AUSTRALIAN PRODUCT INFORMATION – BETMIGA® (MIRABEGRON) PROLONGED-RELEASE FILM-COATED TABLETS

1 NAME OF THE MEDICINE

Mirabegron

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BETMIGA contains mirabegron 25 mg or 50 mg as the active ingredient.

For the full list of excipients, see Section 6.1 - LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

BETMIGA is available as prolonged-release film-coated tablets for oral administration. The tablets are presented as the following:
25 mg: an oval, brown film-coated tablet, debossed with the  (Astellas logo) and "325"
50 mg: an oval, yellow film-coated tablet, debossed with the  (Astellas logo) and "355"

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults (including Elderly Patients)
The recommended starting dose of BETMIGA is 25 mg once daily. Based on individual patient efficacy and tolerability the dose may be increased to 50 mg once daily.

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

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 m2 as estimated by MDRD). In patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m2), the recommended dose 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 m2 or patients requiring haemodialysis) (see Section 5.2 - PHARMACOKINETIC PROPERTIES - Pharmacokinetic Characteristics in Special Populations).

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 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 Section 5.2 - PHARMACOKINETIC PROPERTIES - Pharmacokinetic Characteristics in Special Populations).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Patients with severe uncontrolled hypertension (systolic ≥180mmHg and /or diastolic ≥110mmHg).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Increases in Blood Pressure and Heart Rate

BETMIGA can increase blood pressure and heart rate. Blood pressure should be measured at baseline and monitored periodically during BETMIGA treatment, especially in hypertensive patients (see Section 5.1 - PHARMACODYNAMIC PROPERTIES: Pharmacodynamic Effects: Effects on Pulse Rate and Blood Pressure in Patients with Overactive Bladder (OAB)).

BETMIGA is contraindicated in patients with severe uncontrolled hypertension (defined as systolic blood pressure greater than or equal to 180mmHg and/or diastolic blood pressure greater or equal to 110mmHg) (see Section 4.3 - CONTRAINDICATIONS). There is limited data in patients with moderate (grade 2) hypertension (systolic blood pressure 160-169mmHg and/or diastolic 100-109mmHg) and thus, caution is advised.

Patients with Congenital or Acquired QT Prolongation

Consider observations from the QT study (see Section 5.1 - PHARMACODYNAMIC PROPERTIES: Pharmacodynamic Effects: Effect on QT Interval) in clinical decisions to prescribe BETMIGA to patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong QT interval (see Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION: Other).

Urinary Retention in Patients with Bladder Outlet Obstruction and in Patients Taking Antimuscarinic Medications for OAB

Urinary retention in patients with 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 BETMIGA-treated patients; however, BETMIGA should be administered with caution to patients with BOO and with caution in patients taking antimuscarinic agents (see Section 5.1 - PHARMACODYNAMIC PROPERTIES: Pharmacodynamic Effects: Urodynamics).

Angioedema

Angioedema of the face, lips, tongue, and/or larynx has been reported with BETMIGA. In some cases angioedema occurred after the first dose. Cases of angioedema have been reported to occur hours after the first dose or after multiple doses. Angioedema associated with upper airway swelling may be life threatening. If involvement of the tongue, hypopharynx, or larynx occurs, promptly discontinue BETMIGA and initiate appropriate therapy and/or measures necessary to ensure a patent airway.

Patients Taking Drugs Metabolised by CYP2D6

Mirabegron is a moderate CYP2D6 inhibitor and systemic exposure to CYP2D6 substrates such as metoprolol and despiramine is increased when co-administered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index drugs metabolised by CYP2D6 such as thioridazine, flecainide and propafenone (see Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION).

Use in 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.

Use in renal impairment

BETMIGA has not been studied in patients with End Stage Renal Disease (eGFR <15 mL/min/1.73 m2 or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population.

Use in the elderly

No dose adjustment is necessary for the elderly (see Section 5.2 - PHARMACOKINETIC PROPERTIES - Pharmacokinetic Characteristics in Special Populations).

Paediatric use

The safety and efficacy of BETMIGA in patients below 18 years of age have not yet been established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In Vitro Data

Clinically relevant drug interactions between mirabegron and medicines that inhibit, induce or are a substrate for one of the cytochrome P450 (CYP) isozymes or transporters are not expected except for the inhibitory effect of mirabegron on the metabolism of CYP2D6 substrates. Mirabegron is transported and metabolized through multiple pathways. Mirabegron is a substrate for CYP3A4, CYP2D6, butyrylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT), the efflux transporter P-glycoprotein (P-gp) and the influx organic cation transporters (OCT) OCT1, OCT2, and OCT3. Sulfonylurea hypoglycaemic agents 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.

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 is unlikely to inhibit the metabolism of co-administered drugs 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 inhibited P-gp-mediated

drug transport at high concentrations. Mirabegron is predicted not to cause clinically relevant inhibition of OCT-mediated drug transport.

In Vivo Data

CYP2D6 Polymorphism
In healthy subjects who are genotypically poor metabolizers of CYP2D6 substrates (used as a surrogate for CYP2D6 inhibition), mean Cmax and AUCinf of a single 160 mg dose of a mirabegron immediate-release (IR) formulation were 14% and 19% higher than in extensive metabolizers, 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 metabolizers.

Drug-Drug Interactions
Drug interaction studies were conducted to investigate the effect of co-administered drugs on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of co-administered drugs (e.g. ketoconazole, rifampin, solifenacin, tamsulosin, and oral contraceptives). No dose adjustment is recommended when these drugs are co-administered with mirabegron.

The following are drug interactions for which monitoring is recommended:

Drugs Metabolised by CYP2D6
Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure of drugs metabolized by CYP2D6 enzyme such as metoprolol and desipramine is increased when co-administered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary when BETMIGA is co-administered with these drugs, especially with narrow therapeutic index CYP2D6 substrates, such as thioridazine, flecainide and propafenone (see Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS: Patients Taking Drugs Metabolised by CYP2D6).

Digoxin
When given in combination, mirabegron increased mean digoxin Cmax from 1.01 to 1.3 ng/mL (29%) and AUC from 16.7 to 19.3 ng.h/mL (27%). Therefore, for patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should initially be considered. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect.

Warfarin
The mean Cmax of S- and R-warfarin was increased by approximately 4% and AUC by approximately 9% when administered as a single dose of 25 mg after multiple doses of 100 mg mirabegron. Following a single dose administration of 25 mg warfarin, mirabegron had no effect on the warfarin pharmacodynamic endpoints such as International Normalized Ratio (INR) and prothrombin time. However, the effect of mirabegron on multiple doses of warfarin and on warfarin pharmacodynamic end points such as INR and prothrombin time has not been fully investigated.

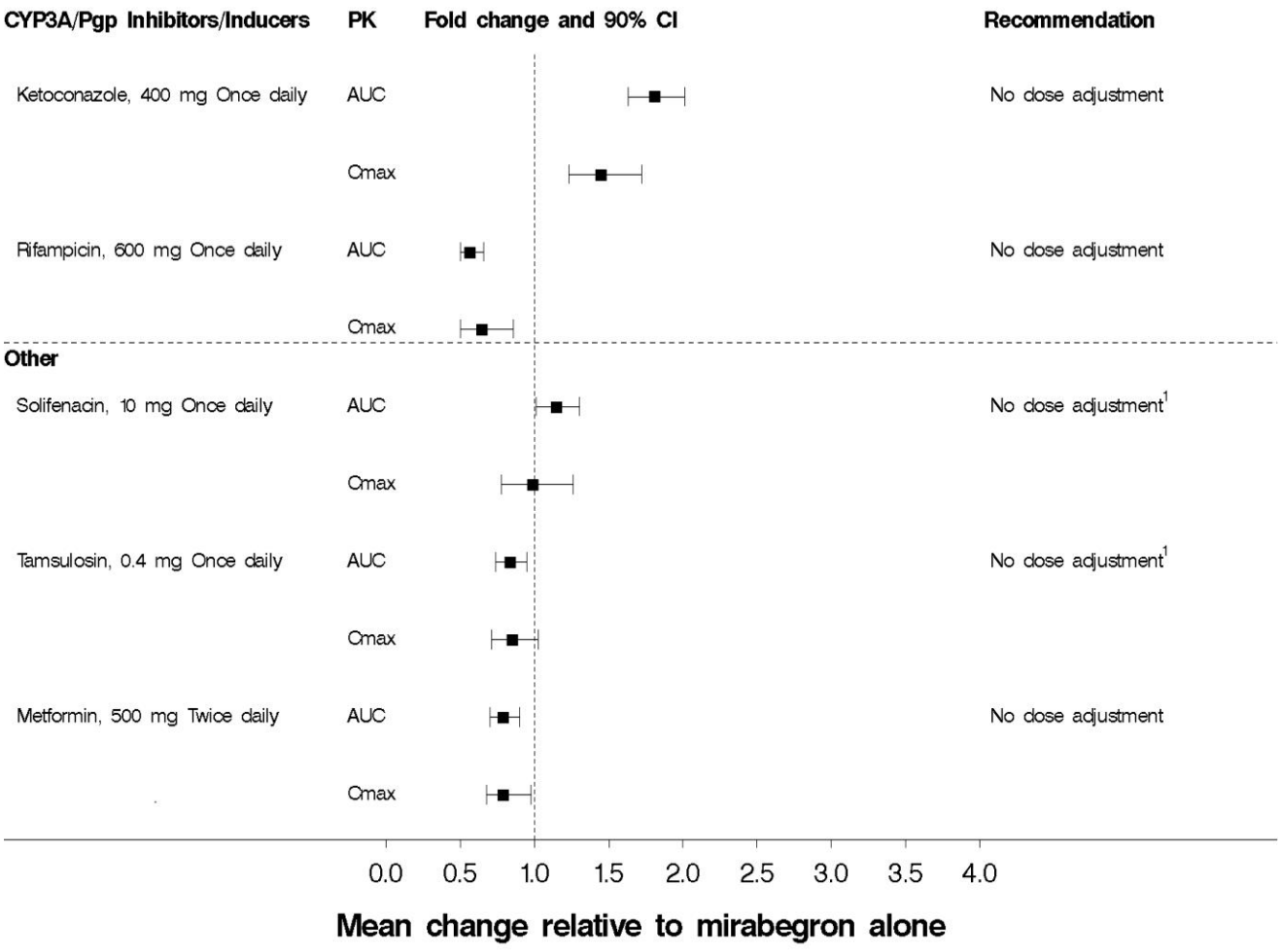
Other

Mirabegron, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies (see see Section 5.1 - PHARMACODYNAMIC PROPERTIES: Pharmacodynamic Effects:

Effect on QT Interval). 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 (see Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS). Examples of drugs that are known to prolong the QT interval include: quinidine, sotalol, amiodarone, mesoridazine, haloperidol, erythromycin, clarithromycin.

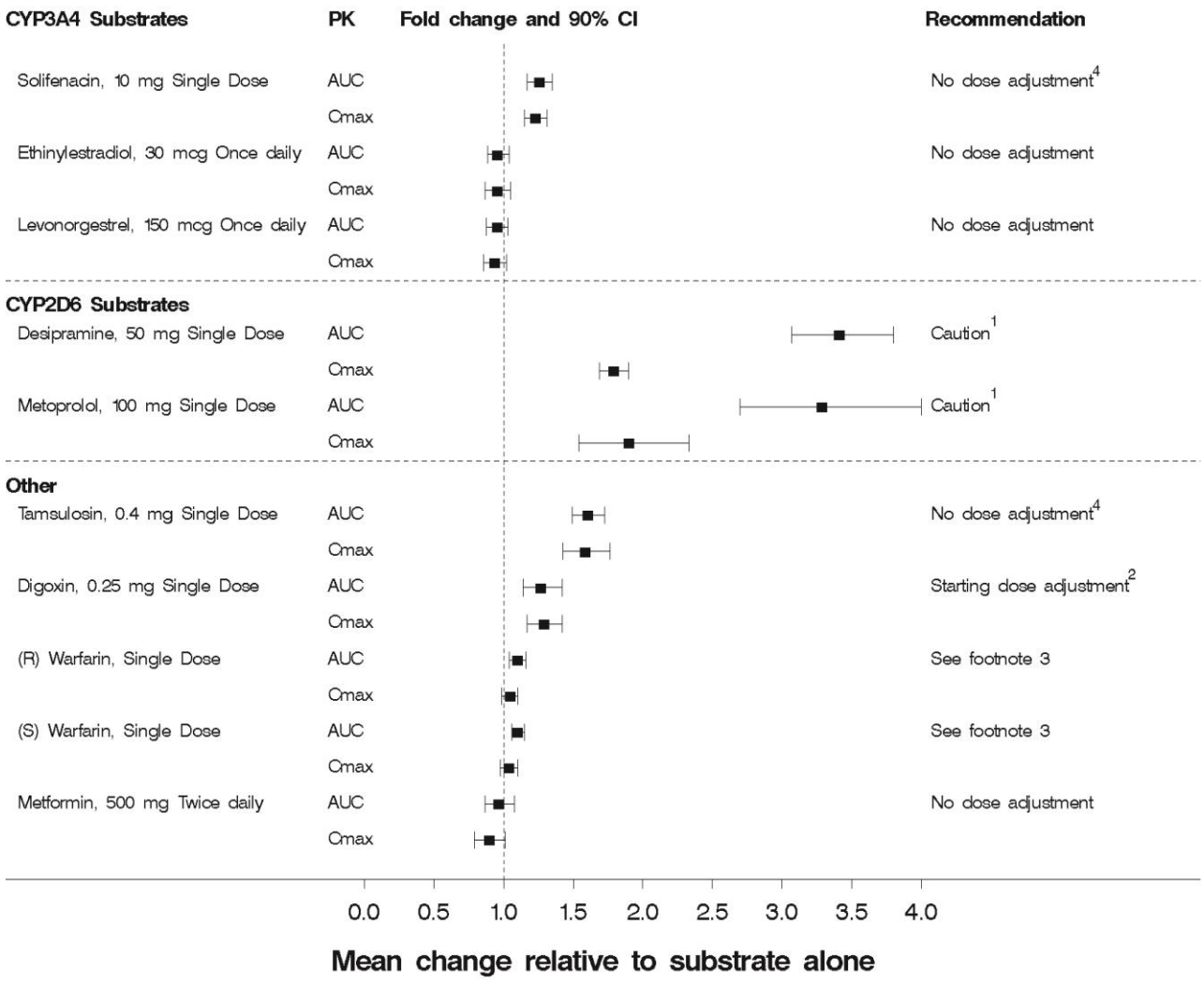
Figures 1 and 2 show the magnitude of these interactions on the pharmacokinetic parameters and the recommendations for dose adjustment, if any.

Figure 1. Effect of Co-administered Medicines on Exposure of Mirabegron and Dose Recommendation



(1) Although no dose adjustment is recommended with solifenacin or tamsulosin based on the lack of pharmacokinetic interaction, BETMIGA should be administered with caution to patients taking antimuscarinic medications for the treatment of OAB and in patients with clinically significant BOO because of the risk of urinary retention (see Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS).
CI: Confidence interval

Figure 2. Effect of Mirabegron on Exposure of Co-administered Medicines



(1) Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates such as metoprolol and desipramine is increased when co-administered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index CYP2D6 substrates, such as thioridazine, flecainide, and propafenone (see Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS and Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

(2) For patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should initially be prescribed. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect (see Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

(3) Warfarin was administered as a single 25 mg dose of the racemate (a mixture of R-warfarin and S-warfarin). Based on this single dose study, mirabegron had no effect on the warfarin pharmacodynamic endpoints such as INR and prothrombin time. However, the effect of mirabegron on multiple doses of warfarin and on warfarin pharmacodynamic end points such as INR and prothrombin time has not been fully investigated (see and Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

(4) Although no dose adjustment is recommended with solifenacin or tamsulosin based on the lack of pharmacokinetic interaction, BETMIGA should be administered with caution to patients taking antimuscarinic medications for the treatment of OAB and in BOO because of the risk of urinary retention (see Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS).

CI: Confidence interval

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There were no treatment-related effects of mirabegron on fertility in animals at non-lethal doses (human equivalent dose ≥ 22-fold of Maximum Recommended Human Dose).

The effect of mirabegron on human fertility has not been established.

Use in pregnancy – Pregnancy Category B3

There are no adequate and well-controlled studies using mirabegron in pregnant women. Mirabegron was shown to cross the placenta in pregnant rats, resulting in fetal exposure. Toxicokinetic studies in rabbits, but not in rats, showed an approximately two-fold increase in mirabegron exposure during pregnancy, but this was not observed in rats. The effect of pregnancy on human pharmacokinetics is unknown. Animal studies indicate a low probability of direct or indirect harmful effects with respect to reproductive toxicity at therapeutic doses. Systemic exposure at the embryofetal NOAEL (rabbits and rats) and peri-postnatal NOAEL (rats) was similar to (rabbits) or up to six times higher (rats) than the therapeutic exposure level at the maximum recommended human dose. Reversible adverse developmental findings consisting of delayed ossification and wavy ribs in rats and decreased fetal body weights in rabbits occurred at exposures greater than or equal to 22 and 14 times, respectively, the maximum recommended therapeutic dose. At maternally toxic exposures decreased fetal weights were observed in rats and rabbits, and additional findings in rabbits included fetal death, dilated aorta, and cardiomegaly. Increased postnatal mortality and reduced pup weight were observed in rats whose dams were exposed to mirabegron levels 22 times higher than therapeutic levels during pregnancy and lactation, but there were no adverse behavioural or developmental effects. As a precautionary measure, it is preferable to avoid the use of mirabegron during pregnancy.

Use in lactation

Mirabegron is excreted in the milk of rodents and therefore is predicted to be present in human milk. 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. 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. Mirabegron should not be administered during breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machinery have been performed. There is no indication in the preclinical or clinical studies that BETMIGA affects the ability to drive or operate machinery, or impairs mental ability. Dizziness, somnolence and blurred vision were infrequently reported adverse events in the clinical studies.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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 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 mirabegron, and 4% of the patients discontinued due to adverse effects. Most adverse drug reactions were mild to moderate in severity.

Table 1 lists adverse events that were reported in Studies 046, 047 and 074 at an incidence greater than placebo and in 1% or more of patients treated with BETMIGA 25 mg or 50 mg once daily for up to 12 weeks. The most commonly reported adverse reactions (greater than 2% of BETMIGA patients and greater than placebo) were hypertension, nasopharyngitis, urinary tract infection and headache.

Table 1. Percentages of Patients with Adverse Events, Exceeding Placebo Rate and Reported by 1% or More Patients Treated With BETMIGA 25 mg or 50 mg Once Daily in Studies 046, 047, and 074

	Placebo (%)	BETMIGA 25 mg (%)	BETMIGA 50 mg (%)
Number of Patients	**1380**	**432**	**1375**
Hypertension*	7.6	11.3	7.5
Nasopharyngitis	2.5	3.5	3.9
Urinary Tract Infection	1.8	4.2	2.9
Headache	3.0	2.1	3.2
Constipation	1.4	1.6	1.6
Upper Respiratory Tract Infection	1.7	2.1	1.5
Arthralgia	1.1	1.6	1.3
Diarrhea	1.3	1.2	1.5
Tachycardia	0.6	1.6	1.2
Abdominal Pain	0.7	1.4	0.6
Fatigue	1.0	1.4	1.2

**Includes reports of blood pressure above the normal range, and BP increased from baseline, occurring predominantly in subjects with baseline hypertension.*

Other adverse reactions reported by less than 1% of patients treated with BETMIGA in Studies 046, 047, 074 included:

Cardiac disorders: palpitations, blood pressure increased (see Section 5.1 - PHARMACODYNAMIC PROPERTIES: Pharmacodynamic Effects: Effects on Pulse Rate and Blood Pressure in Patients with Overactive Bladder (OAB))

Eye disorders: glaucoma (see Section 5.1 - PHARMACODYNAMIC PROPERTIES: Pharmacodynamic Effects: Effect on Intraocular Pressure (IOP))

Gastrointestinal disorders: dyspepsia, gastritis, abdominal distension

Infections and infestations: sinusitis, rhinitis

Investigations: GGT increased, AST increased, ALT increased, LDH increased

Renal and urinary disorders: nephrolithiasis, bladder pain

Reproductive system and breast disorders: vulvovaginal pruritus, vaginal infection

Skin and subcutaneous tissue disorders: urticaria, leukocytoclastic vasculitis, rash, pruritus, purpura, lip oedema

Table 2 lists the rates of the most commonly reported adverse reactions, derived from all adverse events in patients treated with BETMIGA 50 mg for up to 52 weeks in long term safety Study 049. The most commonly reported adverse reactions (>3% of BETMIGA patients) were hypertension, urinary tract infection, headache, and nasopharyngitis.

Table 2: Percentages of Patients with Adverse Events, Reported by Greater Than 2% of Patients Treated With BETMIGA 50 mg Once Daily in Long Term Safety Study 049

	BETMIGA 50 mg (%)	**Tolterodine ER 4 mg (%)**
Number of Patients	**812**	**812**
Hypertension	9.2	9.6
Urinary Tract Infection	5.9	6.4
Headache	4.1	2.5
Nasopharyngitis	3.9	3.1
Back Pain	2.8	1.6
Constipation	2.8	2.7
Dry Mouth	2.8	8.6
Dizziness	2.7	2.6
Sinusitis	2.7	1.5
Influenza	2.6	3.4
Arthralgia	2.1	2.0
Cystitis	2.1	2.3

The following events have been reported in association with mirabegron use in worldwide post-marketing experience:

Cardiac disorders: atrial fibrillation

Gastrointestinal disorders: nausea

Skin and subcutaneous tissue disorders: angioedema

Urologic: urinary retention (see Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Mirabegron is an agonist of the human beta 3-adrenoceptor (AR) as demonstrated by in vitro laboratory experiments using the cloned human beta 3-AR. Although mirabegron showed very low intrinsic activity for cloned human beta 1- and beta 2-AR, results in humans indicate that some beta 1-AR stimulation occurs at mirabegron doses of 50 to 200 mg. Mirabegron showed relaxation of bladder smooth muscle in rat and human isolated tissue, increased 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-AR 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-AR induced increases in cAMP. Therefore beta 3-AR 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.

<u>Pharmacodynamic Effects</u>

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 a 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.

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 (CI) did not exceed 10 ms 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 ms (upper bound of the one-sided 95% CI 5.72 ms). In males, the difference was 2.89 ms (upper bound of the one-sided 95% CI 4.90 ms). At a mirabegron dose of 200 mg, the QTcI interval did not exceed 10 ms at any time point in males, while in females the upper bound of the one-sided 95% CI did exceed 10 ms between 0.5-6 h, with a maximum difference from placebo at 5 hours where the mean effect was 10.42 ms (upper bound of the one-sided 95% CI 13.44 ms). 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 Overactive Bladder (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 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 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 trials

Efficacy of mirabegron 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 naive 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), but this study did not directly compare mirabegron to tolterodine.

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).

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 randomized, active controlled, long term study (1 year) illustrated that response to mirabegron therapy was sustained throughout the treatment period.

Table 3. Co-primary and Selected Secondary Efficacy Endpoints at End of Treatment for Pooled Studies

	Pooled studies (046, 047, 074)	
Parameter	**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

Parameter	Pooled studies (046, 047, 074)	
	Placebo	Mirabegron 50 mg
Mean change from baseline†	-0.98	-1.38
Mean difference from placebo† (95% CI)	--	-0.40 (-0.57, -0.23)
p-value	--	< 0.001#
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 4. 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 25 mg	Mirabegron 50 mg
Mean number of incontinence episodes per 24 hours (FAS-I) (Co-primary)								
n	291	293	300	325	312	262	254	257
Mean baseline	2.67	2.83	2.63	3.03	2.77	2.43	2.65	2.51
Mean change from baseline†	-1.17	-1.57	-1.27	-1.13	-1.47	-0.96	-1.36	-1.38
Mean difference from placebo†	--	-0.41	-0.10	--	-0.34	--	-0.40	-0.42
95% Confidence Interval	--	(-0.72, -0.09)	(-0.42, 0.21)	--	(-0.66, -0.03)	--	(-0.74, -0.06)	(-0.76, -0.08)
p-value	--	0.003#	0.11	--	0.026#	--	0.005#	0.001#
Mean number of micturitions per 24 hours (FAS) (Co-primary)								
n	480	473	475	433	425	415	410	426

Parameter	Study 046			Study 047		Study 074		
	Placebo	**Mirabegron 50 mg**	**Tolterodine ER 4 mg**	**Placebo**	**Mirabegron 50 mg**	**Placebo**	**Mirabegron 25 mg**	**Mirabegron 50 mg**
Mean baseline	11.71	11.65	11.55	11.51	11.80	11.48	11.68	11.66
Mean change from baseline†	-1.34	-1.93	-1.59	-1.05	-1.66	-1.18	-1.65	-1.60
Mean difference from placebo†	--	-0.60	-0.25	--	-0.61	--	-0.47	-0.42
95% Confidence Interval	--	(-0.90, -0.29)	(-0.55, 0.06)	--	(-0.98, -0.24)	--	(-0.82, -0.13)	(-0.76, -0.08)
p-value	--	< 0.001#	0.11	--	0.001#	--	0.007#	0.015#
Mean volume voided (mL) per micturition (FAS) (Secondary)								
n	480	472	475	433	424	415	410	426
Mean baseline	156.7	161.1	158.6	157.5	156.3	164.0	165.2	159.3
Mean change from baseline†	12.3	24.2	25.0	7.0	18.2	8.3	12.8	20.7
Mean difference from placebo†	--	11.9	12.6	--	11.1	--	4.6	12.4
95% Confidence Interval	--	(6.3, 17.4)	(7.1, 18.2)	--	(4.4, 17.9)	--	(-1.6, 10.8)	(6.3, 18.6)
p-value	--	< 0.001#	< 0.001*	--	0.001#	--	0.15‡	< 0.001#
Mean level of urgency (FAS) (Secondary)								
n	480	472	473	432	425	413	410	426
Mean baseline	2.37	2.40	2.41	2.45	2.45	2.36	2.37	2.41
Mean change from baseline†	-0.22	-0.31	-0.29	-0.08	-0.19	-0.15	-0.22	-0.29
Mean difference from placebo†	--	-0.09	-0.07	--	-0.11	--	-0.07	-0.14
95% Confidence Interval	--	(-0.17, -0.02)	(-0.15, 0.01)	--	(-0.18, -0.04)	--	(-0.15, 0.01)	(-0.22, -0.06)
p-value	--	0.018*	0.085	--	0.004*	--	0.083‡	< 0.001‡
Mean number of urgency incontinence episodes per 24 hours (FAS-I) (Secondary)								
n	283	286	289	319	297	256	247	251
Mean baseline	2.43	2.52	2.37	2.56	2.42	2.24	2.45	2.33
Mean change from baseline†	-1.11	-1.46	-1.18	-0.89	-1.32	-0.95	-1.31	-1.33
Mean difference from	--	-0.35	-0.07	--	-0.43	--	-0.36	-0.39

Parameter	Study 046			Study 047		Study 074		
	Placebo	**Mirabegron 50 mg**	**Tolterodine ER 4 mg**	**Placebo**	**Mirabegron 50 mg**	**Placebo**	**Mirabegron 25 mg**	**Mirabegron 50 mg**
placebo†								
95% Confidence Interval	--	(-0.65, -0.05)	(-0.38, 0.23)	--	(-0.72, -0.15)	--	(-0.67, -0.05)	(-0.69, -0.08)
p-value	--	0.003*	0.26	--	0.005*	--	0.004‡	0.002‡
Mean number of episodes with urgency grades 3 or 4 per 24 hours (FAS) (Secondary)								
n	479	470	472	432	424	413	410	426
Mean baseline	5.78	5.72	5.79	5.61	5.90	5.42	5.57	5.80
Mean change from baseline†	-1.65	-2.25	-2.07	-0.82	-1.57	-1.35	-1.68	-1.94
Mean difference from placebo†	--	-0.60	-0.42	--	-0.75	--	-0.33	-0.59
95% Confidence Interval	--	(-1.02, -0.18)	(-0.84, -0.00)	--	(-1.20, -0.30)	--	(-0.76, 0.10)	(-1.01, -0.16)
p-value	--	0.005*	0.050*	--	0.001*	--	0.13‡	0.007‡
Treatment satisfaction – visual analogue scale (FAS) (Secondary)								
n	428	414	425	390	387	377	389	388
Mean baseline	4.11	3.95	3.87	5.5	5.4	5.13	5.15	5.13
Mean change from baseline†	1.89	2.55	2.44	0.7	1.5	1.05	1.54	1.88
Mean difference from placebo†	--	0.66	0.55	--	0.8	--	0.49	0.83
95% Confidence Interval	--	(0.25, 1.07)	(0.14, 0.95)	--	(0.4, 1.3)	--	(0.07, 0.91)	(0.41, 1.25)
p-value	--	0.001*	0.008*	--	< 0.001*	--	0.024*	< 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.

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 Patients with Prior OAB Antimuscarinic Therapy

	Pooled Studies (046, 047, 074)		**Study 046**		
Parameter	**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 studies 046 (EU / Australia), 047 (North America [NA]) and 074 (EU / 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After oral administration of mirabegron in healthy volunteers mirabegron is absorbed to reach peak plasma concentrations (Cmax) 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 Cmax 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 Cmax and AUCtau by approximately 2.9- and 2.6-fold, respectively, whereas a 4-fold increase in dose from 50 mg to 200 mg mirabegron increased Cmax and AUCtau 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.

Co-administration of a 50 mg tablet with a high-fat meal reduced mirabegron Cmax and AUC by 45% and 17%, respectively. A low-fat meal decreased mirabegron Cmax 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 (Vss) 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 14C-mirabegron were about 2-fold higher than in plasma.

Metabolism

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. 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 and UGT in the metabolism of mirabegron, in addition to CYP3A4 and CYP2D6

Excretion

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% 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.

Pharmacokinetic Characteristics in Special Populations

Age / Gender / Race
No dose adjustment is necessary for the elderly. The Cmax 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).

No dose adjustment is necessary based on gender or race. The Cmax and AUC are approximately 40% to 50% higher in females than in males. Gender differences in Cmax and AUC are attributed to differences in body weight and bioavailability. The pharmacokinetics of mirabegron are not influenced by race.

Renal Impairment
Following single dose administration of 100 mg mirabegron in volunteers with mild renal impairment (eGFR 60 to 89 mL/min/1.73 m2 as estimated by MDRD), mean mirabegron Cmax 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 m2), Cmax and AUC were increased by 23% and 66%, respectively. In volunteers with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m2), mean Cmax 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 m2 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 Cmax 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 Cmax 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

Genotoxicity

Mirabegron showed no evidence of genotoxicity in the Ames bacterial reverse mutation assay, did not induce chromosomal aberrations in human peripheral blood lymphocytes *in vitro*, and was not clastogenic in the rat micronucleus assay

Carcinogenicity

Long-term carcinogenicity studies were conducted in rats and mice dosed orally with mirabegron for two years. Mirabegron showed no carcinogenic potential at systemic exposures 25 to 45-fold higher in rats and 23-fold higher in mice than the human systemic exposure at the maximum recommended therapeutic dose.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

BETMIGA contains the following excipients: macrogols, hyprolose, butylated hydroxytoluene, magnesium stearate, hypromellose, iron oxide yellow, and iron oxide red (25 mg tablet only).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

BETMIGA is available in strengths of 25 mg or 50 mg, as prolonged-release film-coated tablets. The tablets are packed in blisters in cartons containing 10, 20, 30, 60, 90 or 200 tablets.
(Note: Not all pack sizes may be marketed)

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

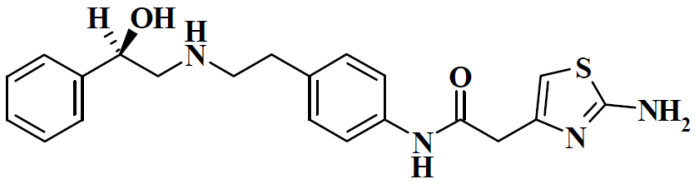
6.7 PHYSICOCHEMICAL PROPERTIES

Mirabegron is white to off-white crystals or powder. It is freely soluble in dimethyl sulfoxide, soluble in methanol and insoluble in water.

The dissociation constant (pKa) is 4.5 and 8.0.

Chemical structure

Chemical structure:



Chemical name: 2-(2-amino-1,3-thiazol-4-yl)-*N*-[4-(2-{[(2*R*)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide

Molecular formula: $C_{21}H_{24}N_4O_2S$

CAS number

CAS registry number: 223673-61-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Astellas Pharma Australia Pty Ltd
Suite 2.01, 2 Banfield Road
Macquarie Park, NSW 2113

Tel: 1800 751 755 (Medical Information)
Email: aaumedinfo@astellas.com (Medical Information)
Website: www.astellas.com.au

9 DATE OF FIRST APPROVAL

17 October 2013

10 DATE OF REVISION

14 July 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Updated the sponsor address