

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## **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**

#### Overactive bladder in adults

Betmiga prolonged-release tablets are indicated for symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

#### Neurogenic detrusor overactivity in the paediatric population

Betmiga prolonged-release tablets are indicated for treatment of neurogenic detrusor overactivity (NDO) in paediatric patients aged 3 to less than 18 years.

### **4.2 Posology and method of administration**

#### Posology

#### Overactive bladder

*Adults (including elderly patients)*

The recommended dose is 50 mg once daily.

### Neurogenic detrusor overactivity in the paediatric population

Paediatric patients 3 to less than 18 years of age with NDO may be administered Betmiga prolonged-release tablets or Betmiga granules for prolonged-release oral suspension based on the body weight of the patient. The prolonged-release tablets may be administered to patients weighing 35 kg or more; the granules for prolonged-release oral suspension are recommended for patients below 35 kg. Patients administered 6 ml oral suspension dose may be switched to 25 mg tablet dose and patients administered 10 ml oral suspension dose may be switched to 50 mg tablet dose.

The recommended starting dose of Betmiga prolonged-release tablets is 25 mg once daily with food. If needed, the dose may be increased to a maximum dose of 50 mg once daily with food after 4 to 8 weeks. During long-term therapy, patients should be periodically evaluated for treatment continuation and for potential dose adjustment, at least annually or more frequently if indicated.

### Missed dose

Patients should be instructed to take any missed doses, unless more than 12 hours have passed since the missed dose. If more than 12 hours have passed, the missed dose can be skipped, and the next dose should be taken at the usual time.

### Special populations

#### *Renal and hepatic impairment*

Betmiga has not been studied in patients with end stage renal disease (ESRD) (estimated glomerular filtration rate (eGFR) < 15 ml/min/1.73 m<sup>2</sup>), patients requiring haemodialysis, or patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in these patient populations (see sections 4.4 and 5.2).

The following table provides the daily dosing recommendations for adult OAB patients with renal or hepatic impairment (see sections 4.4, 4.5 and 5.2).

**Table 1: Daily dosing recommendations for adult OAB patients with renal or hepatic impairment**

Parameter	Classification	Dose (mg)
Renal impairment <sup>(1)</sup>	Mild/Moderate*	50
	Severe**	25
	ESRD	Not recommended
Hepatic impairment <sup>(2)</sup>	Mild*	50
	Moderate**	25
	Severe	Not recommended

1. Mild/Moderate: eGFR 30 to 89 ml/min/1.73 m<sup>2</sup>; Severe: eGFR 15 to 29 ml/min/1.73 m<sup>2</sup>; ESRD: eGFR < 15 ml/min/1.73 m<sup>2</sup>.

2. Mild: Child-Pugh Class A; Moderate: Child-Pugh Class B; Severe: Child-Pugh Class C.

\* In patients with mild to moderate renal impairment or mild hepatic impairment concomitantly receiving strong CYP3A inhibitors, the recommended dose is no more than 25 mg.

\*\* Not recommended for use in patients with severe renal impairment or moderate hepatic impairment concomitantly receiving strong CYP3A inhibitors.

The following table provides the daily dosing recommendations for paediatric NDO patients aged 3 to less than 18 years with renal or hepatic impairment weighing 35 kg or more (see sections 4.4 and 5.2).

**Table 2: Daily dosing recommendations for paediatric NDO patients aged 3 to less than 18 years with renal or hepatic impairment weighing 35 kg or more**

Parameter	Classification	Starting dose (mg)	Maximum dose (mg)
Renal impairment <sup>(1)</sup>	Mild/Moderate*	25	50
	Severe**	25	25
	ESRD	Not recommended	
Hepatic impairment <sup>(2)</sup>	Mild*	25	50
	Moderate**	25	25
	Severe	Not recommended	

1. Mild/Moderate: eGFR 30 to 89 ml/min/1.73 m<sup>2</sup>; Severe: eGFR 15 to 29 ml/min/1.73 m<sup>2</sup>; ESRD: eGFR < 15 ml/min/1.73 m<sup>2</sup>. No dose adjustment is necessary for patients with mild to moderate renal impairment.

2. Mild: Child-Pugh Class A; Moderate: Child-Pugh Class B; Severe: Child-Pugh Class C.

\* In patients with mild to moderate renal impairment or mild hepatic impairment concomitantly receiving strong CYP3A inhibitors, the recommended dose is no more than the starting dose.

\*\* Not recommended for use in patients with severe renal impairment or moderate hepatic impairment concomitantly receiving strong CYP3A inhibitors.

#### *Gender*

No dose adjustment is necessary according to gender.

#### Paediatric population

##### Overactive bladder

The safety and efficacy of mirabegron in children below 18 years of age with OAB have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

##### Neurogenic detrusor overactivity

The safety and efficacy of mirabegron in children below 3 years of age have not yet been established.

#### Method of administration

##### *Overactive bladder in adults*

The tablet is to be taken with liquids, swallowed whole, and is not to be chewed, divided, or crushed. It may be taken with or without food.

##### *Neurogenic detrusor overactivity in the paediatric population*

The tablet is to be taken with liquids, swallowed whole, and is not to be chewed, divided, or crushed. It should be taken with food.

### **4.3 Contraindications**

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Severe uncontrolled hypertension defined as systolic blood pressure  $\geq$  180 mm Hg and/or diastolic blood pressure  $\geq$  110 mm Hg.

## 4.4 Special warnings and precautions for use

### Renal impairment

Betmiga has not been studied in patients with ESRD (eGFR < 15 ml/min/1.73 m<sup>2</sup>) 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 (eGFR 15 to 29 ml/min/1.73 m<sup>2</sup>); based on a pharmacokinetic study (see section 5.2) a dose of 25 mg once daily is recommended in this population. This medicinal product is not recommended for use in patients with severe renal impairment (eGFR 15 to 29 ml/min/1.73 m<sup>2</sup>) 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. This medicinal product is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors (see section 4.5).

### Hypertension

#### *Overactive bladder in adults*

Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with mirabegron, 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).

#### *Neurogenic detrusor overactivity in the paediatric population*

Mirabegron can increase blood pressure in paediatric patients. Blood pressure increases may be larger in children (3 to less than 12 years of age) than in adolescents (12 to less than 18 years of age). Blood pressure should be measured at baseline and periodically during treatment with mirabegron.

### 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 medicinal products for OAB

Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medicinal products for the treatment of OAB has been reported in post-marketing 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 medicinal products 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

#### *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 (eGFR 30 to 89 ml/min/1.73 m<sup>2</sup>) 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 (see section 4.2). Betmiga is not recommended in patients with severe renal impairment (eGFR 15 to 29 ml/min/1.73 m<sup>2</sup>) 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 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.

#### *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 C<sub>max</sub> and a 229% increase in AUC of a single dose of metoprolol. Multiple once daily dosing of mirabegron resulted in a 79% increase in C<sub>max</sub> 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  $C_{max}$  and AUC by 29% and 27%, respectively, of the P-gp substrate digoxin in healthy volunteers. For patients who are initiating a combination of mirabegron 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.

#### Paediatric population

Interaction studies have only been performed in adults.

### **4.6 Fertility, pregnancy and lactation**

#### Women of childbearing potential

Betmiga is not recommended in women of childbearing potential not using contraception.

#### Pregnancy

There are no or limited amount of data from the use of mirabegron in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Betmiga is not recommended during pregnancy.

#### 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 used 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 8 433 adult patients with OAB, of which 5 648 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 this medicinal product, 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 adult 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 adults with OAB in the three 12-week phase 3 double blind, placebo-controlled studies.

The frequency of adverse reactions is defined as follows: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1\ 000$  to  $< 1/100$ ); rare ( $\geq 1/10\ 000$  to  $< 1/1\ 000$ ); very rare ( $< 1/10\ 000$ ) and not known (cannot be established from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.



<b>MedDRA System organ class</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Very rare</b>	<b>Not known (cannot be estimated from the available data)</b>
Infections and infestations	Urinary tract infection	Vaginal infection Cystitis			
Psychiatric disorders					Insomnia* Confusional state*
Nervous system disorders	Headache* Dizziness*				
Eye disorders			Eyelid oedema		
Cardiac disorders	Tachycardia	Palpitation Atrial fibrillation			
Vascular disorders				Hypertensive crisis*	
Gastrointestinal disorders	Nausea* Constipation* Diarrhoea*	Dyspepsia Gastritis	Lip oedema		
Hepatobiliary disorders		GGT increased AST increased ALT increased			
Skin and subcutaneous tissue disorders		Urticaria Rash Rash macular Rash papular Pruritus	Leukocytoclastic vasculitis Purpura Angioedema*		
Musculoskeletal and connective tissue disorders		Joint swelling			
Renal and urinary disorders			Urinary retention*		
Reproductive system and breast disorders		Vulvovaginal pruritus			
Investigations		Blood pressure increased			

\*observed during post-marketing experience

#### Paediatric population

The safety of mirabegron tablets and oral suspension was evaluated in 86 paediatric patients aged 3 to less than 18 years with neurogenic detrusor overactivity in a 52-week, open-label, baseline-controlled, multicentre, dose titration study. The most commonly reported adverse reactions observed in the paediatric population were urinary tract infection, constipation, and nausea.

In the paediatric patients with NDO, no severe adverse reactions were reported.

The safety of mirabegron tablets and oral suspension was evaluated in 26 paediatric patients aged 5 to less than 18 years of age with overactive bladder in a 12-week, double-blind, randomised, multicentre, parallel group, placebo-controlled sequential dose titration study. The most commonly reported adverse reactions observed in the paediatric population were nasopharyngitis, fatigue and mood swing.

Overall, the safety profile in children and adolescents is similar to that observed in adults.

#### 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 adult 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 adult 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, drugs for urinary frequency and incontinence, 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 adult 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.

### *Effects on blood pressure in paediatric patients with NDO*

Mirabegron can increase blood pressure in paediatric patients. Blood pressure increases may be larger in children (3 to less than 12 years of age) than in adolescents (12 to less than 18 years of age). Blood pressure should be measured at baseline and periodically during treatment with mirabegron.

### *Effect on intraocular pressure (IOP)*

Mirabegron 100 mg once daily did not increase IOP in healthy adult 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

#### *Overactive bladder in adult patients*

Efficacy of mirabegron was evaluated in three phase 3 randomised, 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 medicinal products. 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 3 and 4).

**Table 3: Co-primary and selected secondary efficacy endpoints at end of treatment for pooled studies in adults**

Parameter	Pooled studies (046, 047, 074)	
	Placebo	Mirabegron 50 mg
<b>Mean number of incontinence episodes per 24 hours (FAS-I) (Co-primary)</b>		
n	878	862
Mean baseline	2.73	2.71
Mean change from baseline*	-1.10	-1.49
Mean difference from placebo* (95% CI)	--	-0.40 (-0.58, -0.21)
p-value	--	< 0.001 <sup>‡</sup>
<b>Mean number of micturitions per 24 hours (FAS) (Co-primary)</b>		
n	1 328	1 324
Mean baseline	11.58	11.70
Mean change from baseline*	-1.20	-1.75
Mean difference from placebo* (95% CI)	--	-0.55 (-0.75, -0.36)
p-value	--	< 0.001 <sup>‡</sup>
<b>Mean volume voided (ml) per micturition (FAS) (Secondary)</b>		
n	1 328	1 322
Mean baseline	159.2	159.0
Mean change from baseline*	9.4	21.4
Mean difference from placebo* (95% CI)	--	11.9 (8.3, 15.5)
p-value	--	< 0.001 <sup>‡</sup>
<b>Mean level of urgency (FAS) (Secondary)</b>		
n	1 325	1 323
Mean baseline	2.39	2.42
Mean change from baseline*	-0.15	-0.26
Mean difference from placebo* (95% CI)	--	-0.11 (-0.16, -0.07)
p-value	--	< 0.001 <sup>‡</sup>
<b>Mean number of urgency incontinence episodes per 24 hours (FAS-I) (Secondary)</b>		
n	858	834
Mean baseline	2.42	2.42
Mean change from baseline*	-0.98	-1.38
Mean difference from placebo* (95% CI)	--	-0.40 (-0.57, -0.23)
p-value	--	< 0.001 <sup>‡</sup>
<b>Mean number of episodes with urgency grades 3 or 4 per 24 hours (FAS) (Secondary)</b>		
n	1 324	1 320
Mean baseline	5.61	5.80
Mean change from baseline*	-1.29	-1.93
Mean difference from placebo* (95% CI)	--	-0.64 (-0.89, -0.39)
p-value	--	< 0.001 <sup>‡</sup>
<b>Treatment satisfaction – visual analogue scale (FAS) (Secondary)</b>		
n	1 195	1 189
Mean baseline	4.87	4.82
Mean change from baseline*	1.25	2.01
Mean difference from placebo* (95% CI)	--	0.76 (0.52, 1.01)
p-value	--	< 0.001 <sup>†</sup>

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 randomised 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 4: Co-primary and selected secondary efficacy endpoints at end of treatment for studies 046, 047 and 074 in adults**

Parameter	Study 046			Study 047		Study 074	
	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg
<b>Mean number of incontinence episodes per 24 hours (FAS-I) (Co-primary)</b>							
n	291	293	300	325	312	262	257
Mean baseline	2.67	2.83	2.63	3.03	2.77	2.43	2.51
Mean change from baseline*	-1.17	-1.57	-1.27	-1.13	-1.47	-0.96	-1.38
Mean difference from placebo*	--	-0.41	-0.10	--	-0.34	--	-0.42
95% Confidence Interval	--	(-0.72, -0.09)	(-0.42, 0.21)	--	(-0.66, -0.03)	--	(-0.76, -0.08)
p-value	--	0.003 <sup>‡</sup>	0.11	--	0.026 <sup>‡</sup>	--	0.001 <sup>‡</sup>
<b>Mean number of micturitions per 24 hours (FAS) (Co-primary)</b>							
n	480	473	475	433	425	415	426
Mean baseline	11.71	11.65	11.55	11.51	11.80	11.48	11.66
Mean change from baseline*	-1.34	-1.93	-1.59	-1.05	-1.66	-1.18	-1.60
Mean difference from placebo*	--	-0.60	-0.25	--	-0.61	--	-0.42
95% Confidence Interval	--	(-0.90, -0.29)	(-0.55, 0.06)	--	(-0.98, -0.24)	--	(-0.76, -0.08)
p-value	--	< 0.001 <sup>‡</sup>	0.11	--	0.001 <sup>‡</sup>	--	0.015 <sup>‡</sup>

Parameter	Study 046			Study 047		Study 074	
	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg
<b>Mean volume voided (ml) per micturition (FAS) (Secondary)</b>							
n	480	472	475	433	424	415	426
Mean baseline	156.7	161.1	158.6	157.5	156.3	164.0	159.3
Mean change from baseline*	12.3	24.2	25.0	7.0	18.2	8.3	20.7
Mean difference from placebo*	--	11.9	12.6	--	11.1	--	12.4
95% Confidence Interval	--	(6.3, 17.4)	(7.1, 18.2)	--	(4.4, 17.9)	--	(6.3, 18.6)
p-value	--	< 0.001‡	< 0.001†	--	0.001‡	--	< 0.001‡
<b>Mean level of urgency (FAS) (Secondary)</b>							
n	480	472	473	432	425	413	426
Mean baseline	2.37	2.40	2.41	2.45	2.45	2.36	2.41
Mean change from baseline*	-0.22	-0.31	-0.29	-0.08	-0.19	-0.15	-0.29
Mean difference from placebo*	--	-0.09	-0.07	--	-0.11	--	-0.14
95% Confidence Interval	--	(-0.17, -0.02)	(-0.15, 0.01)	--	(-0.18, -0.04)	--	(-0.22, -0.06)
p-value	--	0.018†	0.085	--	0.004†	--	< 0.001§
<b>Mean number of urgency incontinence episodes per 24 hours (FAS-I) (Secondary)</b>							
n	283	286	289	319	297	256	251
Mean baseline	2.43	2.52	2.37	2.56	2.42	2.24	2.33
Mean change from baseline*	-1.11	-1.46	-1.18	-0.89	-1.32	-0.95	-1.33
Mean difference from placebo*	--	-0.35	-0.07	--	-0.43	--	-0.39
95% Confidence Interval	--	(-0.65, -0.05)	(-0.38, 0.23)	--	(-0.72, -0.15)	--	(-0.69, -0.08)
p-value	--	0.003†	0.26	--	0.005†	--	0.002§

Parameter	Study 046			Study 047		Study 074	
	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg
<b>Mean number of episodes with urgency grades 3 or 4 per 24 hours (FAS) (Secondary)</b>							
n	479	470	472	432	424	413	426
Mean baseline	5.78	5.72	5.79	5.61	5.90	5.42	5.80
Mean change from baseline*	-1.65	-2.25	-2.07	-0.82	-1.57	-1.35	-1.94
Mean difference from placebo*	--	-0.60	-0.42	--	-0.75	--	-0.59
95% Confidence Interval	--	(-1.02, -0.18)	(-0.84, -0.00)	--	(-1.20, -0.30)	--	(-1.01, -0.16)
p-value	--	0.005†	0.050†	--	0.001†	--	0.007§
<b>Treatment satisfaction – visual analogue scale (FAS) (Secondary)</b>							
n	428	414	425	390	387	377	388
Mean baseline	4.11	3.95	3.87	5.5	5.4	5.13	5.13
Mean change from baseline*	1.89	2.55	2.44	0.7	1.5	1.05	1.88
Mean difference from placebo*	--	0.66	0.55	--	0.8	--	0.83
95% Confidence Interval	--	(0.25, 1.07)	(0.14, 0.95)	--	(0.4, 1.3)	--	(0.41, 1.25)
p-value	--	0.001†	0.008†	--	< 0.001†	--	< 0.001†

\* 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 randomised 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 randomised, 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 5).

**Table 5: Co-primary efficacy endpoints for adult patients with prior OAB antimuscarinic therapy**

Parameter	Pooled studies (046, 047, 074)		Study 046		
	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg
<b>Patients with prior OAB antimuscarinic therapy</b>					
<b>Mean number of incontinence episodes per 24 hours (FAS-I)</b>					
n	518	506	167	164	160
Mean baseline	2.93	2.98	2.97	3.31	2.86
Mean change from baseline*	-0.92	-1.49	-1.00	-1.48	-1.10
Mean difference from placebo*	--	-0.57	--	-0.48	-0.10
95% Confidence Interval	--	(-0.81, -0.33)	--	(-0.90, -0.06)	(-0.52, 0.32)
<b>Mean number of micturitions per 24 hours (FAS)</b>					
n	704	688	238	240	231
Mean baseline	11.53	11.78	11.90	11.85	11.76
Mean change from baseline*	-0.93	-1.67	-1.06	-1.74	-1.26
Mean difference from placebo*	--	-0.74	--	-0.68	-0.20
95% Confidence Interval	--	(-1.01, -0.47)	--	(-1.12, -0.25)	(-0.64, 0.23)
<b>Patients with prior OAB antimuscarinic therapy who discontinued due to insufficient effect</b>					
<b>Mean number of incontinence episodes per 24 hours (FAS-I)</b>					
n	336	335	112	105	102
Mean baseline	3.03	2.94	3.15	3.50	2.63
Mean change from baseline*	-0.86	-1.56	-0.87	-1.63	-0.93
Mean difference from placebo*	--	-0.70	--	-0.76	-0.06
95% Confidence Interval	--	(-1.01, -0.38)	--	(-1.32, -0.19)	(-0.63, 0.50)
<b>Mean number of micturitions per 24 hours (FAS)</b>					
n	466	464	159	160	155
Mean baseline	11.60	11.67	11.89	11.49	11.99
Mean change from baseline*	-0.86	-1.54	-1.03	-1.62	-1.11
Mean difference from placebo*	--	-0.67	--	-0.59	-0.08
95% Confidence Interval	--	(-0.99, -0.36)	--	(-1.15, -0.04)	(-0.64, 0.47)

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 randomised 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.

### *Neurogenic detrusor overactivity in paediatric patients*

Efficacy of mirabegron tablets and oral suspension was evaluated in a 52-week, open-label, baseline-controlled, multicentre, dose titration study for the treatment of NDO in paediatric patients. Patients had a diagnosis of NDO with involuntary detrusor contractions with detrusor pressure increase greater than 15 cm H<sub>2</sub>O and performed clean intermittent catheterisation (CIC). Patients  $\geq 35$  kg received tablets and patients  $< 35$  kg (or  $\geq 35$  kg but unable to tolerate tablets) received oral suspension. For all patients, mirabegron was administered orally once daily with food. The starting dose was a 25 mg tablet or between 3-6 ml of oral suspension (depending on patient weight). This dose was up-titrated to 50 mg tablet or between 6-11 ml of oral suspension (depending on body weight). The dose titration period was a maximum of 8 weeks followed by a dose maintenance period of at least 52 weeks.

A total of 86 patients aged 3 to less than 18 years of age received mirabegron. Of these, 71 patients completed treatment through week 24 and 70 completed 52 weeks of treatment. A total of 68 patients had valid urodynamic measurements for evaluation of efficacy. The study population included 39 (45.3%) males and 47 (54.7%) females. The optimised maintenance dose within this study population included 94% of patients at the maximum dose, and 6% of patients at the starting dose.

The most common (in greater than 10% of all patients) background medical conditions related to NDO in children and adolescents included in the study were congenital central nervous system anomaly (54.5% and 48.4%, respectively), meningomyelocele (27.3% and 19.4%, respectively), and spina bifida (10.9% and 12.9%, respectively). In adolescents, 12.9% had a spinal cord injury.

The primary efficacy endpoint was change from baseline in maximum cystometric capacity (MCC) after 24 weeks of mirabegron treatment. Improvements in MCC were observed in all patient groups (see Table 6).

**Table 6: Primary efficacy endpoint in paediatric patients with NDO**

Parameter	Children aged 3 to < 12 years (N=43)* Mean (SD)	Adolescents aged 12 to < 18 years (N=25)* Mean (SD)
<b>Maximum cystometric capacity (ml)</b>		
Baseline	158.6 (94.5)	238.9 (99.1)
Week 24	230.7 (129.1)	352.1 (125.2)
Change from baseline	72.0 (87.0)	113.2 (82.9)
95% Confidence Interval	(45.2, 98.8)	(78.9, 147.4)

\* N is the number of patients who took at least one dose and provided valid values for MCC at baseline and week 24.

The secondary efficacy endpoints were change from baseline in bladder compliance, number of overactive detrusor contractions, detrusor pressure at end of bladder-filling, bladder volume prior to first detrusor contraction, maximum catheterised urine volume per day, and number of leakage episodes per day after 24 weeks of mirabegron treatment (see Table 7).

**Table 7: Secondary efficacy endpoints in paediatric patients with NDO**

Parameter	Children aged 3 to < 12 years (N=43)* Mean (SD)	Adolescents aged 12 to < 18 years (N=25)* Mean (SD)
<b>Bladder compliance (ml/cm H<sub>2</sub>O)†</b>		
Baseline	14.5 (50.7)	11.0 (10.0)
Week 24	29.6 (52.8)	23.8 (15.3)
Change from baseline	14.6 (42.0)	13.5 (15.0)
95% Confidence Interval	(-0.3, 29.5)	(6.7, 20.4)
<b>Number of overactive detrusor contractions (&gt; 15 cm H<sub>2</sub>O)†</b>		
Baseline	3.0 (3.8)	2.0 (2.9)
Week 24	1.0 (2.2)	1.4 (2.3)
Change from baseline	-1.8 (4.1)	-0.7 (3.8)
95% Confidence Interval	(-3.2, -0.4)	(-2.4, 0.9)
<b>Detrusor pressure (cm H<sub>2</sub>O) at end of bladder-filling†</b>		
Baseline	42.2 (26.2)	38.6 (17.9)
Week 24	25.6 (21.2)	27.8 (27.8)
Change from baseline	-18.1 (19.9)	-13.1 (19.9)
95% Confidence Interval	(-24.8, -11.3)	(-22.0, -4.3)
<b>Bladder volume prior to first detrusor contraction (&gt; 15 cm H<sub>2</sub>O)†</b>		
Baseline	115.8 (87.0)	185.2 (121.2)
Week 24	207.9 (97.8)	298.7 (144.4)
Change from baseline	93.1 (88.1)	121.3 (159.8)
95% Confidence Interval	(64.1, 122.1)	(53.8, 188.8)
<b>Maximum catheterised urine volume per day (ml)†</b>		
Baseline	300.1 (105.7)	367.5 (119.0)
Week 24	345.9 (84.6)	449.9 (146.6)
Change from baseline	44.2 (98.3)	81.3 (117.7)
95% Confidence Interval	(13.2, 75.2)	(30.4, 132.3)
<b>Number of leakage episodes per day†</b>		
Baseline	3.2 (3.7)	1.8 (1.7)
Week 24	0.7 (1.2)	0.9 (1.2)
Change from baseline	-2.0 (3.2)	-1.0 (1.1)
95% Confidence Interval	(-3.2, -0.7)	(-1.5, -0.5)

\* N is the number of patients who took at least one dose and provided valid values for MCC at baseline and week 24.

† Number of patients (children/adolescents) with data available for both baseline and week 24; Bladder compliance: n=33/21; Number of overactive detrusor contractions: n=36/22; Detrusor pressure at end of bladder-filling: n=36/22; Bladder volume prior to first detrusor contraction: n=38/24; Maximum catheterised urine volume per day: n=41/23; Number of leakage episodes per day: n=26/21.

Patient- or clinician-reported questionnaire endpoints included acceptability, change from baseline in the Pediatric Incontinence Questionnaire (PIN-Q), change from baseline in the Patient Global Impression of Severity Scale (PGI-S), and Clinician Global Impression of Change (CGI-C) (see Table 8).

**Table 8: Patient- or clinician-reported questionnaire endpoints in paediatric patients with NDO**

Parameter	Children aged 3 to < 12 years (N=43)* Mean (SD)	Adolescents aged 12 to < 18 years (N=25)* Mean (SD)
<b>Pediatric Incontinence Questionnaire (PIN-Q) score†</b>		
Baseline	30.8 (15.7)	29.4 (14.6)
Week 24	30.6 (15.2)	25.2 (15.5)
Change from baseline	2.0 (10.5)	-4.9 (14.1)
95% Confidence Interval	(-2.4, 6.4)	(-11.3, 1.5)
<b>Total Patient Global Impression of Severity Scale (PGI-S) score†</b>		
Baseline	2.2 (0.8)	2.3 (0.9)
Week 24	2.6 (0.8)	3.0 (0.7)
Change from baseline	0.3 (1.2)	0.6 (1.0)
95% Confidence Interval	(-0.1, 0.8)	(0.1, 1.0)
<b>Total Clinician Global Impression of Change (CGI-C) at week 24, N (%)†</b>		
Very Much Improved	6 (14.6%)	10 (41.7%)
Much Improved	24 (58.5%)	7 (29.2%)
Minimally Improved	6 (14.6%)	5 (20.8%)
No Change	4 (9.8%)	1 (4.2%)
Minimally Worse	1 (2.4%)	1 (4.2%)
Much Worse	0	0
Very Much Worse	0	0

\* N is the number of patients who took at least one dose and provided valid values for MCC at baseline and week 24.

† Number of patients (children/adolescents) with data available for both baseline and week 24. PIN-Q score: n=24/21, Total PGI-S score: n=25/22; Total CGI-C at week 24: n=41/24.

## *Paediatric population*

### *Overactive bladder*

Efficacy of mirabegron tablets and oral suspension was evaluated in a 12-week, double-blind, randomised, multicentre, parallel group, placebo-controlled sequential dose titration study for the treatment of OAB in paediatric patients (5 to less than 18 years of age). Patients  $\geq 35$  kg received tablets and patients  $< 35$  kg (or  $\geq 35$  kg but unable to swallow tablets) received oral suspension. For all patients, mirabegron was administered orally once daily with food. The starting dose was a 25 mg tablet or between 3-6 ml of oral suspension (depending on patient weight). This dose was up-titrated to 50 mg tablet or between 6-11 ml of oral suspension (depending on patient weight). Dose titration to the higher dose was conducted after 4 weeks on treatment, unless the investigator decided otherwise.

A total of 23 children (aged 5 to less than 12 years) and 3 adolescents (aged 12 to less than 18 years of age) received study drug: 13 subjects received placebo and 13 subjects received mirabegron. Ten of the 12 subjects in the placebo group and 9 of 11 subjects in the mirabegron group completed the study through 12 weeks of treatment.

The primary efficacy endpoint was the change from baseline in the mean number of micturitions per 24 hours after 12 weeks of treatment and was assessed only in children (aged 5 to less than 12 years). Due to the small number of subjects, a proper assessment of the efficacy endpoints was not possible, and the observed results were inconclusive.

The adjusted LS mean (SEM) change from baseline to week 12/end of treatment in the frequency of micturition events per 24 hours was -3.84 (0.89) in children on placebo and -1.62 (0.89) in children on mirabegron. The LS mean (SEM) difference between treatment groups (placebo minus mirabegron) was not statistically significant: 2.22 (1.34) (90% CI: -0.15, 4.59;  $P = 0.121$ ).

The European Medicines Agency has waived the obligation to submit the results of studies with Betmiga in all subsets of the paediatric population in “Treatment of idiopathic overactive bladder” (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

### Absorption

#### *Adults*

After oral administration of mirabegron in healthy volunteers mirabegron is absorbed to reach peak plasma concentrations ( $C_{max}$ ) 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  $C_{max}$  and AUC increased more than dose proportionally over the dose range. In the overall adult population of males and females, a 2-fold increase in dose from 50 mg to 100 mg mirabegron increased  $C_{max}$  and  $AUC_{tau}$  by approximately 2.9- and 2.6-fold, respectively, whereas a 4-fold increase in dose from 50 mg to 200 mg mirabegron increased  $C_{max}$  and  $AUC_{tau}$  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.

#### *Paediatric population*

The median  $T_{max}$  of mirabegron following oral administration of a single dose of mirabegron tablets or oral suspension in patients under fed state was 4-5 hours. Population pharmacokinetic analysis predicted that the median  $T_{max}$  of mirabegron tablets or oral suspension at steady-state was 3-4 hours.

The bioavailability of the oral suspension formulation is lower than that of the tablet. The ratio of the population mean exposure ( $AUC_{tau}$ ) of the oral suspension to the tablet is approximately 45%.

## Effect of food on absorption

### *Adults*

Co-administration of a 50 mg tablet with a high-fat meal reduced mirabegron  $C_{\max}$  and AUC by 45% and 17%, respectively. A low-fat meal decreased mirabegron  $C_{\max}$  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.

### *Paediatric population*

The population pharmacokinetic model predicted that the patients receiving mirabegron in the fed state would have 44.7% of steady-state  $AUC_{\tau}$  relative to an equal dose administered in the fasted state. This value is consistent with the  $AUC_{\text{inf}}$  results seen in the single-dose food effects studies for mirabegron. In the phase 3 paediatric study, mirabegron was administered with food and demonstrated both safety and efficacy. Dosing recommendations are based upon the exposures expected in the fed state. Therefore, in paediatric patients, mirabegron should be taken with food at the recommended dose.

## Distribution

### *Adults*

Mirabegron is extensively distributed. The volume of distribution at steady-state ( $V_{ss}$ ) is approximately 1 670 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  $^{14}\text{C}$ -mirabegron were about 2-fold higher than in plasma.

### *Paediatric population*

Mirabegron volume of distribution was relatively large and increased with increasing body weight in accordance with allometric principles based on population pharmacokinetic analysis. Age, sex and patient population had no impact on volume of distribution after accounting for potential differences in body weight.

## Biotransformation

Mirabegron is metabolised via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Mirabegron is the major circulating component following a single dose of  $^{14}\text{C}$ -mirabegron. Two major metabolites were observed in adult 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 metabolised 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 adult subjects who are genotypically poor metabolisers of CYP2D6 substrates (used as a surrogate for CYP2D6 inhibition), mean  $C_{\max}$  and  $AUC_{\inf}$  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 adult patients who are CYP2D6 poor metabolisers.

### Elimination

#### *Adults*

Total body clearance ( $CL_{\text{tot}}$ ) 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  $CL_{\text{tot}}$ . 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  $^{14}\text{C}$ -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.

#### *Paediatric population*

Mirabegron clearance was predicted to increase in patients with increasing body weight in accordance with allometric principles based on population pharmacokinetic analysis. The apparent clearance parameter was impacted significantly by dose, formulation, and food effects on relative bioavailability. Values of apparent clearance were highly variable but generally similar between children and adolescents, despite body weight differences, because of these effects on bioavailability.

### Age

#### *Adults*

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

#### *Paediatric population*

In patients 3 to less than 18 years of age, age was not predicted to have any impact on key mirabegron pharmacokinetic parameters after accounting for differences in body weight. Models including age did not result in meaningful improvements to the paediatric population pharmacokinetic model, indicating that inclusion of body weight was sufficient to address differences in mirabegron pharmacokinetics due to age.

### Gender

#### *Adults*

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.

#### *Paediatric population*

Gender has no meaningful impact on mirabegron pharmacokinetics in the paediatric population from 3 to less than 18 years of age.

## Race

The pharmacokinetics of mirabegron in adults are not influenced by race.

## Renal impairment

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

## Hepatic impairment

Following single dose administration of 100 mg Betmiga in adult volunteers with mild hepatic impairment (Child-Pugh Class A), mean mirabegron C<sub>max</sub> and AUC were increased by 9% and 19% relative to adult volunteers with normal hepatic function. In adult volunteers with moderate hepatic impairment (Child-Pugh Class B), mean C<sub>max</sub> 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**

Pre-clinical 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 and reduced plasma leptin levels were noted. 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*.

Mirabegron had no discernible effect on gonadotropic or sex steroid hormone levels. In addition, 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.

The overall safety profile seen in juvenile rats was comparable to that observed in adult animals. Juvenile rats orally administered mirabegron for 13 weeks showed elevated liver enzymes with an increase in liver weights without histopathological findings at systemic exposures approximately 12-fold higher than the projected human systemic exposure in children. Repeat dose safety studies performed in juvenile rats showed no effect on physical development or sexual maturation. Mirabegron administration from weaning through sexual maturation had no effect on mating ability, fertility or embryofetal development. Mirabegron administration increased lipolysis and food consumption and decreased body weight gain in juvenile rats.

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

Macrogol 8000 and 2 000 000  
Hydroxypropylcellulose  
Butylhydroxytoluene  
Magnesium stearate

#### Film coating

##### *Betmiga 25 mg prolonged-release tablets:*

Hypromellose 2910, 6 mPa.s  
Macrogol 8000  
Iron oxide yellow (E172)  
Iron oxide red (E172)

##### *Betmiga 50 mg prolonged-release tablets:*

Hypromellose 2910, 6 mPa.s  
Macrogol 8000  
Iron oxide yellow (E172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **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.

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 - 006

EU/1/12/809/008 - 013

EU/1/12/809/015 - 018

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

Date of first authorisation: 20 December 2012

Date of latest renewal: 18 September 2017

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

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

## **1. NAME OF THE MEDICINAL PRODUCT**

Betmiga 8 mg/ml granules for prolonged-release oral suspension

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

One bottle contains 8.3 g of mirabegron granules for prolonged-release oral suspension (830 mg of mirabegron).

After reconstitution, one bottle contains 105 ml of oral suspension. Each ml of oral suspension contains 8 mg of mirabegron.

### Excipient(s) with known effect

Each ml of oral suspension contains 0.5 mg ethyl parahydroxybenzoate (E214).

Each ml of oral suspension contains 1.4 mg methyl parahydroxybenzoate (E218).

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Granules for prolonged-release oral suspension.

Yellowish white granules.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Betmiga granules for prolonged-release oral suspension is indicated for treatment of neurogenic detrusor overactivity (NDO) in paediatric patients aged 3 to less than 18 years.

### **4.2 Posology and method of administration**

#### Posology

Paediatric patients 3 to less than 18 years of age with NDO may be administered Betmiga granules for prolonged-release oral suspension or Betmiga prolonged-release tablets based on the body weight of the patient.

The recommended dose of Betmiga granules for prolonged-release oral suspension is determined based on patient weight and should be administered once daily with food. Treatment should be initiated at the recommended starting dose. Thereafter, the dose may be increased to the lowest effective dose. The maximum dose should not be exceeded. Patients who reach 35 kg or more while on treatment may be switched from oral suspension to tablet formulation if they can swallow tablets. Patients administered 6 ml oral suspension dose may be switched to 25 mg tablet dose and patients administered 10 ml oral suspension dose may be switched to 50 mg tablet dose. During long-term therapy, patients should be periodically evaluated for treatment continuation and for potential dose adjustment, at least annually or more frequently if indicated.

The following table provides the doses for oral suspension by body weight range.

**Table 1: Daily oral suspension dosing recommendations for paediatric NDO patients aged 3 to less than 18 years according to patient body weight**

Body weight range (kg)	Starting dose (ml)	Maximum dose (ml)
11 to < 22	3	6
22 to < 35	4	8
≥ 35	6	10

#### Missed dose

Patients should be instructed to take any missed doses, unless more than 12 hours have passed since the missed dose. If more than 12 hours have passed, the missed dose can be skipped, and the next dose should be taken at the usual time.

#### Special populations

##### *Renal and hepatic impairment*

Betmiga granules for prolonged-release oral suspension has not been studied in patients with end stage renal disease (ESRD) (estimated glomerular filtration rate (eGFR) < 15 ml/min/1.73 m<sup>2</sup>), patients requiring haemodialysis, or patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in these patient populations (see sections 4.4 and 5.2).

The following table provides the daily dosing recommendations for paediatric NDO patients aged 3 to less than 18 years with renal or hepatic impairment based on body weight (see sections 4.4 and 5.2).

**Table 2: Daily oral suspension dosing recommendations for paediatric NDO patients aged 3 to less than 18 years with renal or hepatic impairment according to patient body weight**

Parameter	Classification	Body weight range (kg)	Starting dose (ml)	Maximum dose (ml)
Renal impairment <sup>(1)</sup>	Mild/Moderate*	11 to < 22	3	6
		22 to < 35	4	8
		≥ 35	6	10
	Severe**	11 to < 22	3	3
		22 to < 35	4	4
		≥ 35	6	6
	ESRD	Not recommended		
Hepatic impairment <sup>(2)</sup>	Mild*	11 to < 22	3	6
		22 to < 35	4	8
		≥ 35	6	10
	Moderate**	11 to < 22	3	3
		22 to < 35	4	4
		≥ 35	6	6
	Severe	Not recommended		

1. Mild/Moderate: eGFR 30 to 89 ml/min/1.73 m<sup>2</sup>; Severe: eGFR 15 to 29 ml/min/1.73 m<sup>2</sup>; ESRD: eGFR < 15 ml/min/1.73 m<sup>2</sup>. No dose adjustment is necessary for patients with mild to moderate renal impairment.

2. Mild: Child-Pugh Class A; Moderate: Child-Pugh Class B; Severe: Child-Pugh Class C.

\* In patients with mild to moderate renal impairment or mild hepatic impairment concomitantly receiving strong CYP3A inhibitors, the recommended dose is no more than the starting dose.

\*\* Not recommended for use in patients with severe renal impairment or moderate hepatic impairment concomitantly receiving strong CYP3A inhibitors.

#### *Gender*

No dose adjustment is necessary according to gender.

## Paediatric population

### Overactive bladder

The safety and efficacy of mirabegron in children below 18 years of age with OAB have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

### Neurogenic detrusor overactivity

The safety and efficacy of mirabegron in children below 3 years of age have not yet been established.

## Method of administration

Mirabegron granules for prolonged-release oral suspension is intended for oral use and should be taken once daily with food.

The granules should be reconstituted with 100 ml water prior to administration. If a measuring cup is provided, it should be used to measure the water volume to use for reconstitution. Instructions on reconstitution of the medicinal product before administration are provided in section 6.6. After reconstitution, the oral suspension is pale brownish yellow suspension.

The oral syringe and adaptor provided with Betmiga granules for prolonged-release oral suspension should be used to measure and administer the correct dose.

## **4.3 Contraindications**

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Severe uncontrolled hypertension defined as systolic blood pressure  $\geq 180$  mm Hg and/or diastolic blood pressure  $\geq 110$  mm Hg.

## **4.4 Special warnings and precautions for use**

### Renal impairment

Mirabegron has not been studied in patients with ESRD ( $\text{eGFR} < 15 \text{ ml/min/1.73 m}^2$ ) 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 ( $\text{eGFR} 15$  to  $29 \text{ ml/min/1.73 m}^2$ ); based on a pharmacokinetic study (see section 5.2) a dose no more than the starting dose is recommended in this population. This medicinal product is not recommended for use in patients with severe renal impairment ( $\text{eGFR} 15$  to  $29 \text{ ml/min/1.73 m}^2$ ) concomitantly receiving strong CYP3A inhibitors (see section 4.5).

### Hepatic impairment

Mirabegron 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. This medicinal product 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 in paediatric patients. Blood pressure increases may be larger in children (3 to less than 12 years of age) than in adolescents (12 to less than 18 years of age). Blood pressure should be measured at baseline and periodically during treatment with mirabegron.

### Patients with congenital or acquired QT prolongation

Mirabegron, 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 medicinal products for overactive bladder (OAB)

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

### Excipients

Mirabegron granules for prolonged-release oral suspension contains ethyl parahydroxybenzoate (E214) and methyl parahydroxybenzoate (E218). This may cause allergic reactions (possibly delayed).

This medicinal product contains less than 1 mmol sodium (23 mg) per 10 ml of oral suspension, that is to say essentially 'sodium-free'.

## **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*

#### *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 mirabegron is combined with inhibitors of CYP3A and/or P-gp. However, in patients with mild to moderate renal impairment (eGFR 30 to 89 ml/min/1.73 m<sup>2</sup>) or mild hepatic impairment (Child-Pugh Class A)

concomitantly receiving strong CYP3A inhibitors, such as itraconazole, ketoconazole, ritonavir and clarithromycin, the recommended dose is no more than the starting dose (see section 4.2). Mirabegron is not recommended in patients with severe renal impairment (eGFR 15 to 29 ml/min/1.73 m<sup>2</sup>) 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 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.

#### *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 C<sub>max</sub> and a 229% increase in AUC of a single dose of metoprolol. Multiple once daily dosing of mirabegron resulted in a 79% increase in C<sub>max</sub> 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 C<sub>max</sub> and AUC by 29% and 27%, respectively, of the P-gp substrate digoxin in healthy volunteers. For patients who are initiating a combination of mirabegron 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 mirabegron 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.

#### Paediatric population

Interaction studies have only been performed in adults.

### **4.6 Fertility, pregnancy and lactation**

#### Women of childbearing potential

Betmiga granules for prolonged-release oral suspension is not recommended in women of childbearing potential not using contraception.

## Pregnancy

There are no or limited amount of data from the use of mirabegron in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Betmiga granules for prolonged-release oral suspension is not recommended during pregnancy.

## 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 granules for prolonged-release oral suspension should not be used 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 granules for prolonged-release oral suspension 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 mirabegron tablets was evaluated in 8 433 adult patients with OAB, of which 5 648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 622 patients received mirabegron 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 this medicinal product, 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 adult patients treated with mirabegron 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 mirabegron 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving mirabegron 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving mirabegron 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving mirabegron 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 adults with OAB in the three 12-week phase 3 double blind, placebo-controlled studies.

The frequency of adverse reactions is defined as follows: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1\ 000$  to  $< 1/100$ ); rare ( $\geq 1/10\ 000$  to  $< 1/1\ 000$ ); very rare ( $< 1/10\ 000$ ) and not known (cannot be established from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.



<b>MedDRA System organ class</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Very rare</b>	<b>Not known (cannot be estimated from the available data)</b>
Infections and infestations	Urinary tract infection	Vaginal infection Cystitis			
Psychiatric disorders					Insomnia* Confusional state*
Nervous system disorders	Headache* Dizziness*				
Eye disorders			Eyelid oedema		
Cardiac disorders	Tachycardia	Palpitation Atrial fibrillation			
Vascular disorders				Hypertensive crisis*	
Gastrointestinal disorders	Nausea* Constipation* Diarrhoea*	Dyspepsia Gastritis	Lip oedema		
Hepatobiliary disorders		GGT increased AST increased ALT increased			
Skin and subcutaneous tissue disorders		Urticaria Rash Rash macular Rash papular Pruritus	Leukocytoclastic vasculitis Purpura Angioedema*		
Musculoskeletal and connective tissue disorders		Joint swelling			
Renal and urinary disorders			Urinary retention*		
Reproductive system and breast disorders		Vulvovaginal pruritus			
Investigations		Blood pressure increased			

\*observed during post-marketing experience

#### Paediatric population

The safety of mirabegron tablets and oral suspension was evaluated in 86 paediatric patients aged 3 to less than 18 years with neurogenic detrusor overactivity in a 52-week, open-label, baseline-controlled, multicentre, dose titration study. The most commonly reported adverse reactions observed in the paediatric population were urinary tract infection, constipation, and nausea.

In the paediatric patients with NDO, no severe adverse reactions were reported.

The safety of mirabegron tablets and oral suspension was evaluated in 26 paediatric patients aged 5 to less than 18 years of age with overactive bladder in a 12-week, double-blind, randomised, multicentre,

parallel group, placebo-controlled sequential dose titration study. The most commonly reported adverse reactions observed in the paediatric population were nasopharyngitis, fatigue and mood swing.

Overall, the safety profile in children and adolescents is similar to that observed in adults.

#### 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 adult 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 adult 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, drugs for urinary frequency and incontinence, 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*

Mirabegron 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*

Mirabegron 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 adult patients with OAB*

In OAB patients (mean age of 59 years) across three 12-week phase 3 double blind, placebo-controlled studies receiving mirabegron 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.

### *Effects on blood pressure in paediatric patients with NDO*

Mirabegron can increase blood pressure in paediatric patients. Blood pressure increases may be larger in children (3 to less than 12 years of age) than in adolescents (12 to less than 18 years of age). Blood pressure should be measured at baseline and periodically during treatment with mirabegron.

### *Effect on intraocular pressure (IOP)*

Mirabegron 100 mg once daily did not increase IOP in healthy adult subjects after 56 days of treatment. In a phase 1 study assessing the effect of mirabegron 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

#### *Overactive bladder in adult patients*

Efficacy of mirabegron was evaluated in three phase 3 randomised, 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 medicinal products. 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 3 and 4).

**Table 3: Co-primary and selected secondary efficacy endpoints at end of treatment for pooled studies in adults**

Parameter	Pooled studies (046, 047, 074)	
	Placebo	Mirabegron 50 mg
<b>Mean number of incontinence episodes per 24 hours (FAS-I) (Co-primary)</b>		
n	878	862
Mean baseline	2.73	2.71
Mean change from baseline*	-1.10	-1.49
Mean difference from placebo* (95% CI)	--	-0.40 (-0.58, -0.21)
p-value	--	< 0.001‡
<b>Mean number of micturitions per 24 hours (FAS) (Co-primary)</b>		
n	1 328	1 324
Mean baseline	11.58	11.70
Mean change from baseline*	-1.20	-1.75
Mean difference from placebo* (95% CI)	--	-0.55 (-0.75, -0.36)
p-value	--	< 0.001‡
<b>Mean volume voided (ml) per micturition (FAS) (Secondary)</b>		
n	1 328	1 322
Mean baseline	159.2	159.0
Mean change from baseline*	9.4	21.4
Mean difference from placebo* (95% CI)	--	11.9 (8.3, 15.5)
p-value	--	< 0.001‡
<b>Mean level of urgency (FAS) (Secondary)</b>		
n	1 325	1 323
Mean baseline	2.39	2.42
Mean change from baseline*	-0.15	-0.26
Mean difference from placebo* (95% CI)	--	-0.11 (-0.16, -0.07)
p-value	--	< 0.001‡
<b>Mean number of urgency incontinence episodes per 24 hours (FAS-I) (Secondary)</b>		
n	858	834
Mean baseline	2.42	2.42
Mean change from baseline*	-0.98	-1.38
Mean difference from placebo* (95% CI)	--	-0.40 (-0.57, -0.23)
p-value	--	< 0.001‡
<b>Mean number of episodes with urgency grades 3 or 4 per 24 hours (FAS) (Secondary)</b>		
n	1 324	1 320
Mean baseline	5.61	5.80
Mean change from baseline*	-1.29	-1.93
Mean difference from placebo* (95% CI)	--	-0.64 (-0.89, -0.39)
p-value	--	< 0.001‡
<b>Treatment satisfaction – visual analogue scale (FAS) (Secondary)</b>		
n	1 195	1 189
Mean baseline	4.87	4.82
Mean change from baseline*	1.25	2.01
Mean difference from placebo* (95% CI)	--	0.76 (0.52, 1.01)
p-value	--	< 0.001†

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 randomised 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 4: Co-primary and selected secondary efficacy endpoints at end of treatment for studies 046, 047 and 074 in adults**

Parameter	Study 046			Study 047		Study 074	
	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg
<b>Mean number of incontinence episodes per 24 hours (FAS-I) (Co-primary)</b>							
n	291	293	300	325	312	262	257
Mean baseline	2.67	2.83	2.63	3.03	2.77	2.43	2.51
Mean change from baseline*	-1.17	-1.57	-1.27	-1.13	-1.47	-0.96	-1.38
Mean difference from placebo*	--	-0.41	-0.10	--	-0.34	--	-0.42
95% Confidence Interval	--	(-0.72, -0.09)	(-0.42, 0.21)	--	(-0.66, -0.03)	--	(-0.76, -0.08)
p-value	--	0.003‡	0.11	--	0.026‡	--	0.001‡
<b>Mean number of micturitions per 24 hours (FAS) (Co-primary)</b>							
n	480	473	475	433	425	415	426
Mean baseline	11.71	11.65	11.55	11.51	11.80	11.48	11.66
Mean change from baseline*	-1.34	-1.93	-1.59	-1.05	-1.66	-1.18	-1.60
Mean difference from placebo*	--	-0.60	-0.25	--	-0.61	--	-0.42
95% Confidence Interval	--	(-0.90, -0.29)	(-0.55, 0.06)	--	(-0.98, -0.24)	--	(-0.76, -0.08)
p-value	--	< 0.001‡	0.11	--	0.001‡	--	0.015‡

Parameter	Study 046			Study 047		Study 074	
	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg
<b>Mean volume voided (ml) per micturition (FAS) (Secondary)</b>							
n	480	472	475	433	424	415	426
Mean baseline	156.7	161.1	158.6	157.5	156.3	164.0	159.3
Mean change from baseline*	12.3	24.2	25.0	7.0	18.2	8.3	20.7
Mean difference from placebo*	--	11.9	12.6	--	11.1	--	12.4
95% Confidence Interval	--	(6.3, 17.4)	(7.1, 18.2)	--	(4.4, 17.9)	--	(6.3, 18.6)
p-value	--	< 0.001‡	< 0.001†	--	0.001‡	--	< 0.001‡
<b>Mean level of urgency (FAS) (Secondary)</b>							
n	480	472	473	432	425	413	426
Mean baseline	2.37	2.40	2.41	2.45	2.45	2.36	2.41
Mean change from baseline*	-0.22	-0.31	-0.29	-0.08	-0.19	-0.15	-0.29
Mean difference from placebo*	--	-0.09	-0.07	--	-0.11	--	-0.14
95% Confidence Interval	--	(-0.17, -0.02)	(-0.15, 0.01)	--	(-0.18, -0.04)	--	(-0.22, -0.06)
p-value	--	0.018†	0.085	--	0.004†	--	< 0.001§
<b>Mean number of urgency incontinence episodes per 24 hours (FAS-I) (Secondary)</b>							
n	283	286	289	319	297	256	251
Mean baseline	2.43	2.52	2.37	2.56	2.42	2.24	2.33
Mean change from baseline*	-1.11	-1.46	-1.18	-0.89	-1.32	-0.95	-1.33
Mean difference from placebo*	--	-0.35	-0.07	--	-0.43	--	-0.39
95% Confidence Interval	--	(-0.65, -0.05)	(-0.38, 0.23)	--	(-0.72, -0.15)	--	(-0.69, -0.08)
p-value	--	0.003†	0.26	--	0.005†	--	0.002§

Parameter	Study 046			Study 047		Study 074	
	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg
<b>Mean number of episodes with urgency grades 3 or 4 per 24 hours (FAS) (Secondary)</b>							
n	479	470	472	432	424	413	426
Mean baseline	5.78	5.72	5.79	5.61	5.90	5.42	5.80
Mean change from baseline*	-1.65	-2.25	-2.07	-0.82	-1.57	-1.35	-1.94
Mean difference from placebo*	--	-0.60	-0.42	--	-0.75	--	-0.59
95% Confidence Interval	--	(-1.02, -0.18)	(-0.84, -0.00)	--	(-1.20, -0.30)	--	(-1.01, -0.16)
p-value	--	0.005†	0.050†	--	0.001†	--	0.007§
<b>Treatment satisfaction – visual analogue scale (FAS) (Secondary)</b>							
n	428	414	425	390	387	377	388
Mean baseline	4.11	3.95	3.87	5.5	5.4	5.13	5.13
Mean change from baseline*	1.89	2.55	2.44	0.7	1.5	1.05	1.88
Mean difference from placebo*	--	0.66	0.55	--	0.8	--	0.83
95% Confidence Interval	--	(0.25, 1.07)	(0.14, 0.95)	--	(0.4, 1.3)	--	(0.41, 1.25)
p-value	--	0.001†	0.008†	--	< 0.001†	--	< 0.001†

\* 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 randomised 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.

Mirabegron 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 randomised, 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 5).

**Table 5: Co-primary efficacy endpoints for adult patients with prior OAB antimuscarinic therapy**

Parameter	Pooled studies (046, 047, 074)		Study 046		
	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg
<b>Patients with prior OAB antimuscarinic therapy</b>					
<b>Mean number of incontinence episodes per 24 hours (FAS-I)</b>					
n	518	506	167	164	160
Mean baseline	2.93	2.98	2.97	3.31	2.86
Mean change from baseline*	-0.92	-1.49	-1.00	-1.48	-1.10
Mean difference from placebo*	--	-0.57	--	-0.48	-0.10
95% Confidence Interval	--	(-0.81, -0.33)	--	(-0.90, -0.06)	(-0.52, 0.32)
<b>Mean number of micturitions per 24 hours (FAS)</b>					
n	704	688	238	240	231
Mean baseline	11.53	11.78	11.90	11.85	11.76
Mean change from baseline*	-0.93	-1.67	-1.06	-1.74	-1.26
Mean difference from placebo*	--	-0.74	--	-0.68	-0.20
95% Confidence Interval	--	(-1.01, -0.47)	--	(-1.12, -0.25)	(-0.64, 0.23)
<b>Patients with prior OAB antimuscarinic therapy who discontinued due to insufficient effect</b>					
<b>Mean number of incontinence episodes per 24 hours (FAS-I)</b>					
n	336	335	112	105	102
Mean baseline	3.03	2.94	3.15	3.50	2.63
Mean change from baseline*	-0.86	-1.56	-0.87	-1.63	-0.93
Mean difference from placebo*	--	-0.70	--	-0.76	-0.06
95% Confidence Interval	--	(-1.01, -0.38)	--	(-1.32, -0.19)	(-0.63, 0.50)
<b>Mean number of micturitions per 24 hours (FAS)</b>					
n	466	464	159	160	155
Mean baseline	11.60	11.67	11.89	11.49	11.99
Mean change from baseline*	-0.86	-1.54	-1.03	-1.62	-1.11
Mean difference from placebo*	--	-0.67	--	-0.59	-0.08
95% Confidence Interval	--	(-0.99, -0.36)	--	(-1.15, -0.04)	(-0.64, 0.47)

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 randomised 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.

### *Neurogenic detrusor overactivity in paediatric patients*

Efficacy of mirabegron oral suspension and tablets was evaluated in a 52-week, open-label, baseline-controlled, multicentre, dose titration study for the treatment of NDO in paediatric patients. Patients had a diagnosis of NDO with involuntary detrusor contractions with detrusor pressure increase greater than 15 cm H<sub>2</sub>O and performed clean intermittent catheterisation (CIC). Patients  $\geq 35$  kg received tablets and patients  $< 35$  kg (or  $\geq 35$  kg but unable to tolerate tablets) received oral suspension. For all patients, mirabegron was administered orally once daily with food. The starting dose was a 25 mg tablet or between 3-6 ml of oral suspension (depending on patient weight). This dose was up-titrated to 50 mg tablet or between 6-11 ml of oral suspension (depending on body weight). The dose titration period was a maximum of 8 weeks followed by a dose maintenance period of at least 52 weeks.

A total of 86 patients aged 3 to less than 18 years of age received mirabegron. Of these, 71 patients completed treatment through week 24 and 70 completed 52 weeks of treatment. A total of 68 patients had valid urodynamic measurements for evaluation of efficacy. The study population included 39 (45.3%) males and 47 (54.7%) females. The optimised maintenance dose within this study population included 94% of patients at the maximum dose, and 6% of patients at the starting dose.

The most common (in greater than 10% of all patients) background medical conditions related to NDO in children and adolescents included in the study were congenital central nervous system anomaly (54.5% and 48.4%, respectively), meningomyelocele (27.3% and 19.4%, respectively), and spina bifida (10.9% and 12.9%, respectively). In adolescents, 12.9% had a spinal cord injury.

The primary efficacy endpoint was change from baseline in maximum cystometric capacity (MCC) after 24 weeks of mirabegron treatment. Improvements in MCC were observed in all patient groups (see Table 6).

**Table 6: Primary efficacy endpoint in paediatric patients with NDO**

Parameter	Children aged 3 to < 12 years (N=43)* Mean (SD)	Adolescents aged 12 to < 18 years (N=25)* Mean (SD)
<b>Maximum cystometric capacity (ml)</b>		
Baseline	158.6 (94.5)	238.9 (99.1)
Week 24	230.7 (129.1)	352.1 (125.2)
Change from baseline	72.0 (87.0)	113.2 (82.9)
95% Confidence Interval	(45.2, 98.8)	(78.9, 147.4)

\* N is the number of patients who took at least one dose and provided valid values for MCC at baseline and week 24.

The secondary efficacy endpoints were change from baseline in bladder compliance, number of overactive detrusor contractions, detrusor pressure at end of bladder-filling, bladder volume prior to first detrusor contraction, maximum catheterised urine volume per day, and number of leakage episodes per day after 24 weeks of mirabegron treatment (see Table 7).

**Table 7: Secondary efficacy endpoints in paediatric patients with NDO**

Parameter	Children aged 3 to < 12 years (N=43)* Mean (SD)	Adolescents aged 12 to < 18 years (N=25)* Mean (SD)
<b>Bladder compliance (ml/cm H<sub>2</sub>O)†</b>		
Baseline	14.5 (50.7)	11.0 (10.0)
Week 24	29.6 (52.8)	23.8 (15.3)
Change from baseline	14.6 (42.0)	13.5 (15.0)
95% Confidence Interval	(-0.3, 29.5)	(6.7, 20.4)
<b>Number of overactive detrusor contractions (&gt; 15 cm H<sub>2</sub>O)†</b>		
Baseline	3.0 (3.8)	2.0 (2.9)
Week 24	1.0 (2.2)	1.4 (2.3)
Change from baseline	-1.8 (4.1)	-0.7 (3.8)
95% Confidence Interval	(-3.2, -0.4)	(-2.4, 0.9)
<b>Detrusor pressure (cm H<sub>2</sub>O) at end of bladder-filling†</b>		
Baseline	42.2 (26.2)	38.6 (17.9)
Week 24	25.6 (21.2)	27.8 (27.8)
Change from baseline	-18.1 (19.9)	-13.1 (19.9)
95% Confidence Interval	(-24.8, -11.3)	(-22.0, -4.3)
<b>Bladder volume prior to first detrusor contraction (&gt; 15 cm H<sub>2</sub>O)†</b>		
Baseline	115.8 (87.0)	185.2 (121.2)
Week 24	207.9 (97.8)	298.7 (144.4)
Change from baseline	93.1 (88.1)	121.3 (159.8)
95% Confidence Interval	(64.1, 122.1)	(53.8, 188.8)
<b>Maximum catheterised urine volume per day (ml)†</b>		
Baseline	300.1 (105.7)	367.5 (119.0)
Week 24	345.9 (84.6)	449.9 (146.6)
Change from baseline	44.2 (98.3)	81.3 (117.7)
95% Confidence Interval	(13.2, 75.2)	(30.4, 132.3)
<b>Number of leakage episodes per day†</b>		
Baseline	3.2 (3.7)	1.8 (1.7)
Week 24	0.7 (1.2)	0.9 (1.2)
Change from baseline	-2.0 (3.2)	-1.0 (1.1)
95% Confidence Interval	(-3.2, -0.7)	(-1.5, -0.5)

\* N is the number of patients who took at least one dose and provided valid values for MCC at baseline and week 24.

† Number of patients (children/adolescents) with data available for both baseline and week 24; Bladder compliance: n=33/21; Number of overactive detrusor contractions: n=36/22; Detrusor pressure at end of bladder-filling: n=36/22; Bladder volume prior to first detrusor contraction: n=38/24; Maximum catheterised urine volume per day: n=41/23; Number of leakage episodes per day: n=26/21.

Patient- or clinician-reported questionnaire endpoints included acceptability, change from baseline in the Pediatric Incontinence Questionnaire (PIN-Q), change from baseline in the Patient Global Impression of Severity Scale (PGI-S), and Clinician Global Impression of Change (CGI-C) (see Table 8).

**Table 8: Patient- or clinician-reported questionnaire endpoints in paediatric patients with NDO**

Parameter	Children aged 3 to < 12 years (N=43)* Mean (SD)	Adolescents aged 12 to < 18 years (N=25)* Mean (SD)
<b>Pediatric Incontinence Questionnaire (PIN-Q) score†</b>		
Baseline	30.8 (15.7)	29.4 (14.6)
Week 24	30.6 (15.2)	25.2 (15.5)
Change from baseline	2.0 (10.5)	-4.9 (14.1)
95% Confidence Interval	(-2.4, 6.4)	(-11.3, 1.5)
<b>Total Patient Global Impression of Severity Scale (PGI-S) score†</b>		
Baseline	2.2 (0.8)	2.3 (0.9)
Week 24	2.6 (0.8)	3.0 (0.7)
Change from baseline	0.3 (1.2)	0.6 (1.0)
95% Confidence Interval	(-0.1, 0.8)	(0.1, 1.0)
<b>Total Clinician Global Impression of Change (CGI-C) at week 24, N (%)†</b>		
Very Much Improved	6 (14.6%)	10 (41.7%)
Much Improved	24 (58.5%)	7 (29.2%)
Minimally Improved	6 (14.6%)	5 (20.8%)
No Change	4 (9.8%)	1 (4.2%)
Minimally Worse	1 (2.4%)	1 (4.2%)
Much Worse	0	0
Very Much Worse	0	0

\* N is the number of patients who took at least one dose and provided valid values for MCC at baseline and week 24.

† Number of patients (children/adolescents) with data available for both baseline and week 24. PIN-Q score: n=24/21, Total PGI-S score: n=25/22; Total CGI-C at week 24: n=41/24.

## *Paediatric population*

### *Overactive bladder*

Efficacy of mirabegron tablets and oral suspension was evaluated in a 12-week, double-blind, randomised, multicentre, parallel group, placebo-controlled sequential dose titration study for the treatment of OAB in paediatric patients (5 to less than 18 years of age). Patients  $\geq 35$  kg received tablets and patients  $< 35$  kg (or  $\geq 35$  kg but unable to swallow tablets) received oral suspension. For all patients, mirabegron was administered orally once daily with food. The starting dose was a 25 mg tablet or between 3-6 ml of oral suspension (depending on patient weight). This dose was up-titrated to 50 mg tablet or between 6-11 ml of oral suspension (depending on patient weight). Dose titration to the higher dose was conducted after 4 weeks on treatment, unless the investigator decided otherwise.

A total of 23 children (aged 5 to less than 12 years) and 3 adolescents (aged 12 to less than 18 years of age) received study drug: 13 subjects received placebo and 13 subjects received mirabegron. Ten of the 12 subjects in the placebo group and 9 of 11 subjects in the mirabegron group completed the study through 12 weeks of treatment.

The primary efficacy endpoint was the change from baseline in the mean number of micturations per 24 hours after 12 weeks of treatment and was assessed only in children (aged 5 to less than 12 years). Due to the small number of subjects, a proper assessment of the efficacy endpoints was not possible, and the observed results were inconclusive.

The adjusted LS mean (SEM) change from baseline to week 12/end of treatment in the frequency of micturition events per 24 hours was -3.84 (0.89) in children on placebo and -1.62 (0.89) in children on mirabegron. The LS mean (SEM) difference between treatment groups (placebo minus mirabegron) was not statistically significant: 2.22 (1.34) (90% CI: -0.15, 4.59;  $P = 0.121$ ).

The European Medicines Agency has waived the obligation to submit the results of studies with Betmiga granules for prolonged-release oral suspension in all subsets of the paediatric population in “Treatment of idiopathic overactive bladder” (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

### Absorption

#### *Tablets*

#### Adults

After oral administration of mirabegron in healthy adult volunteers mirabegron is absorbed to reach peak plasma concentrations ( $C_{\max}$ ) 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  $C_{\max}$  and AUC increased more than dose proportionally over the dose range. In the overall adult population of males and females, a 2-fold increase in dose from 50 mg to 100 mg mirabegron increased  $C_{\max}$  and  $AUC_{\tau}$  by approximately 2.9- and 2.6-fold, respectively, whereas a 4-fold increase in dose from 50 mg to 200 mg mirabegron increased  $C_{\max}$  and  $AUC_{\tau}$  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.

### *Tablets or granules for oral suspension*

#### Paediatric population

The median  $T_{max}$  of mirabegron following oral administration of a single dose of mirabegron oral suspension or tablets in patients under fed state was 4-5 hours. Population pharmacokinetic analysis predicted that the median  $T_{max}$  of mirabegron oral suspension or tablets at steady-state was 3-4 hours.

The bioavailability of the oral suspension formulation is lower than that of the tablet. The ratio of the population mean exposure ( $AUC_{tau}$ ) of the oral suspension to the tablet is approximately 45%.

#### Effect of food on absorption

##### *Tablets*

##### Adults

Co-administration of a 50 mg tablet with a high-fat meal reduced mirabegron  $C_{max}$  and AUC by 45% and 17%, respectively. A low-fat meal decreased mirabegron  $C_{max}$  and AUC by 75% and 51%, respectively. In the phase 3 studies in adults, 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.

### *Tablets or granules for oral suspension*

#### Paediatric population

The population pharmacokinetic model predicted that the patients receiving mirabegron in the fed state would have 44.7% of steady-state  $AUC_{tau}$  relative to an equal dose administered in the fasted state. This value is consistent with the  $AUC_{inf}$  results seen in the single-dose food effects studies for mirabegron. In the phase 3 paediatric study, mirabegron was administered with food and demonstrated both safety and efficacy. Dosing recommendations are based upon the exposures expected in the fed state. Therefore, in paediatric patients, mirabegron should be taken with food at the recommended dose.

#### Distribution

##### *Tablets*

##### Adults

Mirabegron is extensively distributed. The volume of distribution at steady-state ( $V_{ss}$ ) is approximately 1 670 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.

### *Tablets or granules for oral suspension*

#### Paediatric population

Mirabegron volume of distribution was relatively large and increased with increasing body weight in accordance with allometric principles based on population pharmacokinetic analysis. Age, sex and patient population had no impact on volume of distribution after accounting for potential differences in body weight.

## Biotransformation

Mirabegron is metabolised via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Mirabegron is the major circulating component following a single dose of  $^{14}\text{C}$ -mirabegron. Two major metabolites were observed in adult 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 metabolised 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 adult subjects who are genotypically poor metabolisers of CYP2D6 substrates (used as a surrogate for CYP2D6 inhibition), mean  $C_{\text{max}}$  and  $\text{AUC}_{\text{inf}}$  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 adult patients who are CYP2D6 poor metabolisers.

## Elimination

### *Tablets*

### Adults

Total body clearance ( $\text{CL}_{\text{tot}}$ ) from plasma is approximately 57 l/h. The terminal elimination half-life ( $t_{1/2}$ ) is approximately 50 hours. Renal clearance ( $\text{CL}_{\text{R}}$ ) is approximately 13 l/h, which corresponds to nearly 25% of  $\text{CL}_{\text{tot}}$ . 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  $^{14}\text{C}$ -mirabegron to healthy adult 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.

### *Tablets or granules for oral suspension*

### Paediatric population

Mirabegron clearance was predicted to increase with increasing body weight in accordance with allometric principles based on population pharmacokinetic analysis. The apparent clearance parameter was impacted significantly by dose, formulation, and food effects on relative bioavailability. Values of apparent clearance were highly variable but generally similar between children and adolescents, despite body weight differences, because of these effects on bioavailability.

## Age

### *Tablets*

#### Adults

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

### *Tablets or granules for oral suspension*

#### Paediatric population

In patients 3 to less than 18 years of age, age was not predicted to have any impact on key mirabegron pharmacokinetic parameters after accounting for differences in body weight. Models including age did not result in meaningful improvements to the paediatric population pharmacokinetic model, indicating that inclusion of body weight was sufficient to address differences in mirabegron pharmacokinetics due to age.

## Gender

### *Tablets*

#### Adults

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.

### *Tablets or granules for oral suspension*

#### Paediatric population

Gender has no meaningful impact on mirabegron pharmacokinetics in the paediatric population from 3 to less than 18 years of age.

## Race

The pharmacokinetics of mirabegron in adults are not influenced by race.

## Renal impairment

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

## Hepatic impairment

Following single-dose administration of 100 mg mirabegron in adult volunteers with mild hepatic impairment (Child-Pugh Class A), mean mirabegron  $C_{\max}$  and AUC were increased by 9% and 19% relative to adult volunteers with normal hepatic function. In adult 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

Pre-clinical 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 and reduced plasma leptin levels were noted. 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*.

Mirabegron had no discernible effect on gonadotropic or sex steroid hormone levels. In addition, 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.

The overall safety profile seen in juvenile rats was comparable to that observed in adult animals. Juvenile rats orally administered mirabegron for 13 weeks showed elevated liver enzymes with an increase in liver weights without histopathological findings at systemic exposures approximately 12-fold higher than the projected human systemic exposure in children. Repeat dose safety studies performed in juvenile rats showed no effect on physical development or sexual maturation. Mirabegron administration from weaning through sexual maturation had no effect on mating ability, fertility or embryofoetal development. Mirabegron administration increased lipolysis and food consumption and decreased body weight gain in juvenile rats.

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

Sodium polystyrene sulfonate  
Hydrochloric acid, dilute  
Xanthan gum  
Hypromellose  
Mannitol (E421)  
Magnesium stearate  
Acesulfame potassium  
Methyl parahydroxybenzoate (E218)  
Ethyl parahydroxybenzoate (E214)  
Simethicone  
Silica, colloidal hydrated

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### **6.3 Shelf life**

#### Unopened bottle

3 years.

#### After reconstitution

Store reconstituted suspension below 25 °C for up to 28 days after the date the suspension is prepared. Do not refrigerate or freeze.

### **6.4 Special precautions for storage**

This medicinal product does not require any special temperature storage conditions. Store the bottle in the unopened pouch in order to protect from moisture until the time of reconstitution.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

### **6.5 Nature and contents of container**

There are two presentations of Betmiga granules for prolonged-release oral suspension, and both are supplied as several components for reconstitution. One presentation contains:

- In the carton: pouch, 5 ml oral syringe, adaptor, and package leaflet
- In the pouch: measuring cup, amber polyethylene terephthalate (PET) bottle (118 ml) with polypropylene (PP) screw-cap, and desiccant

The other presentation contains:

- In the carton: pouch, 5 ml oral syringe, adaptor, and package leaflet
- In the pouch: amber polyethylene terephthalate (PET) bottle (118 ml) with polypropylene (PP) screw-cap, and desiccant

Not all pack sizes may be marketed.

The measuring cup has a graduation of 10 ml (max 60 ml) and the oral syringe has a graduation of 0.1 ml and 0.5 ml (max 5 ml).

### **6.6 Special precautions for disposal and other handling**

Store the oral syringe and adaptor under clean and dry conditions and protect from sunlight and heat.

Use the measuring cup (if provided) to reconstitute the granules prior to administration (see below for instructions on reconstitution). After reconstitution with 100 ml of water, the oral suspension is pale brownish yellow suspension.

After the granules have been reconstituted, shake the bottle vigorously for 1 minute before each use. The oral syringe provided with Betmiga granules for prolonged-release oral suspension must be used with the adaptor to measure and administer the correct dose.

### Instructions for reconstitution

1. Open the carton and remove the pouch, syringe, and adaptor. Keep the bottle in the unopened pouch until the time of reconstitution.
2. When ready to perform the reconstitution, open the pouch and remove the bottle and measuring cup.
3. Throw away the empty pouch and desiccant. Do not swallow the desiccant.
4. Tap the top of the closed bottle several times to loosen the granules.
5. Place the bottle on a flat surface and remove the cap.
6. Measure a total of 100 ml of water and pour it into the bottle. If a measuring cup is provided, use the measuring cup to first measure 50 ml of water and pour it into the bottle. Use the cup again to measure another 50 ml of water and pour it into the bottle.
7. Replace the cap on the bottle. Immediately shake vigorously for 1 minute, then let it stand for 10 to 30 minutes. Again, shake vigorously for 1 minute.
8. Record 28 days from the date of reconstitution on the bottle label.
9. Place the bottle on a flat surface and remove the cap.
10. Firmly press the adaptor into the neck of the bottle.
11. Make sure that the top of the adaptor is even with the top of the bottleneck. The adaptor should remain in the neck of the bottle until the end of the 28-day shelf life period.
12. Replace the cap on the bottle.

### Cleaning of the oral syringe

After use, clean the oral syringe with warm water.

The oral syringe can be used throughout the 28-day shelf life after first opening (see section 6.3).

### Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Throw away any remaining medicinal product 28 days after reconstitution.

## **7. MARKETING AUTHORISATION HOLDER**

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

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

EU/1/12/809/019  
EU/1/12/809/020

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

Date of first authorisation: 20 December 2012

Date of latest renewal: 18 September 2017

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

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://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

Delpharm Meppel B.V.  
Hogemaat 2  
7942 JG Meppel  
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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs 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 marketing authorisation holder (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**

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)**

EU/1/12/809/001	10 prolonged-release tablets
EU/1/12/809/002	20 prolonged-release tablets
EU/1/12/809/003	30 prolonged-release tablets
EU/1/12/809/004	60 prolonged-release tablets
EU/1/12/809/005	90 prolonged-release tablets
EU/1/12/809/006	200 prolonged-release tablets
EU/1/12/809/015	50 prolonged-release tablets
EU/1/12/809/016	100 prolonged-release tablets

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

betmiga 25 mg

**17. UNIQUE IDENTIFIER - 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**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)**

EU/1/12/809/008	10 prolonged-release tablets
EU/1/12/809/009	20 prolonged-release tablets
EU/1/12/809/010	30 prolonged-release tablets
EU/1/12/809/011	60 prolonged-release tablets
EU/1/12/809/012	90 prolonged-release tablets
EU/1/12/809/013	200 prolonged-release tablets
EU/1/12/809/017	50 prolonged-release tablets
EU/1/12/809/018	100 prolonged-release tablets

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

betmiga 50 mg

**17. UNIQUE IDENTIFIER - 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
--

<b>BLISTER</b>
----------------

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Betmiga 25 mg prolonged-release tablets  
mirabegron

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Astellas Pharma Europe B.V.

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. OTHER</b>
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<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
--

<b>BLISTER</b>
----------------

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Betmiga 50 mg prolonged-release tablets  
mirabegron

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Astellas Pharma Europe B.V.

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. OTHER</b>
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**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Betmiga 8 mg/ml granules for prolonged-release oral suspension  
mirabegron

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

One bottle contains 830 mg of mirabegron.  
After reconstitution, one bottle contains 105 ml of oral suspension. Each ml of oral suspension contains 8 mg of mirabegron.

**3. LIST OF EXCIPIENTS**

Contains (E214) and (E218).  
See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Granules for prolonged-release oral suspension  
1 bottle contains 8.3 g granules.  
1 bottle and 1 measuring cup in a pouch, 5 ml oral syringe, 1 adaptor.  
105 ml

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

Read the package leaflet before use.  
For oral use after reconstitution with 100 ml of water.  
Shake vigorously for 1 minute before each 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**

Do not swallow the desiccant.

**8. EXPIRY DATE**

EXP

Store reconstituted suspension below 25 °C for up to 28 days after reconstitution.  
Do not refrigerate or freeze.

**9. SPECIAL STORAGE CONDITIONS**

Store the bottle in the unopened pouch in order to protect from moisture until the time of reconstitution.

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

Throw away the unused medicine after 28 days.

**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/1/12/809/019  
EU/1/12/809/020

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

betmiga 8 mg/ml

<b>17. UNIQUE IDENTIFIER - 2D BARCODE</b>
---

2D barcode carrying the unique identifier included.

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

PC  
SN  
NN



**PARTICULARS TO APPEAR ON THE INNER PACKAGING****POUCH****1. NAME OF THE MEDICINAL PRODUCT**

Betmiga 8 mg/ml granules for prolonged-release oral suspension  
mirabegron

**2. STATEMENT OF ACTIVE SUBSTANCE(S)****3. LIST OF EXCIPIENTS****4. PHARMACEUTICAL FORM AND CONTENTS**

Granules for prolonged-release oral suspension  
1 Bottle  
105 ml

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

Read the package leaflet before 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**

Do not swallow the desiccant.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Keep bottle in unopened pouch until time of reconstitution.

**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**

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

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**17. UNIQUE IDENTIFIER – 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING****BOTTLE****1. NAME OF THE MEDICINAL PRODUCT**

Betmiga 8 mg/ml granules for prolonged-release oral suspension  
mirabegron

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

One bottle contains 830 mg of mirabegron.  
After reconstitution, one bottle contains 105 ml of oral suspension. Each ml of oral suspension contains 8 mg of mirabegron.

**3. LIST OF EXCIPIENTS**

Contains ethyl parahydroxybenzoate (E214) and methyl parahydroxybenzoate (E218).  
See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Granules for prolonged-release oral suspension

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

Read the package leaflet before use.  
For oral use after reconstitution with 100 ml of water.  
Shake vigorously for 1 minute before each 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

Store reconstituted suspension below 25 °C for up to 28 days after reconstitution. Do not refrigerate or freeze.

Discard after: \_\_\_\_\_

**9. SPECIAL STORAGE CONDITIONS**

Store the bottle in the unopened pouch in order to protect from moisture until the time of reconstitution.

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

Throw away the unused medicine after 28 days.

**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/1/12/809/019  
EU/1/12/809/020

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE****17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

## **B. PACKAGE LEAFLET**

## **Package leaflet: Information for the user**

### **Betmiga 25 mg prolonged-release tablets** **Betmiga 50 mg prolonged-release tablets** mirabegron

**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 take Betmiga
3. How to take 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 and reduces neurogenic detrusor overactivity.

Betmiga is used to:

- treat the symptoms of a condition called overactive bladder in adults. These symptoms include: 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).
- treat a condition called neurogenic detrusor overactivity in children aged 3 to less than 18 years. Neurogenic detrusor overactivity is a condition in which involuntary bladder contractions occur due to a condition that you are born with or injury to the nerves, which control the bladder. If left untreated, neurogenic detrusor overactivity may lead to damage to your bladder and/or kidneys. Betmiga is used to increase the amount of urine your bladder can hold and reduce urine leakage.

#### **2. What you need to know before you take Betmiga**

##### **Do not take 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 taking 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 or neurogenic detrusor overactivity 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 take Betmiga, especially if you are taking other medicines such as itraconazole, ketoconazole (fungal infections), ritonavir (HIV/AIDS) or clarithromycin (bacterial infections). 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:
  - o medicines used for abnormal heart rhythm such as quinidine, sotalol, procainamide, ibutilide, flecainide, dofetilide, and amiodarone;
  - o medicines used for allergic rhinitis;
  - o antipsychotic medicines (medicines for mental illness) such as thioridazine, mesoridazine, haloperidol, and chlorpromazine;
  - o anti-infectives such as pentamidine, moxifloxacin, erythromycin, and clarithromycin.

Betmiga 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 this medicine.

## **Children and adolescents**

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

Betmiga is not to be used in children under 3 years of age for the treatment of neurogenic detrusor overactivity.

## **Other medicines and Betmiga**

Tell your doctor or pharmacist if you are taking, have recently taken or might take 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 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 must not take Betmiga.

If you are breast-feeding, ask your doctor or pharmacist for advice before taking this medicine. It is likely that this medicine passes into your breast milk. You and your doctor should decide if you should take Betmiga or breast-feed. 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 take Betmiga**

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

#### **Use in adults with overactive bladder**

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 must 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.

#### **Use in children and adolescents (age 3 to less than 18 years) with neurogenic detrusor overactivity**

Take this medicine by mouth once daily. You must take this medicine with liquids and swallow the tablet whole. Do not crush or chew the tablet. Betmiga must be taken with food. Your doctor will tell you which dose you/your child should take. Your doctor will calculate the correct dose for a patient depending on his or her body weight. You should carefully follow their instructions.

#### **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 12 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 taking 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 or neurogenic detrusor overactivity.

Do not stop taking Betmiga without talking to your doctor first, as your symptoms of overactive bladder or neurogenic detrusor overactivity 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** (may affect up to 1 in 10 people)

- Infection of the structures that carry urine (urinary tract infections)
- Headache
- Dizziness
- Increased heart rate (tachycardia)
- Feeling sick (nausea)
- Constipation
- Diarrhoea

**Uncommon** (may affect up to 1 in 100 people)

- Vaginal infection
- Bladder infection (cystitis)
- Feeling your heartbeat (palpitations)
- Heart rhythm problems (atrial fibrillation)
- Indigestion (dyspepsia)
- Infection of the stomach (gastritis)
- Itching, rash or hives (urticaria, rash, rash macular, rash papular, pruritus)
- Swelling of the joints
- Itching of the vulva or vagina (vulvovaginal pruritus)
- Increased blood pressure
- Increase in liver enzymes (GGT, AST and ALT)

**Rare** (may affect up to 1 in 1 000 people)

- Swelling of the eyelid (eyelid oedema)
- Swelling of the lip (lip oedema)
- Inflammation of small blood vessels mainly affecting the skin (leukocytoclastic vasculitis)
- Small purple spots on the skin (purpura)
- 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)
- Inability to completely empty the bladder (urinary retention)

**Very rare** (may affect up to 1 in 10 000 people)

- Severely high blood pressure (hypertensive crisis)

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

- Insomnia
- Confusion

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 or blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

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.  
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.
- 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.

Not all pack sizes may be available in your country.

#### **Marketing Authorisation Holder**

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

#### **Manufacturer**

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Hogemaat 2  
7942 JG Meppel  
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last revised in .**

Detailed information on this medicine is available on the European Medicines Agency web site:

<https://www.ema.europa.eu>.

## **Package leaflet: Information for the user**

### **Betmiga 8 mg/ml granules for prolonged-release oral suspension** mirabegron

**Read all of this leaflet carefully before you start taking 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 take Betmiga
3. How to take 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 neurogenic detrusor overactivity.

Betmiga is used to treat a condition called neurogenic detrusor overactivity in children aged 3 to less than 18 years. Neurogenic detrusor overactivity is a condition in which involuntary bladder contractions occur due to a condition that you are born with or injury to the nerves, which control the bladder. If left untreated, neurogenic detrusor overactivity may lead to damage to your bladder and/or kidneys. Betmiga is used to increase the amount of urine your bladder can hold and reduce urine leakage.

#### **2. What you need to know before you take Betmiga**

##### **Do not take 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 taking 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 neurogenic detrusor overactivity 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 take Betmiga, especially if you are taking other medicines such as itraconazole, ketoconazole (fungal infections), ritonavir (HIV/AIDS) or clarithromycin (bacterial infections). 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:
  - o medicines used for abnormal heart rhythm such as quinidine, sotalol, procainamide, ibutilide, flecainide, dofetilide, and amiodarone;
  - o medicines used for allergic rhinitis;
  - o antipsychotic medicines (medicines for mental illness) such as thioridazine, mesoridazine, haloperidol, and chlorpromazine;
  - o anti-infectives such as pentamidine, moxifloxacin, erythromycin, and clarithromycin.

Betmiga 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 this medicine.

### **Children and adolescents**

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

Betmiga is not to be used in children under 3 years of age for the treatment of neurogenic detrusor overactivity.

### **Other medicines and Betmiga**

Tell your doctor or pharmacist if you are taking, have recently taken or might take 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 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 must not take Betmiga.

If you are breast-feeding, ask your doctor or pharmacist for advice before taking this medicine. It is likely that this medicine passes into your breast milk. You and your doctor should decide if you should take Betmiga or breast-feed. 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.

### **Betmiga contains ethyl parahydroxybenzoate (E214), methyl parahydroxybenzoate (E218), and sodium**

May cause allergic reactions (possibly delayed).

This medicine contains less than 1 mmol sodium (23 mg) per 10 ml of oral suspension, that is to say essentially 'sodium-free'.

### 3. How to take Betmiga

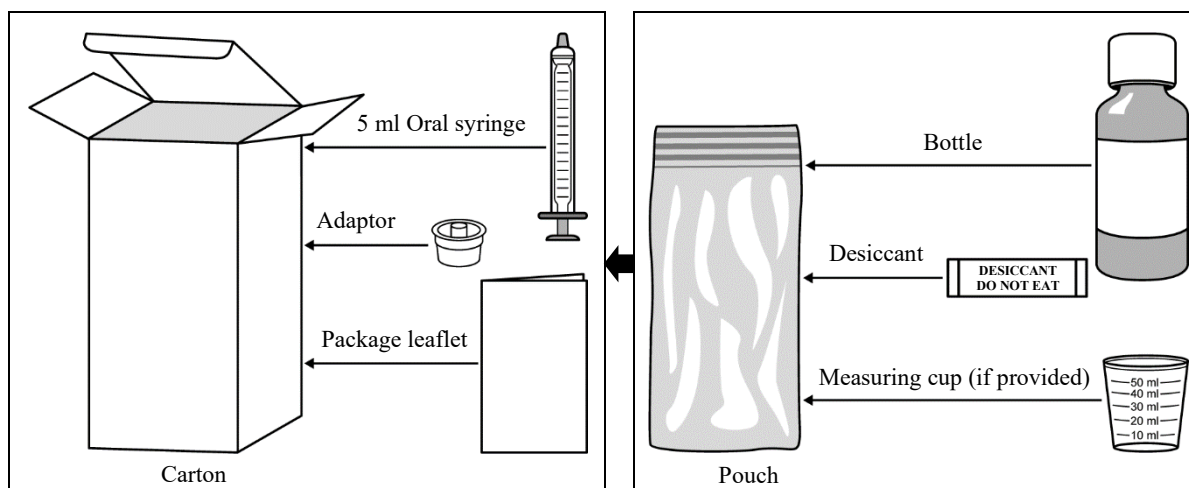
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Take this medicine by mouth once daily. Betmiga must be taken with food. Your doctor will tell you which dose you/your child should take. Your doctor will calculate the correct dose for a patient depending on his or her body weight. You should carefully follow their instructions.

#### How to take Betmiga using an oral syringe

Reconstitution should be made by a pharmacist except in situations in which pharmacists are unable to do so. For situations in which pharmacists are unable to perform the reconstitution, use the measuring cup that is provided to measure the water volume used for reconstitution.

Use the oral syringe and adaptor provided with Betmiga granules for prolonged-release oral suspension to measure the correct dose. If you need to take a dose greater than 5 ml per day, then you will need to use the oral syringe twice to administer the total amount of each dose. The items contained in the packaging are below:



Note: Measuring cup (if provided), bottle, and desiccant are included in the pouch. The pouch is included in the carton along with the oral syringe, adaptor, and package leaflet.

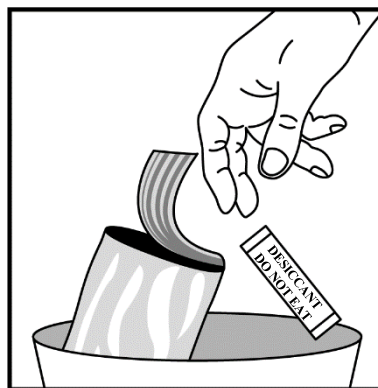
#### Preparation for the first use of a bottle of Betmiga granules for prolonged-release oral suspension (with measuring cup)

Note: If a pharmacist has already performed the reconstitution, please skip this section and proceed to the section (Before each oral administration) below.

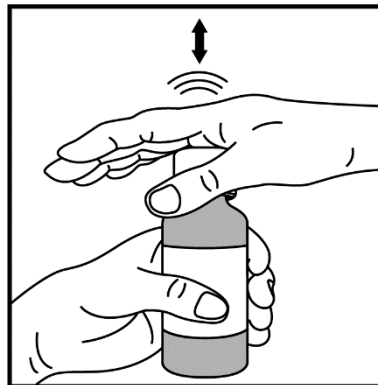
1.
  - Open the carton and remove the pouch, syringe, and adaptor.
  - Keep the bottle in the unopened pouch until the time of reconstitution.
  - Open the pouch and remove the bottle and measuring cup.



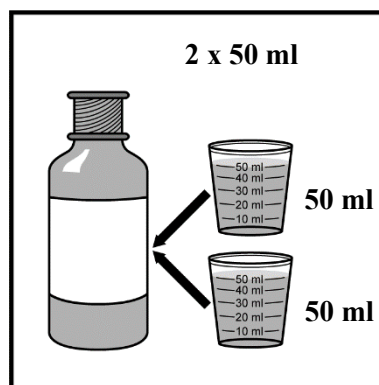
2. • Throw away the empty pouch and desiccant. Do not swallow the desiccant.



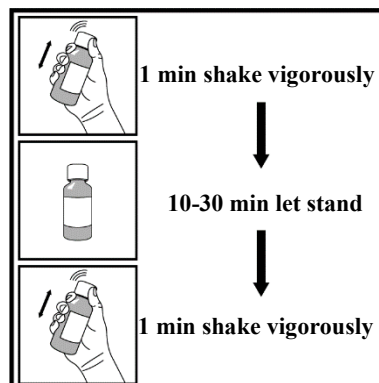
3. • Tap the top of the closed bottle several times to loosen the granules.  
• Place the bottle on a flat surface and remove the cap.



4. • Use the measuring cup to measure 50 ml of water and pour it into the bottle.  
• Use the cup again to measure another 50 ml of water and pour it into the bottle so that a total of 100 ml of water has been added.

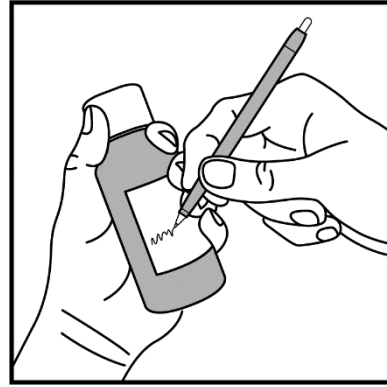


5. • Replace the cap on the bottle.  
• Immediately shake vigorously for 1 minute, then let it stand for 10 to 30 minutes.  
• Again, shake vigorously for 1 minute.

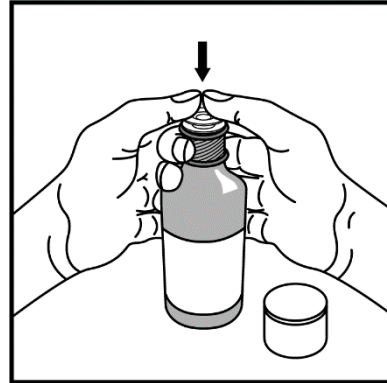




6. • Record 28 days from the date of reconstitution on the bottle label.



7. • Place the bottle on a flat surface and remove the cap.  
• Firmly press the adaptor into the neck of the bottle.  
• Make sure that the top of the adaptor is even with the top of the bottleneck. The adaptor should remain in the neck of the bottle until the end of the 28-day shelf life period.  
• Replace the cap on the bottle.



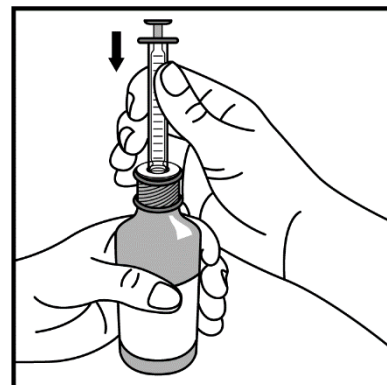
**Before each oral administration**

Note: Shake the bottle vigorously for 1 minute each day to make sure granules are suspended.

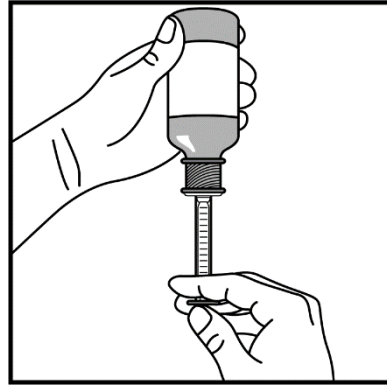
1. • Shake the bottle vigorously for 1 minute.  
• Let it stand until foam on the surface of the suspension is gone (approximately 1 to 2 minutes).



2. • Remove the bottle cap.  
• Insert the oral syringe tip into central opening of the bottle adaptor until it is firmly in place.  
• Do not withdraw the plunger of the syringe.

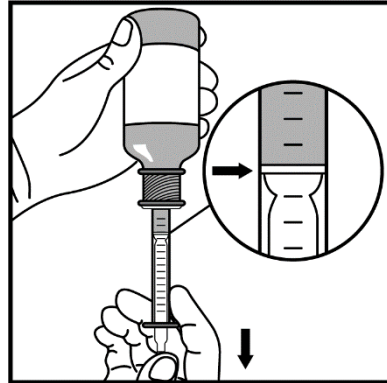


3. • Carefully turn the bottle and syringe upside down.

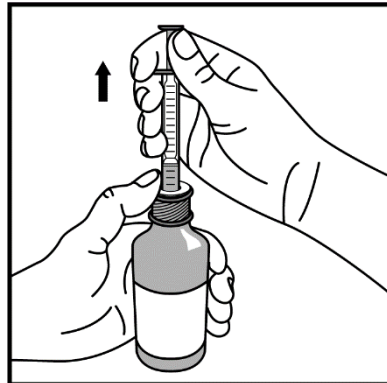


4. • Pull back the plunger of the syringe slowly to withdraw the amount prescribed by your doctor from the upside-down bottle. The medicine must be taken within 1 hour of being transferred into the syringe.
- If your doctor prescribed more than 5 ml, the syringe will need to be used twice.

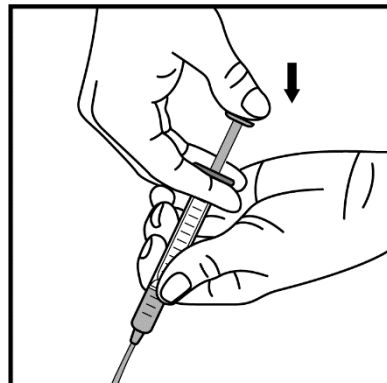
For example, if the dose is 8 ml, withdraw 5 ml first and administer the medicine, then withdraw 3 ml and administer the medicine again.



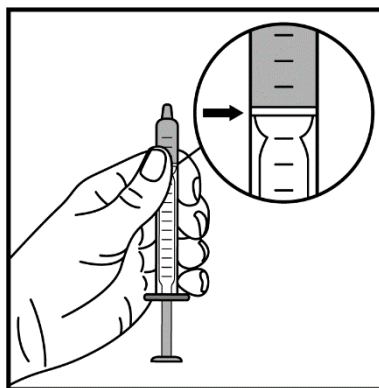
5. • Leave the syringe in place and turn the bottle upright, making sure the plunger of the syringe does not move.
- Gently remove the syringe from the adaptor.
  - After completion of dosing, close the bottle with the cap.



6. • Remove the overage if too much medicine has been accidentally withdrawn.



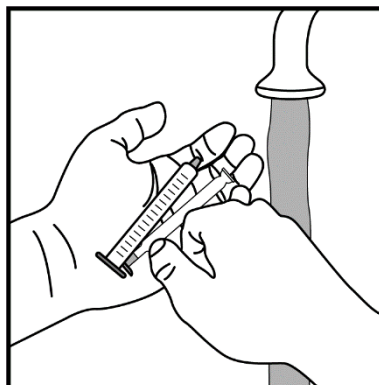
7. • Confirm the correct amount has been measured.



8. • Place the syringe in the mouth and gently push the plunger down to administer the medicine.



9. • Disassemble the syringe and rinse with warm water.  
• Allow time to dry for reuse.



This medicine must not be mixed with other medicines.

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

If you have taken too much Betmiga, or if someone else has accidentally taken Betmiga, 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 unless more than 12 hours have passed since the missed dose. If more than 12 hours have passed, 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 taking Betmiga**

Do not stop treatment with Betmiga if you do not see an immediate effect. Your bladder might need some time to adapt. You should continue taking your medicine. Do not stop taking the medicine when your bladder condition improves. Stopping treatment may result in recurrence of neurogenic detrusor overactivity.

Do not stop taking Betmiga without talking to your doctor first, as your neurogenic detrusor overactivity 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** (may affect up to 1 in 10 people)

- Infection of the structures that carry urine (urinary tract infection)
- Headache
- Dizziness
- Increased heart rate (tachycardia)
- Feeling sick (nausea)
- Constipation
- Diarrhoea

### **Uncommon** (may affect up to 1 in 100 people)

- Vaginal infection
- Bladder infection (cystitis)
- Feeling your heartbeat (palpitations)
- Heart rhythm problems (atrial fibrillation)
- Indigestion (dyspepsia)
- Infection of the stomach (gastritis)
- Itching, rash or hives (urticaria, rash, rash macular, rash papular, pruritus)
- Swelling of the joints
- Itching of the vulva or vagina (vulvovaginal pruritus)
- Increased blood pressure
- Increase in liver enzymes (GGT, AST and ALT)

### **Rare** (may affect up to 1 in 1 000 people)

- Swelling of the eyelid (eyelid oedema)
- Swelling of the lip (lip oedema)
- Inflammation of small blood vessels mainly affecting the skin (leukocytoclastic vasculitis)
- Small purple spots on the skin (purpura)
- 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)
- Inability to completely empty the bladder (urinary retention)

**Very rare** (may affect up to 1 in 10 000 people)

- Severely high blood pressure (hypertensive crisis)

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

- Insomnia
- Confusion

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, pouch, or bottle after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions. Store the bottle in the unopened pouch in order to protect from moisture until the time of reconstitution.

Store the oral syringe under clean and dry conditions and protect from sunlight and heat.

Store reconstituted suspension below 25 °C for up to 28 days after the date the suspension is prepared. Do not refrigerate or freeze. Throw away any remaining medicine 28 days after reconstitution.

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. One bottle of granules for prolonged-release oral suspension contains 830 mg of mirabegron. After reconstitution, one bottle contains 105 ml of oral suspension. Each ml of oral suspension contains 8 mg of mirabegron.
- The other ingredients are methyl parahydroxybenzoate (E218); ethyl parahydroxybenzoate (E214); sodium polystyrene sulfonate; hydrochloric acid, dilute; xanthan gum; hypromellose; mannitol (E421); magnesium stearate; acesulfame potassium; simethicone; silica, colloidal hydrated. See section 2 “Betmiga contains ethyl parahydroxybenzoate (E214), methyl parahydroxybenzoate (E218), and sodium”.

**What Betmiga looks like and contents of the pack**

Betmiga granules for prolonged-release oral suspension are yellowish white granules. After reconstitution, the oral suspension is pale brownish yellow suspension.

There are two presentations of Betmiga granules for prolonged-release oral suspension, and both are supplied as several components for reconstitution. One presentation contains:

- In the carton: pouch, 5 ml oral syringe, adaptor, and package leaflet
- In the pouch: measuring cup, amber polyethylene terephthalate (PET) bottle (118 ml) with polypropylene (PP) screw-cap, and desiccant

The other presentation contains:

- In the carton: pouch, 5 ml oral syringe, adaptor, and package leaflet
- In the pouch: amber polyethylene terephthalate (PET) bottle (118 ml) with polypropylene (PP) screw-cap, and desiccant

Not all pack sizes may be marketed.

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**Manufacturer**

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Detailed information on this medicine is available on the European Medicines Agency web site:  
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