects with symptoms of overactive bladder [online]. In: EU Clinical Trials Register. [Accessed: 3 March 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-001452-39.
6. Astellas Pharma. Study to test the long term safety and efficacy of the beta-3 agonist mirabegron (YM178) in patients with symptoms of overactive bladder: full text view [online]. In: ClinicalTrials.gov. 19 March 2013 [accessed: 3 March 2014]. URL: <http://ClinicalTrials.gov/show/NCT00688688>.
7. Chapple CR, Kaplan SA, Mitcheson D, Klecka J, Cummings J, Drogendijk T et al. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a b3-adrenoceptor agonist, in overactive bladder. Eur Urol 2013; 63(2): 296-305.

Study 044

1. Astellas Pharma Global Development. Post hoc analysis; safety (subgroup and total analysis) [unpublished]. 2014.
2. Astellas Pharma Global Development. Post hoc analysis; efficacy and quality of life (subgroup and total analysis) [unpublished]. 2014.
3. Astellas. A randomized, double-blind, parallel group, placebo and active controlled, multi-center dose ranging study with the beta-3 agonist YM178 in patients with symptomatic overactive bladder: study 178-CL-044 (DRAGON); clinical study report [unpublished]. 2011.
4. Astellas Pharma Europe. A randomized, double-blind, parallel group, placebo and active controlled, multi-center dose ranging study with the beta-3 agonist YM178 in patients with symptomatic overactive bladder (DRAGON) [online]. In: EU Clinical Trials Register. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2005-002256-17.

5. Astellas Pharma. A study of YM178 in patients with symptomatic overactive bladder (DRAGON): full text view [online]. In: ClinicalTrials.gov. 1 July 2013 [accessed: 31 July 2014]. URL: <http://ClinicalTrials.gov/show/NCT00337090>.

6. Chapple CR, Dvorak V, Radziszewski P, Van Kerrebroeck P, Wyndaele JJ, Bosman B et al. A phase II dose-ranging study of mirabegron in patients with overactive bladder. *Int Urogynecol J* 2013; 24(9): 1447-1458.

Study 046

1. Astellas Pharma Global Development. Post hoc analysis; safety (subgroup and total analysis) [unpublished]. 2014.

2. Astellas Pharma Global Development. Post hoc analysis; efficacy and quality of life (subgroup and total analysis) [unpublished]. 2014.

3. Astellas Pharma Europe. A randomized, double-blind, parallel group, placebo and active controlled, multicenter study to assess the efficacy and safety of the beta-3 agonist YM178 (50 mg qd and 100 mg qd) in subjects with symptoms of overactive bladder [online]. In: PharmNet.bund Klinische Prüfungen. [Accessed: 5 March 2014]. URL: <http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm>.

4. Astellas. A randomized, double-blind, parallel group, placebo and active controlled, multicenter study to assess the efficacy and safety of mirabegron in subjects with symptoms of overactive bladder: study 178-CL-046 (SCORPIO); clinical study report [unpublished]. 2011.

5. Astellas Pharma Europe. A randomized, double-blind, parallel group, placebo and active controlled, multicenter study to assess the efficacy and safety of the beta-3 agonist YM178 (50 mg qd and 100 mg qd) in subjects with symptoms of overactive bladder [online]. In: EU Clinical Trials Register. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-001451-19.

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7. Khullar V, Amarenco G, Angulo JC, Cambronero J, Hoye K, Milsom I et al. Efficacy and tolerability of mirabegron, a b3-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. *Eur Urol* 2012; 63(2): 283-295.

Study 048

1. Astellas Pharma Global Development. Post hoc analysis; safety (subgroup and total analysis) [unpublished]. 2014.

2. Astellas Pharma Global Development. Post hoc analysis; efficacy and quality of life (subgroup and total analysis) [unpublished]. 2014.

3. Astellas. A double-blind group comparison study in patients with overactive bladder: study 178-CL-048; phase III study of YM178; clinical study report [unpublished]. 2010.
4. Astellas Pharma. A study to evaluate safety and efficacy of YM178 in patients with overactive bladder: full text view [online]. In: ClinicalTrials.gov. 15 July 2013 [accessed: 31 July 2014]. URL: <http://ClinicalTrials.gov/show/NCT00966004>.
5. Yamaguchi O, Marui E, Kakizaki H, Homma Y, Igawa Y, Takeda M et al. Phase III, randomised, double-blind, placebo-controlled study of the β 3-adrenoceptor agonist mirabegron, 50 mg once daily, in Japanese patients with overactive bladder. BJU Int 2014; 113(6): 951-960.

Study 090

1. Astellas Pharma Global Development. Study 178-CL-090: post hoc baseline characteristics study for ITT [unpublished]. 2014.
2. Astellas Pharma Global Development. Post hoc analysis; safety (subgroup and total analysis) [unpublished]. 2014.
3. Astellas Pharma Global Development. Post hoc analysis; efficacy and quality of life (subgroup and total analysis) [unpublished]. 2014.
4. Astellas Pharma Global Development. A phase 3, randomized, double-blind, parallel group, placebo and active controlled, multicenter study to assess the efficacy and safety of mirabegron (YM178) in Asian patients with symptoms of overactive bladder: study 178-CL-090; clinical study report [unpublished]. 2012.
5. Astellas Pharma. A study of YM178 in subjects with symptoms of overactive bladder: full text view [online]. In: ClinicalTrials.gov. 16 September 2013 [accessed: 3 March 2014]. URL: <http://ClinicalTrials.gov/show/NCT01043666>.

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Please see full dossier assessment for full reference list.

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4. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. *Computat Stat Data Anal* 1994; 17(5): 555-574.

The full report (German version) is published under

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