ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. **NAME OF THE MEDICINAL PRODUCT**

Betmiga 25 mg prolonged-release tablets
Betmiga 50 mg prolonged-release tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Betmiga 25 mg prolonged-release tablets
Each tablet contains 25 mg of mirabegron.

Betmiga 50 mg prolonged-release tablets
Each tablet contains 50 mg of mirabegron.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Prolonged-release tablet.

Betmiga 25 mg tablets
Oval, brown tablet, debossed with the company logo and “325” on the same side.

Betmiga 50 mg tablets
Oval, yellow tablet, debossed with the company logo and “355” on the same side.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

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

4.2 **Posology and method of administration**

**Posology**

*Adults (including elderly patients)*
The recommended dose is 50 mg once daily with or without food.

**Special populations**

*Renal and hepatic impairment*

Betmiga has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m² or patients requiring haemodialysis) or severe hepatic impairment (Child-Pugh Class C) and it is therefore not recommended for use in these patient populations (see sections 4.4 and 5.2).

The following table provides the daily dosing recommendations for subjects with renal or hepatic impairment in the absence and presence of strong CYP3A inhibitors (see sections 4.4, 4.5 and 5.2).
<table>
<thead>
<tr>
<th>Renal impairment(^{(1)})</th>
<th>Mild</th>
<th>50 mg</th>
<th>25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate</td>
<td>50 mg</td>
<td>25 mg</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>25 mg</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Hepatic impairment(^{(2)})</td>
<td>Mild</td>
<td>50 mg</td>
<td>25 mg</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>25 mg</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

1. Mild: GFR 60 to 89 mL/min/1.73 m\(^{2}\); moderate: GFR 30 to 59 mL/min/1.73 m\(^{2}\); severe: GFR 15 to 29 mL/min/1.73 m\(^{2}\).
2. Mild: Child-Pugh Class A; Moderate: Child-Pugh Class B.
3. Strong CYP3A inhibitors see section 4.5

**Gender**

No dose adjustment is necessary according to gender.

**Paediatric population**

The safety and efficacy of mirabegron in children below 18 years of age have not yet been established. No data are available.

**Method of administration**

The tablet is to be taken once daily, with liquids, swallowed whole and is not to be chewed, divided, or crushed.

**4.3 Contraindications**

Mirabegron is contraindicated in patients with
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe uncontrolled hypertension defined as systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg.

**4.4 Special warnings and precautions for use**

**Renal impairment**

Betmiga has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m\(^{2}\) or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m\(^{2}\)); based on a pharmacokinetic study (see section 5.2) a dose reduction to 25 mg is recommended in this population. Betmiga is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m\(^{2}\)) concomitantly receiving strong CYP3A inhibitors (see section 4.5).

**Hepatic impairment**

Betmiga has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. Betmiga is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors (see section 4.5).

**Hypertension**

Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with Betmiga, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg).
Patients with congenital or acquired QT prolongation

Betmiga, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies (see section 5.1). However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients.

Patients with bladder outlet obstruction and patients taking antimuscarinics medications for OAB

Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with Betmiga; however, Betmiga should be administered with caution to patients with clinically significant BOO. Betmiga should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data

Mirabegron is transported and metabolised through multiple pathways. Mirabegron is a substrate for cytochrome P450 (CYP) 3A4, CYP2D6, butyrylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT), the efflux transporter P-glycoprotein (P-gp) and the influx organic cation transporters (OCT) OCT1, OCT2, and OCT3. Studies of mirabegron using human liver microsomes and recombinant human CYP enzymes showed that mirabegron is a moderate and time-dependent inhibitor of CYP2D6 and a weak inhibitor of CYP3A. Mirabegron inhibited P-gp-mediated drug transport at high concentrations.

In vivo data

CYP2D6 polymorphism

CYP2D6 genetic polymorphism has minimal impact on the mean plasma exposure to mirabegron (see section 5.2). Interaction of mirabegron with a known CYP2D6 inhibitor is not expected and was not studied. No dose adjustment is needed for mirabegron when administered with CYP2D6 inhibitors or in patients who are CYP2D6 poor metabolisers.

Drug-drug interactions

The effect of co-administered medicinal products on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of other medicinal products was studied in single and multiple dose studies. Most drug-drug interactions were studied using a dose of 100 mg mirabegron given as oral controlled absorption system (OCAS) tablets. Interaction studies of mirabegron with metoprolol and with metformin used mirabegron immediate-release (IR) 160 mg.

Clinically relevant drug interactions between mirabegron and medicinal products that inhibit, induce or are a substrate for one of the CYP isozymes or transporters are not expected except for the inhibitory effect of mirabegron on the metabolism of CYP2D6 substrates.

Effect of enzyme inhibitors

Mirabegron exposure (AUC) was increased 1.8-fold in the presence of the strong inhibitor of CYP3A/P-gp ketoconazole in healthy volunteers. No dose-adjustment is needed when Betmiga is combined with inhibitors of CYP3A and/or P-gp. However, in patients with mild to moderate renal impairment (GFR 30 to 89 mL/min/1.73 m²) or mild hepatic impairment (Child-Pugh Class A) concomitantly receiving strong CYP3A inhibitors, such as itraconazole, ketoconazole, ritonavir and clarithromycin, the recommended dose is 25 mg once daily with or without food (see section 4.2). Betmiga is not recommended in patients with severe renal impairment (GFR
15 to 29 mL/min/1.73 m²) or patients with moderate hepatic impairment (Child-Pugh Class B) concomitantly receiving strong CYP3A inhibitors (see sections 4.2 and 4.4).

**Effect of enzyme inducers**
Substances that are inducers of CYP3A or P-gp decrease the plasma concentrations of mirabegron. No dose adjustment is needed for mirabegron when administered with therapeutic doses of rifampicin or other CYP3A or P-gp inducers.

**Effect of mirabegron on CYP2D6 substrates**
In healthy volunteers, the inhibitory potency of mirabegron towards CYP2D6 is moderate and the CYP2D6 activity recovers within 15 days after discontinuation of mirabegron. Multiple once daily dosing of mirabegron IR resulted in a 90% increase in Cₘₐₓ and a 229% increase in AUC of a single dose of metoprolol. Multiple once daily dosing of mirabegron resulted in a 79% increase in Cₘₐₓ and a 241% increase in AUC of a single dose of desipramine.

Caution is advised if mirabegron is co-administered with medicinal products with a narrow therapeutic index and significantly metabolised by CYP2D6, such as thioridazine, Type 1C antiarrhythmics (e.g., flecainide, propafenone) and tricyclic antidepressants (e.g., imipramine, desipramine). Caution is also advised if mirabegron is co-administered with CYP2D6 substrates that are individually dose titrated.

**Effect of mirabegron on transporters**
Mirabegron is a weak inhibitor of P-gp. Mirabegron increased Cₘₐₓ and AUC by 29% and 27%, respectively, of the P-gp substrate digoxin in healthy volunteers. For patients who are initiating a combination of Betmiga and digoxin, the lowest dose for digoxin should be prescribed initially. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect. The potential for inhibition of P-gp by mirabegron should be considered when Betmiga is combined with sensitive P-gp substrates e.g. dabigatran.

**Other interactions**
No clinically relevant interactions have been observed when mirabegron was co-administered with therapeutic doses of solifenacin, tamsulosin, warfarin, metformin or a combined oral contraceptive medicinal product containing ethinylestradiol and levonorgestrel. Dose-adjustment is not recommended.

Increases in mirabegron exposure due to drug-drug interactions may be associated with increases in pulse rate.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**
There are limited amount of data from the use of Betmiga in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Betmiga is not recommended during pregnancy and in women of childbearing potential not using contraception.

**Breast-feeding**
Mirabegron is excreted in the milk of rodents and therefore is predicted to be present in human milk (see section 5.3). No studies have been conducted to assess the impact of mirabegron on milk production in humans, its presence in human breast milk, or its effects on the breast-fed child. Betmiga should not be administered during breast-feeding.

**Fertility**
There were no treatment-related effects of mirabegron on fertility in animals (see section 5.3). The effect of mirabegron on human fertility has not been established.
4.7 Effects on ability to drive and use machines

Betmiga has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Betmiga was evaluated in 8433 patients with OAB, of which 5648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 622 patients received Betmiga for at least 1 year (365 days). In the three 12-week phase 3 double blind, placebo controlled studies, 88% of the patients completed treatment with Betmiga, and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity.

The most common adverse reactions reported for patients treated with Betmiga 50 mg during the three 12-week phase 3 double blind, placebo controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 1.2% in patients receiving Betmiga 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving Betmiga 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving Betmiga 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving Betmiga 50 mg. Serious adverse reactions included atrial fibrillation (0.2%).

Adverse reactions observed during the 1-year (long term) active controlled (muscarinic antagonist) study were similar in type and severity to those observed in the three 12-week phase 3 double blind, placebo controlled studies.

Tabulated list of adverse reactions

The table below reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double blind, placebo controlled studies.

The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
<table>
<thead>
<tr>
<th>MedDRA System organ class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Urinary tract infection</td>
<td>Vaginal infection</td>
<td>Cystitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td>Insomnia*</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Eyelid oedema</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Tachycardia</td>
<td>Palpitation</td>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypertensive crisis*</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea*</td>
<td>Constipation*</td>
<td>Dyspepsia</td>
<td>Gastritis</td>
<td>Lip oedema</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Urticaria</td>
<td>Rash</td>
<td>Rash macular</td>
<td>Rash papular</td>
<td>Pruritus</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td>Joint swelling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Vulvovaginal pruritus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Blood pressure increased</td>
<td>GGT increased</td>
<td>AST increased</td>
<td>ALT increased</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td></td>
<td>Urinary retention*</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache*</td>
<td>Dizziness*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*observed during post-marketing experience

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

Mirabegron has been administered to healthy volunteers at single doses up to 400 mg. At this dose, adverse events reported included palpitations (1 of 6 subjects) and increased pulse rate exceeding 100 beats per minute (bpm) (3 of 6 subjects). Multiple doses of mirabegron up to 300 mg daily for 10 days showed increases in pulse rate and systolic blood pressure when administered to healthy volunteers.
Treatment for overdose should be symptomatic and supportive. In the event of overdose, pulse rate, blood pressure, and ECG monitoring is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, Urinary antispasmodics ATC code: G04BD12.

Mechanism of action

Mirabegron is a potent and selective beta 3-adrenoceptor agonist. Mirabegron showed relaxation of bladder smooth muscle in rat and human isolated tissue, increased cyclic adenosine monophosphate (cAMP) concentrations in rat bladder tissue and showed a bladder relaxant effect in rat urinary bladder function models. Mirabegron increased mean voided volume per micturition and decreased the frequency of non-voiding contractions, without affecting voiding pressure, or residual urine in rat models of bladder overactivity. In a monkey model, mirabegron showed decreased voiding frequency. These results indicate that mirabegron enhances urine storage function by stimulating beta 3-adrenoceptors in the bladder.

During the urine storage phase, when urine accumulates in the bladder, sympathetic nerve stimulation predominates. Noradrenaline is released from nerve terminals, leading predominantly to beta adrenoceptor activation in the bladder musculature, and hence bladder smooth muscle relaxation. During the urine voiding phase, the bladder is predominantly under parasympathetic nervous system control. Acetylcholine, released from pelvic nerve terminals, stimulates cholinergic M2 and M3 receptors, inducing bladder contraction. The activation of the M2 pathway also inhibits beta 3-adrenoceptor induced increases in cAMP. Therefore beta 3-adrenoceptor stimulation should not interfere with the voiding process. This was confirmed in rats with partial urethral obstruction, where mirabegron decreased the frequency of non-voiding contractions without affecting the voided volume per micturition, voiding pressure, or residual urine volume.

Pharmacodynamic effects

Urodynamics

Betmiga at doses of 50 mg and 100 mg once daily for 12 weeks in men with lower urinary tract symptoms (LUTS) and bladder outlet obstruction (BOO) showed no effect on cystometry parameters and was safe and well tolerated. The effects of mirabegron on maximum flow rate and detrusor pressure at maximum flow rate were assessed in this urodynamic study consisting of 200 male patients with LUTS and BOO. Administration of mirabegron at doses of 50 mg and 100 mg once daily for 12 weeks did not adversely affect the maximum flow rate or detrusor pressure at maximum flow rate. In this study in male patients with LUTS/BOO, the adjusted mean (SE) change from baseline to end of treatment in post void residual volume (mL) was 0.55 (10.702), 17.89 (10.190), 30.77 (10.598) for the placebo, mirabegron 50 mg and mirabegron 100 mg treatment groups.

Effect on QT interval

Betmiga at doses of 50 mg or 100 mg had no effect on the QT interval individually corrected for heart rate (QTcI interval) when evaluated either by sex or by the overall group.

A thorough QT (TQT) study (n = 164 healthy male and n = 153 healthy female volunteers with a mean age of 33 years) evaluated the effect of repeat oral dosing of mirabegron at the indicated dose (50 mg once daily) and two supra-therapeutic doses (100 and 200 mg once daily) on the QTcI interval. The supra-therapeutic doses represent approximately 2.6- and 6.5-fold the exposure of the therapeutic dose, respectively. A single 400 mg dose of moxifloxacin was used as a positive control. Each dose level of mirabegron and moxifloxacin was evaluated in separate treatment arms each including placebo-control (parallel cross-over design). For both males and females administered mirabegron at 50 mg and 100 mg, the upper bound of the one-sided 95% confidence interval did not exceed 10 msec at any time...
point for the largest time-matched mean difference from placebo in the QTcI interval. In females administered mirabegron at the 50 mg dose, the mean difference from placebo on QTcI interval at 5 hours post dose was 3.67 msec (upper bound of the one-sided 95% CI 5.72 msec). In males, the difference was 2.89 msec (upper bound of the one-sided 95% CI 4.90 msec). At a mirabegron dose of 200 mg, the QTcI interval did not exceed 10 msec at any time point in males, while in females the upper bound of the one-sided 95% confidence interval did exceed 10 msec between 0.5–6 hours, with a maximum difference from placebo at 5 hours where the mean effect was 10.42 msec (upper bound of the one-sided 95% CI 13.44 msec). Results for QTcF and QTcIf were consistent with QTcI.

In this TQT study, mirabegron increased heart rate on ECG in a dose dependent manner across the 50 mg to 200 mg dose range examined. The maximum mean difference from placebo in heart rate ranged from 6.7 bpm with mirabegron 50 mg up to 17.3 bpm with mirabegron 200 mg in healthy subjects.

Effects on pulse rate and blood pressure in patients with OAB
In OAB patients (mean age of 59 years) across three 12-week phase 3 double blind, placebo controlled studies receiving Betmiga 50 mg once daily, an increase in mean difference from placebo of approximately 1 bpm for pulse rate and approximately 1 mm Hg or less in systolic blood pressure/diastolic blood pressure (SBP/DBP) was observed. Changes in pulse rate and blood pressure are reversible upon discontinuation of treatment.

Effect on intraocular pressure (IOP)
Mirabegron 100 mg once daily did not increase IOP in healthy subjects after 56 days of treatment. In a phase 1 study assessing the effect of Betmiga on IOP using Goldmann applanation tonometry in 310 healthy subjects, a dose of mirabegron 100 mg was non-inferior to placebo for the primary endpoint of the treatment difference in mean change from baseline to day 56 in subject-average IOP; the upper bound of the two-sided 95% CI of the treatment difference between mirabegron 100 mg and placebo was 0.3 mm Hg.

Clinical efficacy and safety

Efficacy of Betmiga was evaluated in three phase 3 randomized, double blind, placebo controlled, 12-week studies for the treatment of overactive bladder with symptoms of urgency and frequency with or without incontinence. Female (72%) and male (28%) patients with a mean age of 59 years (range 18–95 years) were included. The study population consisted of approximately 48% antimuscarinic treatment naïve patients as well as approximately 52% patients previously treated with antimuscarinic medication. In one study, 495 patients received an active control (tolterodine prolonged release formulation).

The co-primary efficacy endpoints were (1) change from baseline to end of treatment in mean number of incontinence episodes per 24 hours and (2) change from baseline to end of treatment in mean number of micturitions per 24 hours based on a 3-day micturition diary. Mirabegron demonstrated statistically significant larger improvements compared to placebo for both co-primary endpoints as well as secondary endpoints (see Tables 1 and 2).
Table 1: Co-primary and Selected Secondary Efficacy Endpoints at End of Treatment for Pooled Studies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Mirabegron 50 mg</th>
<th>Pooled studies (046, 047, 074)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of incontinence episodes per 24 hours (FAS-I) (Co-primary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>878</td>
<td>862</td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>2.73</td>
<td>2.71</td>
<td></td>
</tr>
<tr>
<td>Mean change from baseline†</td>
<td>-1.10</td>
<td>-1.49</td>
<td></td>
</tr>
<tr>
<td>Mean difference from placebo† (95% CI)</td>
<td>--</td>
<td>-0.40 (-0.58, -0.21)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>--</td>
<td>&lt;0.001#</td>
<td></td>
</tr>
<tr>
<td>Mean number of micturitions per 24 hours (FAS) (Co-primary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>1328</td>
<td>1324</td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>11.58</td>
<td>11.70</td>
<td></td>
</tr>
<tr>
<td>Mean change from baseline†</td>
<td>-1.20</td>
<td>-1.75</td>
<td></td>
</tr>
<tr>
<td>Mean difference from placebo† (95% CI)</td>
<td>--</td>
<td>-0.55 (-0.75, -0.36)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>--</td>
<td>&lt;0.001#</td>
<td></td>
</tr>
<tr>
<td>Mean volume voided (mL) per micturition (FAS) (Secondary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>1328</td>
<td>1322</td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>159.2</td>
<td>159.0</td>
<td></td>
</tr>
<tr>
<td>Mean change from baseline†</td>
<td>9.4</td>
<td>21.4</td>
<td></td>
</tr>
<tr>
<td>Mean difference from placebo† (95% CI)</td>
<td>--</td>
<td>11.9 (8.3, 15.5)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>--</td>
<td>&lt;0.001#</td>
<td></td>
</tr>
<tr>
<td>Mean level of urgency (FAS) (Secondary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>1325</td>
<td>1323</td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>2.39</td>
<td>2.42</td>
<td></td>
</tr>
<tr>
<td>Mean change from baseline†</td>
<td>-0.15</td>
<td>-0.26</td>
<td></td>
</tr>
<tr>
<td>Mean difference from placebo† (95% CI)</td>
<td>--</td>
<td>-0.11 (-0.16, -0.07)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>--</td>
<td>&lt;0.001#</td>
<td></td>
</tr>
<tr>
<td>Mean number of urgency incontinence episodes per 24 hours (FAS-I) (Secondary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>858</td>
<td>834</td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>2.42</td>
<td>2.42</td>
<td></td>
</tr>
<tr>
<td>Mean change from baseline†</td>
<td>-0.98</td>
<td>-1.38</td>
<td></td>
</tr>
<tr>
<td>Mean difference from placebo† (95% CI)</td>
<td>--</td>
<td>-0.40 (-0.57, -0.23)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>--</td>
<td>&lt;0.001#</td>
<td></td>
</tr>
<tr>
<td>Mean number of episodes with urgency grades 3 or 4 per 24 hours (FAS) (Secondary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>1324</td>
<td>1320</td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>5.61</td>
<td>5.80</td>
<td></td>
</tr>
<tr>
<td>Mean change from baseline†</td>
<td>-1.29</td>
<td>-1.93</td>
<td></td>
</tr>
<tr>
<td>Mean difference from placebo† (95% CI)</td>
<td>--</td>
<td>-0.64 (-0.89, -0.39)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>--</td>
<td>&lt;0.001#</td>
<td></td>
</tr>
<tr>
<td>Treatment satisfaction – visual analogue scale (FAS) (Secondary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>1195</td>
<td>1189</td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>4.87</td>
<td>4.82</td>
<td></td>
</tr>
<tr>
<td>Mean change from baseline†</td>
<td>1.25</td>
<td>2.01</td>
<td></td>
</tr>
<tr>
<td>Mean difference from placebo† (95% CI)</td>
<td>--</td>
<td>0.76 (0.52, 1.01)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>--</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
</tbody>
</table>

Pooled studies consisted of studies 046 (Europe / Australia), 047 (North America [NA]) and 074 (Europe / NA).

† Least squares mean adjusted for baseline, gender, and study.

* Statistically significantly superior compared to placebo at the 0.05 level without multiplicity adjustment.

# Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment.
FAS: Full analysis set, all randomized patients who took at least 1 dose of double blind study drug and who had a micturition measurement in the baseline diary and at least 1 post-baseline visit diary with a micturition measurement.

FAS-I: Subset of FAS who also had at least 1 incontinence episode in the baseline diary.

CI: Confidence Interval

Table 2: Co-primary and Selected Secondary Efficacy Endpoints at End of Treatment for Studies 046, 047 and 074

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study 046</th>
<th>Study 047</th>
<th>Study 074</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Mirabegron 50 mg</td>
<td>Tolterodine ER 4 mg</td>
</tr>
<tr>
<td>Mean number of incontinence episodes per 24 hours (FAS-I) (Co-primary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>291</td>
<td>293</td>
<td>300</td>
</tr>
<tr>
<td>Mean baseline</td>
<td>2.67</td>
<td>2.83</td>
<td>2.63</td>
</tr>
<tr>
<td>Mean change from baseline†</td>
<td>-1.17</td>
<td>-1.57</td>
<td>-1.27</td>
</tr>
<tr>
<td>Mean difference from placebo†</td>
<td>--</td>
<td>-0.41</td>
<td>-0.10</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>--</td>
<td>(-0.72, -0.09)</td>
<td>(-0.42, 0.21)</td>
</tr>
<tr>
<td>p-value</td>
<td>--</td>
<td>0.003#</td>
<td>0.11</td>
</tr>
<tr>
<td>Mean number of micturitions per 24 hours (FAS) (Co-primary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>480</td>
<td>473</td>
<td>475</td>
</tr>
<tr>
<td>Mean baseline</td>
<td>11.71</td>
<td>11.65</td>
<td>11.55</td>
</tr>
<tr>
<td>Mean change from baseline†</td>
<td>-1.34</td>
<td>-1.93</td>
<td>-1.59</td>
</tr>
<tr>
<td>Mean difference from placebo†</td>
<td>--</td>
<td>-0.60</td>
<td>-0.25</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>--</td>
<td>(-0.90, -0.29)</td>
<td>(-0.55, 0.06)</td>
</tr>
<tr>
<td>p-value</td>
<td>--</td>
<td>&lt;0.001#</td>
<td>0.11</td>
</tr>
<tr>
<td>Mean volume voided (mL) per micturition (FAS) (Secondary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>480</td>
<td>472</td>
<td>475</td>
</tr>
<tr>
<td>Mean baseline</td>
<td>156.7</td>
<td>161.1</td>
<td>158.6</td>
</tr>
<tr>
<td>Mean change from baseline†</td>
<td>12.3</td>
<td>24.2</td>
<td>25.0</td>
</tr>
<tr>
<td>Mean difference from placebo†</td>
<td>--</td>
<td>11.9</td>
<td>12.6</td>
</tr>
<tr>
<td>Parameter</td>
<td>Study 046</td>
<td>Study 047</td>
<td>Study 074</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>Mirabegron 50 mg</td>
<td>Tolterodine ER 4 mg</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>--</td>
<td>(6.3, 17.4)</td>
<td>(7.1, 18.2)</td>
</tr>
<tr>
<td>p-value</td>
<td>--</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

**Mean level of urgency (FAS) (Secondary)**

<table>
<thead>
<tr>
<th>n</th>
<th>Placebo</th>
<th>Mirabegron 50 mg</th>
<th>Tolterodine ER 4 mg</th>
<th>Placebo</th>
<th>Mirabegron 50 mg</th>
<th>Placebo</th>
<th>Mirabegron 50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline</td>
<td>2.37</td>
<td>2.40</td>
<td>2.41</td>
<td>2.45</td>
<td>2.45</td>
<td>2.36</td>
<td>2.41</td>
</tr>
<tr>
<td>Mean change from baseline†</td>
<td>-0.22</td>
<td>-0.31</td>
<td>-0.29</td>
<td>-0.08</td>
<td>-0.19</td>
<td>-0.15</td>
<td>-0.29</td>
</tr>
<tr>
<td>Mean difference from placebo†</td>
<td>--</td>
<td>-0.09</td>
<td>-0.07</td>
<td>--</td>
<td>-0.11</td>
<td>--</td>
<td>-0.14</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>--</td>
<td>(-0.17, -0.02)</td>
<td>(-0.15, 0.01)</td>
<td>--</td>
<td>(-0.18, -0.04)</td>
<td>--</td>
<td>(-0.22, -0.06)</td>
</tr>
<tr>
<td>p-value</td>
<td>--</td>
<td>0.018*</td>
<td>0.085</td>
<td>--</td>
<td>0.004*</td>
<td>--</td>
<td>&lt;0.001‡</td>
</tr>
</tbody>
</table>

**Mean number of urgency incontinence episodes per 24 hours (FAS-I) (Secondary)**

<table>
<thead>
<tr>
<th>n</th>
<th>Placebo</th>
<th>Mirabegron 50 mg</th>
<th>Tolterodine ER 4 mg</th>
<th>Placebo</th>
<th>Mirabegron 50 mg</th>
<th>Placebo</th>
<th>Mirabegron 50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline</td>
<td>2.43</td>
<td>2.52</td>
<td>2.37</td>
<td>2.56</td>
<td>2.42</td>
<td>2.24</td>
<td>2.33</td>
</tr>
<tr>
<td>Mean change from baseline†</td>
<td>-1.11</td>
<td>-1.46</td>
<td>-1.18</td>
<td>-0.89</td>
<td>-1.32</td>
<td>-0.95</td>
<td>-1.33</td>
</tr>
<tr>
<td>Mean difference from placebo†</td>
<td>--</td>
<td>-0.35</td>
<td>-0.07</td>
<td>--</td>
<td>-0.43</td>
<td>--</td>
<td>-0.39</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>--</td>
<td>(-0.65, -0.05)</td>
<td>(-0.38, 0.23)</td>
<td>--</td>
<td>(-0.72, -0.15)</td>
<td>--</td>
<td>(-0.69, -0.08)</td>
</tr>
<tr>
<td>p-value</td>
<td>--</td>
<td>0.003*</td>
<td>0.26</td>
<td>--</td>
<td>0.005*</td>
<td>--</td>
<td>0.002‡</td>
</tr>
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</table>

**Mean number of episodes with urgency grades 3 or 4 per 24 hours (FAS) (Secondary)**

<table>
<thead>
<tr>
<th>n</th>
<th>Placebo</th>
<th>Mirabegron 50 mg</th>
<th>Tolterodine ER 4 mg</th>
<th>Placebo</th>
<th>Mirabegron 50 mg</th>
<th>Placebo</th>
<th>Mirabegron 50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline</td>
<td>5.78</td>
<td>5.72</td>
<td>5.79</td>
<td>5.61</td>
<td>5.90</td>
<td>5.42</td>
<td>5.80</td>
</tr>
<tr>
<td>Mean change from baseline†</td>
<td>-1.65</td>
<td>-2.25</td>
<td>-2.07</td>
<td>-0.82</td>
<td>-1.57</td>
<td>-1.35</td>
<td>-1.94</td>
</tr>
<tr>
<td>Mean difference from placebo†</td>
<td>--</td>
<td>-0.60</td>
<td>-0.42</td>
<td>--</td>
<td>-0.75</td>
<td>--</td>
<td>-0.59</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>--</td>
<td>(-1.02, -0.18)</td>
<td>(-0.84, -0.00)</td>
<td>--</td>
<td>(-1.20, -0.30)</td>
<td>--</td>
<td>(-1.01, -0.16)</td>
</tr>
<tr>
<td>p-value</td>
<td>--</td>
<td>0.005*</td>
<td>0.050*</td>
<td>--</td>
<td>0.001*</td>
<td>--</td>
<td>0.007‡</td>
</tr>
<tr>
<td>Parameter</td>
<td>Study 046</td>
<td>Study 047</td>
<td>Study 074</td>
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<td>-----------</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>Mirabegron 50 mg</td>
<td>Tolterodine ER 4 mg</td>
<td>Placebo</td>
<td>Mirabegron 50 mg</td>
<td>Placebo</td>
<td>Mirabegron 50 mg</td>
</tr>
<tr>
<td>n</td>
<td>428</td>
<td>414</td>
<td>425</td>
<td>390</td>
<td>387</td>
<td>377</td>
<td>388</td>
</tr>
<tr>
<td>Mean baseline</td>
<td>4.11</td>
<td>3.95</td>
<td>3.87</td>
<td>5.5</td>
<td>5.4</td>
<td>5.13</td>
<td>5.13</td>
</tr>
<tr>
<td>Mean change from baseline†</td>
<td>1.89</td>
<td>2.55</td>
<td>2.44</td>
<td>0.7</td>
<td>1.5</td>
<td>1.05</td>
<td>1.88</td>
</tr>
<tr>
<td>Mean difference from placebo†</td>
<td>--</td>
<td>0.66</td>
<td>0.55</td>
<td>--</td>
<td>0.8</td>
<td>--</td>
<td>0.83</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>--</td>
<td>(0.25, 1.07)</td>
<td>(0.14, 0.95)</td>
<td>--</td>
<td>(0.4, 1.3)</td>
<td>--</td>
<td>(0.41, 1.25)</td>
</tr>
<tr>
<td>p-value</td>
<td>--</td>
<td>0.001*</td>
<td>0.008*</td>
<td>--</td>
<td>&lt;0.001*</td>
<td>--</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

† Least squares mean adjusted for baseline, gender and geographical region.
* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.
# Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.
‡ Not statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment.
FAS: Full analysis set, all randomized patients who took at least 1 dose of double blind study drug and who had a micturition measurement in the baseline diary and at least 1 post-baseline visit diary with a micturition measurement.
FAS-I: Subset of FAS who also had at least 1 incontinence episode in the baseline diary.

Betmiga 50 mg once daily was effective at the first measured time point of week 4, and efficacy was maintained throughout the 12-week treatment period. A randomized, active controlled, long term study demonstrated that efficacy was maintained throughout a 1-year treatment period.

**Subjective improvement in health-related quality of life measurements**

In the three 12-week phase 3 double blind, placebo controlled studies, treatment of the symptoms of OAB with mirabegron once daily resulted in a statistically significant improvement over placebo on the following health-related quality of life measures: treatment satisfaction and symptom bother.

**Efficacy in patients with or without prior OAB antimuscarinic therapy**

Efficacy was demonstrated in patients with and without prior OAB antimuscarinic therapy. In addition mirabegron showed efficacy in patients who previously discontinued OAB antimuscarinic therapy due to insufficient effect (see Table 3).
Table 3: Co-primary efficacy endpoints for patients with prior OAB antimuscarinic therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pooled studies (046, 047, 074)</th>
<th>Study 046</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Mirabegron 50 mg</td>
</tr>
<tr>
<td>Patients with prior OAB antimuscarinic therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number of incontinence episodes per 24 hours (FAS-I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>518</td>
<td>506</td>
</tr>
<tr>
<td>Mean baseline</td>
<td>2.93</td>
<td>2.98</td>
</tr>
<tr>
<td>Mean change from baseline†</td>
<td>-0.92</td>
<td>-1.49</td>
</tr>
<tr>
<td>Mean difference from placebo†</td>
<td>--</td>
<td>-0.57</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>--</td>
<td>(-0.81, -0.33)</td>
</tr>
<tr>
<td>Mean number of micturitions per 24 hours (FAS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>704</td>
<td>688</td>
</tr>
<tr>
<td>Mean baseline</td>
<td>11.53</td>
<td>11.78</td>
</tr>
<tr>
<td>Mean change from baseline†</td>
<td>-0.93</td>
<td>-1.67</td>
</tr>
<tr>
<td>Mean difference from placebo†</td>
<td>--</td>
<td>-0.74</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>--</td>
<td>(-1.01, -0.47)</td>
</tr>
<tr>
<td>Patients with prior OAB antimuscarinic therapy who discontinued due to insufficient effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number of incontinence episodes per 24 hours (FAS-I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>336</td>
<td>335</td>
</tr>
<tr>
<td>Mean baseline</td>
<td>3.03</td>
<td>2.94</td>
</tr>
<tr>
<td>Mean change from baseline†</td>
<td>-0.86</td>
<td>-1.56</td>
</tr>
<tr>
<td>Mean difference from placebo†</td>
<td>--</td>
<td>-0.70</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>--</td>
<td>(-1.01, -0.38)</td>
</tr>
<tr>
<td>Mean number of micturitions per 24 hours (FAS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>466</td>
<td>464</td>
</tr>
<tr>
<td>Mean baseline</td>
<td>11.60</td>
<td>11.67</td>
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<tr>
<td>Mean change from baseline†</td>
<td>-0.86</td>
<td>-1.54</td>
</tr>
<tr>
<td>Mean difference from placebo†</td>
<td>--</td>
<td>-0.67</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>--</td>
<td>(-0.99, -0.36)</td>
</tr>
</tbody>
</table>

Pooled studies consisted of 046 (Europe / Australia), 047 (North America [NA]) and 074 (Europe / NA).

† Least squares mean adjusted for baseline, gender, study, subgroup, and subgroup by treatment interaction for Pooled Studies and least squares mean adjusted for baseline, gender, geographical region, subgroup, and subgroup by treatment interaction for Study 046.

FAS: Full analysis set, all randomized patients who took at least 1 dose of double blind study drug and who had a micturition measurement in the baseline diary and at least 1 post-baseline visit diary with a micturition measurement.

FAS-I: Subset of FAS who also had at least 1 incontinence episode in the baseline diary.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Betmiga in one or more subsets of the paediatric population in “Treatment of idiopathic overactive bladder” and “Treatment of neurogenic detrusor overactivity” (see section 4.2 for information on paediatric use).
5.2 Pharmacokinetic properties

Absorption

After oral administration of mirabegron in healthy volunteers mirabegron is absorbed to reach peak plasma concentrations ($C_{\text{max}}$) between 3 and 4 hours. The absolute bioavailability increased from 29% at a dose of 25 mg to 35% at a dose of 50 mg. Mean $C_{\text{max}}$ and AUC increased more than dose proportionally over the dose range. In the overall population of males and females, a 2-fold increase in dose from 50 mg to 100 mg mirabegron increased $C_{\text{max}}$ and AUC by approximately 2.9- and 2.6-fold, respectively, whereas a 4-fold increase in dose from 50 mg to 200 mg mirabegron increased $C_{\text{max}}$ and AUC by approximately 8.4- and 6.5-fold. Steady state concentrations are achieved within 7 days of once daily dosing with mirabegron. After once daily administration, plasma exposure of mirabegron at steady state is approximately double that seen after a single dose.

Effect of food on absorption

Co-administration of a 50 mg tablet with a high-fat meal reduced mirabegron $C_{\text{max}}$ and AUC by 45% and 17%, respectively. A low-fat meal decreased mirabegron $C_{\text{max}}$ and AUC by 75% and 51%, respectively. In the phase 3 studies, mirabegron was administered with or without food and demonstrated both safety and efficacy. Therefore, mirabegron can be taken with or without food at the recommended dose.

Distribution

Mirabegron is extensively distributed. The volume of distribution at steady state ($V_{\infty}$) is approximately 1670 L. Mirabegron is bound (approximately 71%) to human plasma proteins, and shows moderate affinity for albumin and alpha-1 acid glycoprotein. Mirabegron distributes to erythrocytes. In vitro erythrocyte concentrations of $^{14}$C-mirabegron were about 2-fold higher than in plasma.

Biotransformation

Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Mirabegron is the major circulating component following a single dose of $^{14}$C-mirabegron. Two major metabolites were observed in human plasma; both are phase 2 glucuronides representing 16% and 11% of total exposure. These metabolites are not pharmacologically active.

Based on in vitro studies, mirabegron is unlikely to inhibit the metabolism of co-administered medicinal products metabolized by the following cytochrome P450 enzymes: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2E1 because mirabegron did not inhibit the activity of these enzymes at clinically relevant concentrations. Mirabegron did not induce CYP1A2 or CYP3A. Mirabegron is predicted not to cause clinically relevant inhibition of OCT-mediated drug transport.

Although in vitro studies suggest a role for CYP2D6 and CYP3A4 in the oxidative metabolism of mirabegron, in vivo results indicate that these isozymes play a limited role in the overall elimination. In vitro and ex vivo studies have shown the involvement from butyrylcholinesterase, UGT and possibly alcohol dehydrogenase (ADH) in the metabolism of mirabegron, in addition to CYP3A4 and CYP2D6.

CYP2D6 polymorphism

In healthy subjects who are genotypically poor metabolisers of CYP2D6 substrates (used as a surrogate for CYP2D6 inhibition), mean $C_{\text{max}}$ and AUC$_{\text{inf}}$ of a single 160 mg dose of a mirabegron IR formulation were 14% and 19% higher than in extensive metabolisers, indicating that CYP2D6 genetic polymorphism has minimal impact on the mean plasma exposure to mirabegron. Interaction of mirabegron with a known CYP2D6 inhibitor is not expected and was not studied. No dose adjustment is needed for mirabegron when administered with CYP2D6 inhibitors or in patients who are CYP2D6 poor metabolisers.
Elimination

Total body clearance (CL_{tot}) from plasma is approximately 57 L/h. The terminal elimination half-life (t_{1/2}) is approximately 50 hours. Renal clearance (CL_R) is approximately 13 L/h, which corresponds to nearly 25% of CL_{tot}. Renal elimination of mirabegron is primarily through active tubular secretion along with glomerular filtration. The urinary excretion of unchanged mirabegron is dose-dependent and ranges from approximately 6.0% after a daily dose of 25 mg to 12.2% after a daily dose of 100 mg. Following the administration of 160 mg ^14C-mirabegron to healthy volunteers, approximately 55% of the radiolabel was recovered in the urine and 34% in the faeces. Unchanged mirabegron accounted for 45% of the urinary radioactivity, indicating the presence of metabolites. Unchanged mirabegron accounted for the majority of the faecal radioactivity.

Age

The C_{max} and AUC of mirabegron and its metabolites following multiple oral doses in elderly volunteers (≥ 65 years) were similar to those in younger volunteers (18–45 years).

Gender

The C_{max} and AUC are approximately 40% to 50% higher in females than in males. Gender differences in C_{max} and AUC are attributed to differences in body weight and bioavailability.

Race

The pharmacokinetics of mirabegron are not influenced by race.

Renal impairment

Following single dose administration of 100 mg Betmiga in volunteers with mild renal impairment (eGFR-MDRD 60 to 89 mL/min/1.73 m^2), mean mirabegron C_{max} and AUC were increased by 6% and 31% relative to volunteers with normal renal function. In volunteers with moderate renal impairment (eGFR-MDRD 30 to 59 mL/min/1.73 m^2), C_{max} and AUC were increased by 23% and 66%, respectively. In volunteers with severe renal impairment (eGFR-MDRD 15 to 29 mL/min/1.73 m^2), mean C_{max} and AUC values were 92% and 118% higher. Mirabegron has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m^2 or patients requiring haemodialysis).

Hepatic impairment

Following single dose administration of 100 mg Betmiga in volunteers with mild hepatic impairment (Child-Pugh Class A), mean mirabegron C_{max} and AUC were increased by 9% and 19% relative to volunteers with normal hepatic function. In volunteers with moderate hepatic impairment (Child-Pugh Class B), mean C_{max} and AUC values were 175% and 65% higher. Mirabegron has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

5.3 Preclinical safety data

Preclinical studies have identified target organs of toxicity that are consistent with clinical observations. Transient increases in liver enzymes and hepatocyte changes (necrosis and decrease in glycogen particles) were seen in rats. An increase in heart rate was observed in rats, rabbits, dogs and monkeys. Genotoxicity and carcinogenicity studies have shown no genotoxic or carcinogenic potential in vivo.

No effects on fertility were seen at sub-lethal doses (human equivalent dose was 19-fold higher than the maximum human recommended dose (MHRD)). The main findings in rabbit embryofetal development studies included malformations of the heart (dilated aorta, cardiomegaly) at systemic exposures 36-fold higher than observed at the MHRD. In addition, malformations of the lung (absent
accessory lobe of the lung) and increased post-implantation loss were observed in the rabbit at systemic exposures 14-fold higher than observed at the MHRD, while in the rat reversible effects on ossification were noted (wavy ribs, delayed ossification, decreased number of ossified sternebrae, metacarpi or metatarsi) at systemic exposures 22-fold higher than observed at the MHRD. The observed embryofetal toxicity occurred at doses associated with maternal toxicity. The cardiovascular malformations observed in the rabbit were shown to be mediated via activation of the beta 1-adrenoceptor.

Pharmacokinetic studies performed with radio-labelled mirabegron have shown that the parent compound and/or its metabolites are excreted in the milk of rats at levels that were approximately 1.7-fold higher than plasma levels at 4 hours post administration (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet
Macrogols
Hydroxypropylcellulose
Butylhydroxytoluene
Magnesium stearate

Film coating Betmiga 25 mg prolonged-release tablets
Hypromellose
Macrogol
Iron oxide yellow (E172)
Iron oxide red (E172)

Film coating Betmiga 50 mg prolonged-release tablets
Hypromellose
Macrogol
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
Shelf life after first opening of the bottle: 6 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu-Alu blisters in cartons containing 10, 20, 30, 50, 60, 90, 100 or 200 tablets.
HDPE bottles with child-resistant polypropylene (PP) caps and a silica gel desiccant containing 90 tablets.

Not all pack sizes may be marketed.
6.6  **Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7.  **MARKETING AUTHORISATION HOLDER**

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

8.  **MARKETING AUTHORISATION NUMBER(S)**

EU/1/12/809/001 - 018

9.  **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 20 December 2012

10.  **DATE OF REVISION OF THE TEXT**

{DD/MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON FOR BLISTERS

1. **NAME OF THE MEDICINAL PRODUCT**

Betmiga 25 mg prolonged-release tablets
mirabegron

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 25 mg of mirabegron

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

<table>
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5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Swallow the tablet whole. Do not crush.
Read the package leaflet before use.
Oral use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

betmiga 25 mg
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Betmiga 50 mg prolonged-release tablets
mirabegron

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg of mirabegron

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 prolonged-release tablets
20 prolonged-release tablets
30 prolonged-release tablets
50 prolonged-release tablets
60 prolonged-release tablets
90 prolonged-release tablets
100 prolonged-release tablets
200 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow the tablet whole. Do not crush.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS
**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Astellas Pharma Europe B.V.  
Sylviusweg 62  
2333 BE Leiden  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

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**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

betmiga 50 mg
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<td>mirabegron</td>
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### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

#### BLISTER

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<td><strong>4. BATCH NUMBER</strong></td>
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<tr>
<td><strong>5. OTHER</strong></td>
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### PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON FOR BOTTLES

1. **NAME OF THE MEDICINAL PRODUCT**
   - Betmiga 25 mg prolonged-release tablets
   - mirabegron

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   - Each tablet contains 25 mg of mirabegron

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**
   - 90 prolonged-release tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   - Swallow the tablet whole. Do not crush.
   - Read the package leaflet before use.
   - Oral use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**
   - Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**
   - Use within 6 months after opening of the bottle

9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/809/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

betmiga 25 mg
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON FOR BOTTLES

1. NAME OF THE MEDICINAL PRODUCT

Betmiga 50 mg prolonged-release tablets mirabegron

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg of mirabegron

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

90 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow the tablet whole. Do not crush. Read the package leaflet before use. Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP Use within 6 months after opening of the bottle

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
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Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/809/014

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

betmiga 50 mg
| PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING |
| BOTTLE LABEL |

1. **NAME OF THE MEDICINAL PRODUCT**

Betmiga 25 mg prolonged-release tablets
mirabegron

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 25 mg of mirabegron

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

90 prolonged-release tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Swallow the tablet whole. Do not crush.
Read the package leaflet before use.
Oral use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP
Use within 6 months after opening of the bottle

9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/809/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
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<th>PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING BOTTLE LABEL</th>
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<td><strong>2. STATEMENT OF ACTIVE SUBSTANCE(S)</strong></td>
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<td>Each tablet contains 50 mg of mirabegron</td>
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<td><strong>3. LIST OF EXCIPIENTS</strong></td>
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<td><strong>4. PHARMACEUTICAL FORM AND CONTENTS</strong></td>
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<td>90 prolonged-release tablets</td>
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<td><strong>5. METHOD AND ROUTE(S) OF ADMINISTRATION</strong></td>
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<tr>
<td>Swallow the tablet whole. Do not crush. Read the package leaflet before use. Oral use.</td>
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<tr>
<td><strong>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</strong></td>
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<td>Keep out of the sight and reach of children.</td>
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<td>EXP Use within 6 months after opening of the bottle</td>
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Sylviusweg 62
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EU/1/12/809/014

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE


16. INFORMATION IN BRAILLE
B. PACKAGE LEAFLET
This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:
1. What Betmiga is and what it is used for
2. What you need to know before you use Betmiga
3. How to use Betmiga
4. Possible side effects
5. How to store Betmiga
6. Contents of the pack and other information

1. What Betmiga is and what it is used for

Betmiga contains the active substance mirabegron. It is a bladder muscle relaxant (a so called beta 3-adrenoceptor agonist), which reduces the activity of an overactive bladder and treats the related symptoms.

Betmiga is used to treat the symptoms of an overactive bladder in adults such as:
- suddenly needing to empty your bladder (called urgency)
- having to empty your bladder more than usual (called increased urinary frequency)
- not being able to control when to empty your bladder (called urgency incontinence)

2. What you need to know before you use Betmiga

Do not use Betmiga:
- if you are allergic to mirabegron or any of the other ingredients of this medicine (listed in section 6)
- if you have very high uncontrolled blood pressure.

Warnings and precautions
Talk to your doctor or pharmacist before using Betmiga:
- if you have trouble emptying your bladder or you have a weak urine stream or if you take other medicines for the treatment of overactive bladder such as anticholinergic medicines
- if you have kidney or liver problems. Your doctor may need to reduce your dose or may tell you not to use Betmiga, especially if you are taking other medicines such asitraconazole, ketoconazole, ritonavir or clarithromycin. Tell your doctor about the medicines that you take.
- if you have an ECG (heart tracing) abnormality known as QT prolongation or you are taking any medicine known to cause this such as
Mirabegron may cause your blood pressure to increase or make your blood pressure worse if you have a history of high blood pressure. It is recommended that your doctor check your blood pressure while you are taking Mirabegron.

**Children and adolescents**

Do not give this medicine to children and adolescents under the age of 18 years because the safety and efficacy of Betmiga in this age group has not been established.

**Other medicines and Betmiga**

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Betmiga may affect the way other medicines work, and other medicines may affect how this medicine works.

- Tell your doctor if you use thioridazine (a medicine for mental illness), propafenone or flecainide (medicines for abnormal heart rhythm), imipramine or desipramine (medicines used for depression). These specific medicines may require dose adjustment by your doctor.

- Tell your doctor if you use digoxin (a medicine for heart failure or abnormal heart rhythm). Blood levels of this medicine are measured by your doctor. If the blood level is out of range, your doctor may adjust the dose of digoxin.

- Tell your doctor if you use dabigatran etexilate (a medicine which is used to reduce the risk of brain or body vessel obstruction by blood clot formation in adult patients with an abnormal heart beat (atrial fibrillation) and additional risk factors). This medicine may require dose adjustment by your doctor.

**Pregnancy and breast-feeding**

If you are pregnant, think you may be pregnant or are planning to have a baby you should not use Betmiga.

If you are breast feeding, ask your doctor or pharmacist for advice before using this medicine. It is likely that this medicine passes into your breast milk. You and your doctor should decide if you should use Betmiga or breastfeed. You should not do both.

**Driving and using machines**

There is no information to suggest that this medicine affects your ability to drive or use machines.

### 3. How to use Betmiga

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one 50 mg tablet by mouth once daily. If you have kidney or liver problems, your doctor may need to reduce your dose to one 25 mg tablet by mouth once daily. You should take this medicine with liquids and swallow the tablet whole. Do not crush or chew the tablet. Betmiga can be taken with or without food.

**If you take more Betmiga than you should**

If you have taken more tablets than you have been told to take, or if someone else accidentally takes your tablets, contact your doctor, pharmacist or hospital for advice immediately.
Symptoms of overdose may include a forceful beating of the heart, an increased pulse rate or an increased blood pressure.

**If you forget to take Betmiga**

If you forget to take your medicine, take the missed dose as soon as you remember. If it is less than 6 hours before your next scheduled dose, skip the dose and continue to take your medicine at the usual time.

Do not take a double dose to make up for a forgotten dose. If you miss several doses, tell your doctor and follow the advice given to you.

**If you stop using Betmiga**

Do not stop treatment with Betmiga early if you do not see an immediate effect. Your bladder might need some time to adapt. You should continue taking your tablets. Do not stop taking them when your bladder condition improves. Stopping treatment may result in recurrence of symptoms of overactive bladder.

Do not stop taking Betmiga without talking to your doctor first, as your overactive bladder symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

**4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most serious side effects may include irregular heart beat (atrial fibrillation). This is an uncommon side effect (may affect up to 1 in 100 people), but if this side effect occurs, immediately stop taking the medicine and seek urgent medical advice.

If you get headaches, especially sudden, migraine-like (throbbing) headaches, tell your doctor. These may be signs of severely elevated blood pressure.

Other side effects include:

**Common side effects (may affect up to 1 in 10 people)**
- Increased heart rate (tachycardia)
- Infection of the structures that carry urine (urinary tract infections)
- Nausea
- Constipation
- Headache
- Diarrhoea
- Dizziness

**Uncommon side effects (may affect up to 1 in 100 people)**
- Bladder infection (cystitis)
- Feeling your heartbeat (palpitations)
- Vaginal infection
- Indigestion (dyspepsia)
- Infection of the stomach (gastritis)
- Swelling of the joints
- Itching of the vulva or vagina (vulvovaginal pruritus)
- Increased blood pressure
- Increase in liver enzymes (GGT, AST and ALT).
- Itching, rash or hives (urticaria, rash, rash macular, rash papular, pruritus)

Rare side effects (may affect up to 1 in 1,000 people)
- Swelling of the eyelid (eyelid oedema)
- Swelling of the lip (lip oedema)
- Swelling of the deeper layers of the skin caused by a build-up of fluid, which can affect any part of the body including the face, tongue or throat and may cause difficulty in breathing (angioedema)
- Small purple spots on the skin (purpura)
- Inflammation of small blood vessels mainly affecting the skin (leukocytoclastic vasculitis).
- Inability to completely empty the bladder (urinary retention)

Very Rare (may affect up to 1 in 10,000 people)
- Hypertensive crisis

Not known (frequency cannot be estimated from the available data)
- Insomnia

Betmiga may increase your chances of not being able to empty your bladder if you have bladder outlet obstruction or if you are taking other medicines to treat overactive bladder. Tell your doctor right away if you are unable to empty your bladder.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Betmiga

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, blister or bottle after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

After first opening of the bottle, the tablets can be stored for 6 months.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Betmiga contains
- The active substance is mirabegron. Each tablet contains 25 mg or 50 mg of mirabegron.
- The other ingredients are:
  Tablet core: Macrogols, hydroxypropylcellulose, butylhydroxytoluene, magnesium stearate
  Film-coating: Hypromellose, macrogol, iron oxide yellow (E172), iron oxide red (E172) (25 mg tablet only).
What Betmiga looks like and contents of the pack
Betmiga 25 mg prolonged release film-coated tablets are oval, brown film-coated tablets, debossed with the company logo and “325” on the same side.
Betmiga 50 mg prolonged release film-coated tablets are oval, yellow film-coated tablets, debossed with the company logo and “355” on the same side.

Betmiga is available in aluminium-aluminium blister in packs containing 10, 20, 30, 50, 60, 90, 100 or 200 tablets and in high density polyethylene (HDPE) bottles with silica gel desiccant and child-resistant closures containing 90 tablets.

Not all pack sizes may be available in your country. The bottle may not be available in your country.

Marketing Authorisation Holder and Manufacturer
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Detailed information on this medicine is available on the European Medicines Agency website:
Annex IV
Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)
**Scientific conclusions**

Taking into account the PRAC Assessment Report on the PSUR for mirabegron, the scientific conclusions of CHMP are as follows:

In post-marketing data, 305 cases of dizziness were reported. Two third had a compatible timeline and half of patients developed dizziness within 7 days of administering mirabegron. Some cases had positive dechallenge and rechallenge. Therefore, dizziness should be included in the section 4.8 of the SmPC.

An important number of constipation cases were reported, showing disproportionality criteria and compatible timelines. Therefore, constipation should be included in the section 4.8 of the SmPC.

Headache is one of the most frequent events reported with a positive timeline. 47.8% of the cases had positive dechallenge with a 2.2% positive rechallenge. Therefore, headache should be included in section 4.8 of the SmPC.

Several cases of diarrhoea were reported with a compatible timeline. At least 6 cases had a positive rechallenge. Therefore, diarrhoea should be included in section 4.8 of the SmPC.

In a cumulative review of hypertensive crisis cases, 3 of the 9 evaluable cases were associated with ischemic cardiac events: 2 with non-ST elevation myocardial infarction and 1 with coronary syndrome. In addition, 1 patient from the pre-authorisation phase was hospitalized due to hypertensive crisis. Therefore, despite of the limited number of cases, hypertensive crisis should be included in section 4.8 of the SmPC.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing mirabegron were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

**Grounds for the variation to the terms of the Marketing Authorisation(s)**

On the basis of the scientific conclusions for mirabegron the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing mirabegron is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation(s) should be varied.