SCHEDULING STATUS:

S3

1 NAME OF THE MEDICINE

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Sugar free.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

Betmiga 25 mg tablets:
Oval, brown film coated tablet, debossed with the Astellas logo and “325”

Betmiga 50 mg tablets:
Oval, yellow film coated tablet, debossed with the Astellas logo and “355”

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Adults (including elderly patients)
The recommended dose of Betmiga is 50 mg once daily.

Paediatric population
The safety and efficacy of Betmiga in children below 18 years of age have not been established. Therefore, use in this age group is not recommended.

Patients with Renal Impairment
No dose adjustment is necessary in patients with mild or moderate renal impairment (eGFR 30 to 89 ml/min/1.73 m^2 as estimated by MDRD). In patients with severe renal impairment (eGFR 15 to 29 ml/min/1.73 m^2), the recommended dose of Betmiga is 25 mg once daily with or without food. Betmiga has not been studied in patients with End Stage Renal Disease (eGFR <15 ml/min/1.73 m^2 or patients requiring haemodialysis). (see Contraindications section 4.3).

Patients with Hepatic Impairment
No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A). In patients with moderate hepatic impairment (Child-Pugh Class B) the recommended dose of Betmiga is 25 mg once daily with or without food. Betmiga has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). (see Contraindications section 4.3).

Method of administration
Betmiga is to be taken once daily, with liquids, swallowed whole and is not to be chewed, divided, or crushed. It may be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients of Betmiga listed in section 6.1.
- Severe end-stage renal impairment (eGFR < 15 ml/min/1.73m^2).
- Severe hepatic impairment (Child-Pugh Class C).
- Severe uncontrolled hypertension defined as systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg.

4.4 Special warnings and precautions for use

Renal Impairment

Betmiga has not been studied in patients with End Stage Renal Disease (eGFR <15 ml/min/1.73 m^2 or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. In patients with severe renal impairment (GFR 15-29 ml/min/1.73 m^2), dosage reduction to 25 mg is recommended. Betmiga is not recommended for use in patients with severe renal impairment (GFR 15-29 ml/min/1.73 m^2) concomitantly receiving strong CYP3A inhibitors (see section 4.5).

Hepatic Impairment

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

Hypertension

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

Patients with Congenital or Acquired QT Prolongation

Betmiga at therapeutic doses, has not demonstrated clinically relevant QT prolongation in healthy patients. However, since patients with a known history of QT prolongation or patients who are taking medicines known to prolong QT interval were not included in these studies the effects of mirabegron in these patients is unknown. Caution should be exercised when administering Betmiga in patients with congenital or acquired QT prolongation.

Patients with Bladder Outlet Obstruction and Patients Taking Antimuscarinic Medication 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 Betmiga. 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 medicines and other forms of interaction

In vitro data

Mirabegron, the active ingredient in Betmiga, is transported and metabolised through multiple pathways. Mirabegron is a substrate for CYP3A4, CYP2D6, butyrylcholinesterase, uridine diphosphoglucuronosyltransferases (UGT), the efflux transporter P-glycoprotein (P-gp) and the influx organic cation transporters (OCT) OCT1, OCT2, and OCT3. Studies of Betmiga 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.
Betmiga is unlikely to inhibit the metabolism of co-administered medicines 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. Betmiga did not induce CYP1A2 or CYP3A4. BETMIGA inhibited P-gp-mediated medicines transport at high concentrations. Betmiga is predicted not to cause clinically relevant inhibition of OCT-mediated drug transport.

In vivo data

Drug-drug Interactions
The effect of co-administered medicines on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of co-medications was studied in single- and multiple-dose studies. Sulfonylurea hypoglycaemic medicines, glibenclamide (a CYP3A4 substrate), gliclazide (a CYP2C9 and CYP3A4 substrate) and tolbutamide (a CYP2C9 substrate) did not affect the *in vitro* metabolism of mirabegron. Mirabegron did not affect the metabolism of glibenclamide or tolbutamide.

Clinically relevant interactions between mirabegron and medicines 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.

Betmiga is unlikely to inhibit the metabolism of co-administered medicines 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. Betmiga

did not induce CYP1A2 or CYP3A. Betmiga inhibited P-gp-mediated medicines transport at high concentrations. Betmiga is predicted not to cause clinically relevant inhibition of OCT-mediated drug transport.

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.
Betmiga is not recommended in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2) or patients with moderate hepatic impairment (Child-Pugh Class B) concomitantly receiving strong CYP3A inhibitors (see Warnings and Special Precautions).

Effect of enzyme inducers
Substances that are inducers of CYP3A or P-gp decrease the plasma concentrations of Betmiga. No dose adjustment is needed for Betmiga 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 Betmiga 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 Betmiga is co-administered with medicinal products with a narrow therapeutic index and significantly metabolised by CYP2D6, such as thioridazine, haloperidol, risperidone, Type 1C antidysrhythmics (e.g. flecainide, propafenone, encainide) and tricyclic antidepressants (e.g. imipramine, desipramine, clomipramine). Caution is also advised if Betmiga is co-administered with CYP2D6 substrates that are individually dose titrated.

Effect of Betmiga on transporters
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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

Safety in pregnancy has not been established.
It is recommended that Betmiga be avoided during pregnancy.

Breastfeeding

Mirabegron may be present in human milk.
Betmiga should not be administered to mothers who are breastfeeding their infants.

4.7 Effects on ability to drive and use machines

Betmiga may cause dizziness, somnolence and blurred vision, which may have an 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 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). Based on three 12-week phase 3 studies, 4 % of the patients discontinued due to Adverse Events. Common adverse reactions (frequency ≥1.0 % and > placebo) reported for patients treated with Betmiga 50 mg were 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. Serious adverse reactions included atrial fibrillation in 0.2% of patients.

Tabulated list of adverse reactions

MedDRA System Organ Class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**
Infections and infestations	Urinary tract infection*	Vaginal infection, Cystitis	
Nervous system disorders		Dizziness, Somnolence, Blurred vision	
Eye disorders			Eyelid oedema
Cardiac disorders	Tachycardia*	Palpitations, Atrial fibrillation	
Gastrointestinal disorders		Dyspepsia, Gastritis	Lip oedema
Skin and subcutaneous tissue disorders		Urticarial rash, Macular rash, Papular rash, Pruritus	Leukocytoclastic vasculitis, Purpura
Musculoskeletal and connective tissue disorders		Joint swelling	

Reproductive system and breast disorders	Vulvovaginal pruritus
Investigations	Increased blood pressure, Increased GGT, Increased AST, Increased ALT

Side Effects observed during post-marketing experience

Psychiatric disorders:	Insomnia, confusional state (frequency not known)
Vascular disorders:	Hypertensive crisis (less frequent)
Gastrointestinal disorders:	Nausea, constipation, diarrhoea (frequent)
Immune system disorders:	Angioedema (less frequent)
Renal and urinary disorders:	Urinary retention (less frequent)
Nervous system disorders:	Headache, dizziness (frequent)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8
or
Astellas Pharma (Pty) Ltd, 7 Mirage Road, Bedfordview, 2007, South Africa
Tel: +27 11 615 9433 Fax: +27 11 615 9427
Drugsafety.za@astellas.com

4.9 Overdose

At doses of 300 and 400 mg, adverse events reported included palpitations, increased pulse rate exceeding 100 bpm and increased systolic blood pressure. 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

Pharmacological classification: A.16.5 Urinary System: Others
ATC code: G04BD12

Mechanism of action

Mirabegron is a potent and selective beta 3-adrenoceptor agonist. Mirabegron showed relaxation of bladder smooth muscle in human isolated tissue. Data from animal models indicate that mirabegron enhances urine storage function by stimulating beta 3-adrenoceptors in the bladder.

Pharmacodynamic effects

Urodynamics

Mirabegron at doses of 50 mg and 100 mg once daily showed no effect on cystometry parameters. In patients with lower urinary tract symptoms (LUTS) and bladder outlet obstruction (BOO) mirabegron did not adversely affect the maximum flow rate or detrusor pressure at maximum flow rate.

Effects on Pulse Rate and Blood Pressure in Patients with Overactive Bladder (OAB)
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.
In OAB patients (mean age of 59 years) using 50 mg or 100 mg daily, no clinically relevant changes were seen in the blood pressure or pulse rate.

Effect on Intraocular Pressure (IOP)
Mirabegron 100 mg once daily did not increase IOP in healthy subjects after 56 days of treatment.

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 8.5- 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 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.

Metabolism

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}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. *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.

Poor metabolizers of CYP2D6:
In poor metabolizers of CYP2D6, used as a surrogate for CYP2D6 inhibition, mean C_{max} and AUC_{inf} of a single 160 mg dose of mirabegron IR were 14 % and 19 % higher than in extensive metabolizers, indicating that CYP2D6 genetic polymorphism has minimal impact on the mean plasma exposure to mirabegron. The interaction of mirabegron with a known CYP2D6 inhibitor 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

No dose adjustment is necessary for the elderly. 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 to 45 years).

Gender

Dose adjustment may be necessary based on 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.

Renal Impairment

Following single dose administration of 100 mg mirabegron in volunteers with mild renal impairment (eGFR 60 to 89 ml/min/1.73 m^2 as estimated by MDRD), 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 30 to 59 ml/min/1.73 m^2), C_{max} and AUC were increased by 23 % and 66 %, respectively. In volunteers with severe renal impairment (eGFR 15 to 29 ml/min/1.73 m^2),

mean C_{max} and AUC values were 92 % and 118 % higher. Mirabegron has not been studied in patients with End Stage Renal Disease (eGFR <15 ml/min/1.73 m^2 or patients requiring haemodialysis).

Hepatic Impairment

Following single dose administration of 100 mg mirabegron 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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet
Macrogol 8,000 and 2,000,000
Hydroxypropylcellulose
Butylhydroxytoluene
Magnesium stearate

Film coating
Betmiga 25 mg prolonged-release tablets
Hypromellose 2910, 6 mPa.s
Macrogol 8,000
Iron oxide yellow (E172)
Iron oxide red (E172)

Betmiga 50 mg prolonged-release tablets
Hypromellose 2910, 6 mPa.s
Macrogol 8,000
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not remove the tablet from the blister until required for use.
Store at or below 25°C.
KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Betmiga 25 mg tablets and Betmiga 50 mg tablets are packed in aluminium-aluminium blisters (Polyamide/Aluminium/PVC laminate foil sealed with an aluminium foil/heat seal coated lidding foil) in cartons containing 30 tablets.

6.6 Special precautions for disposal

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

BETMIGA 25 mg: 47/16.5/0297
BETMIGA 50 mg: 47/16.5/0298

9 DATE OF FIRST AUTHORISATION

30 September 2016

10 DATE OF REVISION OF THE TEXT

12 May 2022