

BETMIGA® 25 MG
BETMIGA® 50 MG

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: Each tablet contains 25 mg of mirabegron.
BETMIGA 50 mg: 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:
Oval, brown tablet, debossed with the company logo and “325” on the same side.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Betmiga (mirabegron) is indicated for the treatment of overactive bladder (OAB) with symptoms of urgency incontinence, urgency, nocturia, and urinary frequency.

4.2 Posology and method of administration

Posology

Adults (including elderly patients)

The recommended dose is 50 mg once daily with or without food.

Special populations

Renal and hepatic impairment

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

The following table provides the daily dosing recommendations for subjects with renal or hepatic impairment in the absence and presence of strong CYP3A inhibitors (see sections 4.4, 4.5 and 5.2).

		Strong CYP3A inhibitors ⁽³⁾	
		Without inhibitor	With inhibitor
Renal impairment ⁽¹⁾	Mild	50 mg	25 mg
	Moderate	50 mg	25 mg
	Severe	25 mg	Not recommended
Hepatic impairment ⁽²⁾	Mild	50 mg	25 mg
	Moderate	25 mg	Not recommended

1. Mild: GFR 60 to 89 mL/min/1.73 m²; moderate: GFR 30 to 59 mL/min/1.73 m²; severe: GFR 15 to 29 mL/min/1.73 m².
2. Mild: Child-Pugh Class A; Moderate: Child-Pugh Class B.
3. Strong CYP3A inhibitors see section 4.5.

Gender

No dose adjustment is necessary according to gender.

Paediatric population

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

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Renal impairment

Betmiga has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m² or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m²); based on a pharmacokinetic study (see section 5.2) a dose reduction to 25 mg is recommended in this population. Betmiga is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m²) concomitantly receiving strong CYP3A inhibitors (see section 4.5).

Hepatic impairment

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

Hypertension

Mirabegron can increase blood pressure. Periodic blood pressure measurements are recommended, especially in hypertensive patients.

Mirabegron is not recommended for use in patients with severe uncontrolled hypertension (defined as systolic blood pressure greater than or equal to 180 mmHg and/or diastolic blood pressure greater than or equal to 110 mmHg).

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.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data

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

In vivo data

CYP2D6 polymorphism

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

Drug-drug interactions

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

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

Effect of enzyme inhibitors

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

Effect of enzyme inducers

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

Effect of mirabegron on CYP2D6 substrates

In healthy volunteers, the inhibitory potency of mirabegron towards CYP2D6 is moderate and the CYP2D6 activity recovers within 15 days after discontinuation of mirabegron. Multiple once daily dosing of mirabegron IR resulted in a 90% increase in C_{max} 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_{max} 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 Betmiga and digoxin, the lowest dose for digoxin should be prescribed initially. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect. The potential for inhibition of P-gp by mirabegron should be considered when Betmiga is combined with sensitive P-gp substrates e.g. dabigatran.

Other interactions

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

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

Fertility

There were no treatment-related effects of mirabegron on fertility in animals (see section 5.3). The effect of mirabegron on human fertility has not been established.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

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

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

Tabulated list of adverse reactions

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

The frequency of adverse reactions is defined as follows: very common ($\geq 1/10$); 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 ($< 1/10,000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA System organ class	Common	Uncommon	Rare
Infections and infestations	Urinary tract infection	Vaginal infection Cystitis	
Eye disorders			Eyelid oedema
Cardiac disorders	Tachycardia	Palpitation Atrial fibrillation	
Gastrointestinal disorders	Nausea Constipation Diarrhoea	Dyspepsia Gastritis	Lip oedema
Skin and subcutaneous tissue disorders		Urticaria Rash Rash macular Rash papular Pruritus	Leukocytoclastic vasculitis Purpura Angioedema
Musculoskeletal and connective tissue disorders		Joint swelling	
Reproductive system and breast disorders		Vulvovaginal pruritus	
Investigations		Blood pressure increased GGT increased AST increased ALT increased	

MedDRA System organ class	Common	Uncommon	Rare
Nervous system disorders	Dizziness Headache		

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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:

- Email to PV@id.astellas.com or
- Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika,
Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Telephone: +62-21-4244691 Ext.1079
Website: <https://e-meso.pom.go.id/ADR>

4.9 Overdose

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

Treatment for overdose should be symptomatic and supportive. In the event of overdose, pulse rate, blood pressure, and ECG monitoring is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

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

Pharmacodynamic effects

Urodynamics

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

Effect on QT interval

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

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

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

Effects on pulse rate and blood pressure in patients with OAB

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

Effect on intraocular pressure (IOP)

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

Clinical efficacy and safety

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

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

Table 1: Co-primary and Selected Secondary Efficacy Endpoints at End of Treatment for Pooled Studies

Parameter	Pooled studies (046, 047, 074)	
	Placebo	Mirabegron 50 mg
Mean number of incontinence episodes per 24 hours (FAS-I) (Co-primary)		
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#
Mean number of micturitions per 24 hours (FAS) (Co-primary)		
n	1328	1324
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#
Mean volume voided (mL) per micturition (FAS) (Secondary)		
n	1328	1322
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#
Mean level of urgency (FAS) (Secondary)		
n	1325	1323
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#
Mean number of urgency incontinence episodes per 24 hours (FAS-I) (Secondary)		
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#

Parameter	Pooled studies (046, 047, 074)	
	Placebo	Mirabegron 50 mg
Mean number of episodes with urgency grades 3 or 4 per 24 hours (FAS) (Secondary)		
n	1324	1320
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#
Treatment satisfaction – visual analogue scale (FAS) (Secondary)		
n	1195	1189
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 randomized patients who took at least 1 dose of double blind study drug and who had a micturition measurement in the baseline diary and at least 1 post-baseline visit diary with a micturition measurement.

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

CI: Confidence Interval.

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

Parameter	Study 046			Study 047		Study 074	
	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg
Mean number of incontinence episodes per 24 hours (FAS-I) (Co-primary)							
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#
Mean number of micturitions per 24 hours (FAS) (Co-primary)							
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

Parameter	Study 046			Study 047		Study 074	
	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg
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#
Mean volume voided (mL) per micturition (FAS) (Secondary)							
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#
Mean level of urgency (FAS) (Secondary)							
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‡
Mean number of urgency incontinence episodes per 24 hours (FAS-I) (Secondary)							
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‡
Mean number of episodes with urgency grades 3 or 4 per 24 hours (FAS) (Secondary)							
n	479	470	472	432	424	413	426
Mean baseline	5.78	5.72	5.79	5.61	5.90	5.42	5.80

Parameter	Study 046			Study 047		Study 074	
	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg
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‡
Treatment satisfaction – visual analogue scale (FAS) (Secondary)							
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 randomized patients who took at least 1 dose of double blind study drug and who had a micturition measurement in the baseline diary and at least 1 post-baseline visit diary with a micturition measurement.

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

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

Subjective improvement in health-related quality of life measurements

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

Efficacy in patients with or without prior OAB antimuscarinic therapy

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

Table 3: Co-primary efficacy endpoints for patients with prior OAB antimuscarinic therapy

Parameter	Pooled studies (046, 047, 074)		Study 046		
	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg
Patients with prior OAB antimuscarinic therapy					
Mean number of incontinence episodes per 24 hours (FAS-I)					
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)
Mean number of micturitions per 24 hours (FAS)					
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)
Patients with prior OAB antimuscarinic therapy who discontinued due to insufficient effect					
Mean number of incontinence episodes per 24 hours (FAS-I)					
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)
Mean number of micturitions per 24 hours (FAS)					
N	466	464	155	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 randomized patients who took at least 1 dose of double blind study drug and who had a micturition measurement in the baseline diary and at least 1 post-baseline visit diary with a micturition measurement.

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

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Betmiga in one or more subsets of the paediatric population in “Treatment of idiopathic overactive

bladder” and “Treatment of neurogenic detrusor overactivity” (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

After oral administration of mirabegron in healthy volunteers mirabegron is absorbed to reach peak plasma concentrations (C_{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 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.

Effect of food on absorption

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.

Distribution

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

Biotransformation

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

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

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

CYP2D6 polymorphism

In healthy subjects who are genotypically poor metabolisers of CYP2D6 substrates (used as a surrogate for CYP2D6 inhibition), mean C_{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 patients who are CYP2D6 poor metabolisers.

Elimination

Total body clearance (CL_{tot}) from plasma is approximately 57 L/h. The terminal elimination half-life ($t_{1/2}$) is approximately 50 hours. Renal clearance (CL_R) is approximately 13 L/h, which corresponds to nearly 25% of CL_{tot} . Renal elimination of mirabegron is primarily through active tubular secretion along with glomerular filtration. The urinary excretion of unchanged mirabegron is dose-dependent and ranges from approximately 6.0% after a daily dose of 25 mg to 12.2% after a daily dose of 100 mg. Following the administration of 160 mg ^{14}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.

Age

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

Gender

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

Race

The pharmacokinetics of mirabegron are not influenced by race.

Renal impairment

Following single dose administration of 100 mg Betmiga in volunteers with mild renal impairment (eGFR-MDRD 60 to 89 mL/min/1.73 m²), mean mirabegron C_{max} and AUC were increased by 6% and 31% relative to volunteers with normal renal function. In volunteers with moderate renal impairment (eGFR-MDRD 30 to 59 mL/min/1.73 m²), C_{max} and AUC were increased by 23% and 66%, respectively. In volunteers with severe renal impairment (eGFR-MDRD 15 to 29 mL/min/1.73 m²), mean C_{max} and AUC values were 92% and 118% higher. Mirabegron has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m² or patients requiring haemodialysis).

Hepatic impairment

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

5.3 Preclinical safety data

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. An increase in heart rate was observed in rats, rabbits, dogs and monkeys. Genotoxicity and carcinogenicity studies have shown no genotoxic or carcinogenic potential *in vivo*.

No effects on fertility were seen at sub-lethal doses (human equivalent dose was 19-fold higher than the maximum human recommended dose (MHRD)). The main findings in rabbit embryofetal

development studies included malformations of the heart (dilated aorta, cardiomegaly) at systemic exposures 36-fold higher than observed at the MHRD. In addition, malformations of the lung (absent accessory lobe of the lung) and increased post-implantation loss were observed in the rabbit at systemic exposures 14-fold higher than observed at the MHRD, while in the rat reversible effects on ossification were noted (wavy ribs, delayed ossification, decreased number of ossified sternebrae, metacarpi or metatarsi) at systemic exposures 22-fold higher than observed at the MHRD. The observed embryofetal toxicity occurred at doses associated with maternal toxicity. The cardiovascular malformations observed in the rabbit were shown to be mediated via activation of the beta 1-adrenoceptor.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet

Macrogols

Hydroxypropylcellulose

Butylhydroxytoluene

Magnesium stearate

Film coating

Hypromellose

Macrogol

Iron oxide yellow

Iron oxide red(only for 25 mg tablet)

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for disposal

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

PACKAGING:

Betmiga 25 mg: Box, 3 blister @ 10 tablets

Betmiga 50 mg: Box, 3 blister @ 10 tablets

SHELF LIFE:

3 years.

STORAGE:

Store below 30°C.

“HARUS DENGAN RESEP DOKTER”

REG NO.:

BETMIGA 25 mg: DKI1620100614A1

BETMIGA 50 mg: DKI1620100614B1

MANUFACTURED BY:

Avara Pharmaceutical Technologies Inc., Norman, USA

RELEASED BY:

Delpharm Meppel B.V., Meppel, The Netherlands

MARKETING AUTHORIZATION HOLDER:

PT. Combiphar, Bandung Barat, Indonesia

MARKETED BY:

PT. Astellas Pharma Indonesia, Jakarta, Indonesia

Informasi untuk Pasien
Betmiga[®] 25 mg tablet lepas lambat
Betmiga[®] 50 mg tablet lepas lambat
Mirabegron

Bacalah leaflet ini dengan seksama sebelum anda mengkonsumsi obat ini karena laeflet ini mengandung informasi penting untuk anda.

- Simpanlah leaflet ini. Anda mungkin perlu untuk membacanya lagi.
- Jika anda memiliki pertanyaan lebih lanjut, silahkan tanya kepada dokter atau apoteker anda.
- Obat ini diresepkan hanya untuk anda. Jangan memberikannya kepada orang lain, hal tersebut mungkin akan membahayakan bagi mereka, walaupun tanda gejala dan penyakit mereka sama seperti anda.
- Jika anda mengalami efek samping, bicarakan dengan dokter atau apoteker anda. Hal ini termasuk efek samping yang mungkin tidak tercantum dalam leaflet ini.

Apa saja yang ada didalam leaflet ini :

1. Apa itu Betmiga[®] dan digunakan untuk apa
2. Apa yang perlu diketahui sebelum menggunakan Betmiga[®]
3. Bagaimana cara menggunakan Betmiga[®]
4. Kemungkinan efek samping
5. Bagaimana cara penyimpanan Betmiga[®]
6. Isi kemasan dan informasi lainnya

1. Apa itu Betmiga[®] dan digunakan untuk apa

Betmiga[®] mengandung zat aktif Mirabegron. Ini merupakan relaksan otot kandung kemih (disebut juga beta 3-adrenoceptor agonist), yang dapat mengurangi aktivitas dari kandung kemih yang terlalu aktif dan mengatasi gejala yang berkaitan dengan penyakit tersebut.

Betmiga[®] digunakan untuk mengatasi gejala *overactive bladder* (OAB) pada orang dewasa seperti :

- Tiba-tiba perlu untuk mengosongkan kandung kemih atau berkemih (disebut *urgency*)
- Harus mengosongkan kandung kemih anda lebih sering dari biasanya (disebut peningkatan frekuensi berkemih)
- Tidak sanggup untuk mengatur kapan harus mengosongkan kandung kemih anda (disebut *urgency incontinence*)

2. Apa yang perlu diketahui sebelum menggunakan Betmiga[®]

Kapan tidak boleh menggunakan Betmiga[®]?

- Jika alergi terhadap salah satu dari komponen Betmiga[®] (tercantum pada bagian 6).

Peringatan dan Perhatian

Bicarakan dengan dokter atau apoteker anda sebelum menggunakan Betmiga[®], bila anda :

- Memiliki masalah dengan pengosongan kandung kemih atau anda memiliki pancaran urin yang lemah atau anda mengkonsumsi obat lain untuk mengatasi *overactive bladder* (OAB) seperti obat anti kolinergik.
- Memiliki masalah pada ginjal dan hati anda. Dokter anda mungkin perlu untuk mengurangi dosis atau memberitahu anda untuk tidak menggunakan Betmiga[®], khususnya bila anda menggunakan bersama-sama dengan obat-obatan lain seperti itraconazole, ketoconazole, ritonavir, atau clarithromycin. Beritahukan kepada dokter anda mengenai obat-obatan yang anda konsumsi.
- Memiliki tekanan darah tinggi.
- Memiliki kelainan ECG yang dikenal sebagai *QT prolongation* atau anda mengkonsumsi obat-obatan lain yang diketahui menyebabkan hal ini seperti :
 - o Obat yang digunakan untuk kelainan irama jantung seperti quinidine, sotalol, procainamide, ibutilide, flecainide, dofetilide, dan amiodarone;
 - o Obat yang digunakan untuk rhinitis alergi.
 - o Obat-obat antipsikotik (obat-obat untuk penyakit kejiwaan) seperti thioridazine, mesoridazine, haloperidol, dan chlorpromazine;
 - o Anti infeksi seperti pentamidine, moxifloxacin, erythromycin, dan clarithromycin.

Anak-anak dan remaja

Tidak untuk diberikan kepada anak-anak dan remaja dibawah usia 18 tahun karena efikasi dan keamanan Betmiga[®] pada kelompok ini belum dapat dipastikan.

Obat lain dan Betmiga[®]

Beritahukan kepada dokter atau apoteker anda apabila anda menggunakan obat lain.

Betmiga[®] mungkin dapat mempengaruhi kerja dari obat lain dan obat lain mungkin dapat mempengaruhi kerja dari Betmiga[®].

- Beritahukan kepada dokter anda apabila anda menggunakan thioridazine (obat untuk penyakit gangguan kejiwaan), propafenone atau flecainide (obat untuk kelainan irama jantung), imipramine atau desipramine (obat yang digunakan untuk depresi). Obat-obatan spesifik ini membutuhkan penyesuaian dosis oleh dokter.
- Beritahukan kepada dokter anda bila anda menggunakan digoxin (obat untuk gagal jantung atau kelainan irama jantung). Kadar obat ini dalam darah harus diukur oleh dokter anda. Apabila kadar obat dalam darah melebihi batas, maka dokter anda mungkin akan melakukan penyesuaian dosis digoxin yang anda gunakan.
- Beritahu dokter anda apabila anda menggunakan dabigatran etexilate (obat untuk pencegahan pembentukan bekuan darah pasca pembedahan pinggul atau lutut). Obat-obat ini mungkin perlu penyesuaian dosis dari dokter anda.

Kehamilan dan menyusui

Apabila anda sedang hamil, atau sedang merencanakan kehamilan anda sebaiknya tidak menggunakan Betmiga[®].

Apabila anda sedang menyusui, silahkan hubungi dokter atau apoteker anda untuk saran sebelum menggunakan obat ini. Kemungkinan besar obat ini dapat melewati air susu anda. Anda dan dokter anda sebaiknya memutuskan apakah anda akan menggunakan Betmiga[®] atau akan menyusui. Anda tidak dapat melakukan keduanya secara bersamaan.

Mengemudi dan menggunakan mesin

Tidak ada informasi yang menyebutkan bahwa obat ini mempengaruhi kemampuan anda mengemudi dan menggunakan mesin.

3. Bagaimana cara menggunakan Betmiga®

Selalu gunakan Betmiga® sesuai petunjuk dokter anda. Anda harus menanyakan kepada dokter atau apoteker anda apabila anda tidak yakin.

Dosis yang direkomendasikan untuk dikonsumsi adalah tablet 50 mg 1 kali sehari. Apabila anda mempunyai gangguan hati atau ginjal, dokter anda mungkin akan mengurangi dosis menjadi 25 mg sehari. Anda sebaiknya menggunakan obat ini dengan air dan menelan tablet ini seutuhnya. Jangan menghancurkan atau mengunyah tablet ini. Betmiga® dapat digunakan dengan atau tanpa makanan.

Apabila anda mengonsumsi Betmiga® lebih banyak dari yang seharusnya

Apabila anda mengonsumsi Betmiga® lebih banyak dari yang seharusnya anda konsumsi, atau apabila seseorang secara tidak sengaja menggunakan obat anda, silahkan hubungi dokter, apoteker, atau rumah sakit terdekat.

Gejala overdosis meliputi detak jantung yang sangat kuat, peningkatan denyut nadi dan tekanan darah.

Apabila anda lupa mengonsumsi Betmiga®

Apabila anda lupa mengonsumsi obat anda, konsumsi sesegera mungkin begitu anda ingat. Bila itu kurang dari 6 jam dari jadwal minum obat anda selanjutnya, lewati dosis yang terlupakan tersebut dan konsumsi obat anda seperti biasa.

Jangan mengonsumsi dosis ganda untuk dosis obat yang terlupakan. Apabila anda lupa mengonsumsi obat ini beberapa kali, beritahukan kepada dokter anda dan ikuti saran yang diberikan.

Apabila anda berhenti mengonsumsi Betmiga®

Jangan menghentikan konsumsi Betmiga® apabila anda tidak segera merasakan efeknya. Kandung kemih anda mungkin membutuhkan waktu untuk beradaptasi. Anda sebaiknya melanjutkan penggunaan obat ini. Jangan berhenti mengonsumsi obat ini apabila keadaan anda sudah membaik. Menghentikan pengobatan dapat menyebabkan kambuhnya gejala *overactive bladder* (OAB).

Jangan menghentikan penggunaan Betmiga® tanpa berkonsultasi dengan dokter anda terlebih dahulu.

Apabila anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, silahkan menanyakan pada dokter atau apoteker anda.

4. Kemungkinan Efek Samping

Seperti obat-obat lainnya, Obat ini dapat menyebabkan efek samping, walaupun tidak semua orang mengalaminya.

Efek samping yang paling serius meliputi denyut jantung yang tidak normal (*atrial fibrillation*). Ini merupakan efek samping yang jarang (dapat mempengaruhi lebih dari 1 dari 1000 orang), tetapi apabila efek samping ini terjadi, segera hentikan penggunaan obat ini dan hubungi dokter anda.

Efek samping lain :

Efek samping yang umum terjadi (dapat mempengaruhi lebih dari 1 dari 10 orang):

- Peningkatan denyut jantung (*tachycardia*)
- Infeksi saluran kemih (*urinary track infection*)
- Mual
- Konstipasi
- Diare
- Pusing
- Sakit kepala

Efek samping yang tidak biasa terjadi (dapat mempengaruhi hingga 1 dari 100 orang):

- Infeksi kandung kemih (*cystitis*)
- Berdebar - debar (*palpitations*)
- Infeksi vaginal
- Gangguan pencernaan (*dyspepsia*)
- Infeksi pencernaan (*gastritis*)
- Pembengkakan sendi
- Gatal pada vulva atau vagina (*vulvovaginal pruritus*)
- Peningkatan tekanan darah
- Peningkatan enzim hati (GGT, AST, dan ALT)
- Ruam dan gatal-gatal (*urticaria, rash, rash macular, rash papular, pruritus*)

Efek samping yang jarang terjadi (dapat mempengaruhi hingga 1 dari 1.000 orang):

- Pembengkakan pada kelopak mata (*eyelid oedema*)
- Pembengkakan pada bibir (*lip oedema*)
- Bercak biru pada permukaan kulit (*purpura*)
- Peradangan pada pembuluh darah kecil terutama pada kulit (*leukocytoclastic vasculitis*)
- Pembengkakan pada lapisan kulit bagian dalam akibat adanya kumpulan cairan yang dapat terjadi pada wajah, lidah, atau tenggorokan dan dapat menyebabkan kesulitan bernapas (*angioedema*)

Betmiga[®] dapat meningkatkan kemungkinan untuk tidak dapat mengosongkan kandung kemih anda apabila anda memiliki obstruksi pengosongan kandung kemih atau apabila anda

menggunakan obat lain untuk mengatasi *overactive bladder (OAB)*. Beritahu dokter anda segera apabila anda tidak dapat mengosongkan kandung kemih anda.

Pelaporan efek samping

Jika Anda mengalami efek samping atau ketidaknyamanan selama atau setelah menggunakan obat ini, bicarakan dengan dokter atau tenaga kesehatan profesional Anda. Anda juga dapat langsung melaporkan efek samping ke PT. Astellas Pharma Indonesia melalui pv@id.astellas.com. Harap diketahui bahwa pelaporan ke PT. Astellas Pharma Indonesia hanya untuk mengumpulkan data dan tidak sebagai pengganti konsultasi pada dokter atau tenaga kesehatan profesional Anda. Dengan melaporkan efek samping, Anda dapat membantu menyediakan informasi keamanan untuk obat ini. Selalu bicarakan pada dokter atau tenaga kesehatan profesional Anda untuk saran medis

5. Bagaimana cara penyimpanan Betmiga®

Jauhkan dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kadaluarsa yang tertera pada karton setelah kata "EXP". Tanggal kadaluarsa mengacu pada hari terakhir dari bulan itu.

Obat ini tidak memerlukan kondisi penyimpanan khusus.

Jangan membuang obat-obatan melalui air limbah atau limbah rumah tangga. Tanyakan apoteker anda bagaimana cara membuang obat-obatan yang tidak anda gunakan lagi. Langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lain

Apa yang terkandung dalam Betmiga®

- Zat aktif mirabegron. Tiap tablet mengandung 25 mg, atau 50 mg mirabegron.
- Bahan lainnya adalah :
 - Inti tablet : Macrogols, hydropropylcellulose, butylhydroxytoluene, magnesium stearate.
 - Lapisan penyalut : Hypermellose, macrogol, iron oxide yellow, iron oxide red (khusus tablet 25 mg).

Seperti apakah bentuk Betmiga® dan isi dari kemasannya

Betmiga® 25 mg tablet lepas lambat salut film berbentuk oval, tablet salut film berwarna coklat, dicetak dengan logo perusahaan dan "325" pada sisi yang sama.

Betmiga® 50 mg tablet lepas lambat salut film berbentuk oval, tablet salut film berwarna ckuning, dicetak dengan logo perusahaan dan "355" pada sisi yang sama.

Betmiga® tersedia dalam blister aluminium dalam kemasan 30tablet.

Pemegang Izin Edar dan Produsen

Produsen

Avara Pharmaceutical Technologies Inc.
3300 Marshall Avenue, Norman, OK
73072, USA

Dirilis oleh

Delpharm Meppel B.V.Hogemaat 2 7942,
JG Meppel, Belanda

Pemegang Izin Edar

PT. Combiphar
Jl. Raya Simpang 383
Padalarang
Bandung Barat, Indonesia

Dipasarkan oleh

PT. Astellas Pharma Indonesia
Plaza Oleos Lt. 5, Jl. TB Simatupang No. 53A
Jakarta 12520, Indonesia

Untuk informasi lebih lanjut mengenai obat ini, harap menghubungi:

PT. Astellas Pharma Indonesia

Tel.: +62 21 22780171

Website: www.astellas.co.id