Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for mirabegron

Proprietary Product Name: Betmiga

Sponsor: Astellas Pharma Australia Pty Ltd

January 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of submission:	New Chemical Entity
Decision:	Approved
Date of decision:	26 September 2013
Active ingredient:	Mirabegron
Product name:	Betmiga
Sponsor's name and address:	Astellas Pharma Australia Pty Ltd Level 4 / 6 Eden Park Drive Macquarie Park NSW 2113
Dose form:	Film-coated prolonged-release tablet
Strengths:	25 mg and 50 mg
Container:	Blister
Pack sizes:	10, 20, 30, 60, 90, 200
Approved therapeutic use:	Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence in patients with overactive bladder (OAB) syndrome.
Route of administration:	Oral
Dosage (abbreviated):	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.
ARTG numbers:	199664 and 199668

Product background

Mirabegron is a first-in-class beta 3 (β3)-adrenergic receptor (also known as β3-adrenoceptor) agonist. This AusPAR describes the application by Astellas Pharma Australia Pty Ltd (the sponsor) to register tablets containing mirabegron for the following indication:

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

Overactive bladder (OAB) is also known as detrusor overactivity. It is a common and distressing condition characterised by urgency, frequency (8 or more voids per 24 h), or nocturia (2 or more voids after falling asleep), with or without urge incontinence. The causes are thought to be multifactorial and are not well characterised. There may be injury to the central inhibitory neural pathway, with or without deregulation of an afferent sensory bladder pathway. A myogenic component is also a possibility. Overactive bladder is more common in women, the overweight, and the elderly. It affects 20-30% of the population older than 75 years; it can also affect children and young adults.

Management starts with conservative measures such as behavioural bladder retraining and lifestyle modification followed, if necessary, by pharmacological treatment. To date, the mainstay of pharmacological treatment has been antimuscarinic (anticholinergic) agents such as oxybutynin and tolterodine. Many patients discontinue therapy due to lack of efficacy or side effects of dry mouth and constipation (also dry eyes, sedation, and concerns about potential effects on cognition).

Mirabegron is a new class of agents that stimulate a subclass of sympathetic receptors in the bladder, the β3-adrenergic receptors, which induces detrusor relaxation, especially around the trigone, increasing bladder storage capacity.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 17 October 2013.

At the time this application was considered by the TGA, a similar application had been approved in the European Union (EU, December 2012), USA (June 2012), Canada (March 2013) and Japan (July 2011) and was under review in approximately 12 other countries, including Switzerland.

Product Information

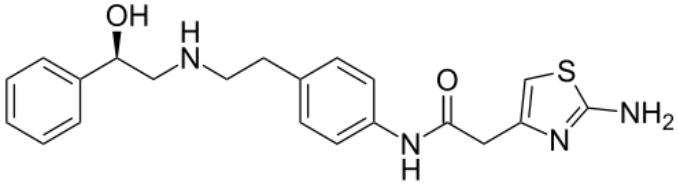
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Mirabegron has the following structure:

Figure 1. Structure of mirabegron



The drug substance is manufactured by chemical synthesis as the *R* enantiomer. It is prepared as a crystalline powder and exhibits polymorphism. The drug substance is

practically insoluble in water; data provided by the sponsor indicate that it is Biopharmaceutical Classification System (BCS) Class 3 agent.

The drug substance specification includes tests and limits for 5 identified related substances.

Drug product

The proposed modified release film-coated tablets have been developed using proprietary technology. Drug release (psuedo-zero-order) is controlled in the gel matrix and subsequent erosion of the matrix throughout the gastrointestinal tract. *In vitro* drug release is relatively unaffected by different pH dissolution medium.

The manufacturing process involves conventional granulation, compression and film-coating.

The tablet cores of the proposed strengths differ in the amounts of drug substance and it is compensated by an excipient. The film coats differ in the amounts of iron oxide colourants used. Thus, the tablets are distinguished by colour and markings ('325' or '355') but not size.

Assay limits comply with requirements of Therapeutic Goods Order 78. Impurity limits are in line with relevant International Conference on Harmonisation (ICH) thresholds.

The stability data provided supports a shelf life of 3 years when stored below 30°C in the proposed packaging.

Clinical trial formulations

The modified release formulation was developed to overcome the considerable decrease in plasma exposure with food and high peak to trough plasma concentrations with once daily dosing that were observed with a preliminary immediate release formulation used in initial clinical trials.

Several modified release formulations, with different dissolution rates, were subsequently evaluated in an effort to reduce the effect of food on the pharmacokinetics (PK) of mirabegron observed with the immediate release formulation in early studies. The 'Oral Controlled Absorption System (OCAS)-M' tablet, which has an intermediate dissolution rate, was selected for further development.

The proposed commercial formulation is identical to the formulation used in the pivotal Phase III clinical safety and efficacy studies and in the majority of the clinical pharmacology studies.

Biopharmaceutics

Study 178-CL-076. Absolute bioavailability

Study 178-CL-076 assessed the absolute bioavailability and PK of three different OCAS formulations (including that proposed for marketing, 'OCAS-M') across a dose range of 25 mg to 100 mg.

After oral administration of 25 mg to 100 mg mirabegron, a greater than dose proportional increase in the maximum concentration (C_{max}) and area under the concentration-time curve over time zero to infinity ($AUC_{0-\infty}$) was observed. As the PK of mirabegron were essentially linear after intravenous (IV) administration, the lack of dose proportionality with the oral formulation is considered to arise from factors associated with absorption.

The absolute bioavailability of the 25 mg dose (proposed commercial formulation) was 29%. The absolute bioavailability of the 50 mg dose (proposed commercial formulation) was 35%. The absolute bioavailability of the corresponding 100 mg dose (not proposed for registration in this submission) was 45%.

The relative bioavailability of the experimental fast- and slow-release formulations relative to the proposed commercial formulation was approximately 1.3 (fast) and 0.9 (slow).

Plasma exposure was approximately 27% and 64% higher in females compared to males after IV and oral (proposed commercial formulation) administration, respectively. This difference is attributed in part to differences in body weight.

Study 178-CL-041. Food effect

Study 178-CL-041 assessed the effect of food on the PK of mirabegron 50 mg (commercial formulation) and a corresponding 100 mg dose in Western healthy subjects.

A high-fat breakfast decreased the C_{max} and $AUC_{0-\infty}$ of mirabegron 50 mg by 45% and 17%, respectively, compared with fasted conditions. Similar reductions were observed with the 100 mg dose. Mean time to achieve the maximum concentration (T_{max}) values was delayed by approximately 0.8 and 1.9 hours, respectively, for the 50 mg and 100 mg dose, compared with fasted conditions.

A greater reduction in mirabegron C_{max} and $AUC_{0-\infty}$ was observed after a low-fat meal compared with a high-fat meal (C_{max} and $AUC_{0-\infty}$ of mirabegron (50 mg) decreased by 75% and 51%, respectively).

In all treatment arms, mean values for C_{max} and $AUC_{0-\infty}$ in female subjects were higher than those in male subjects. The magnitude of the effect of food with either fed condition or mirabegron dose was, in general, comparable in males and females.

Advisory committee considerations

The submission was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) at its 151st meeting in May 2013.

The subcommittee endorsed the issues raised by the TGA regarding chemistry, quality control and biopharmaceutical data.

The PSC advised that the PI should be amended so that reference to taking the recommended dose with or without food under the *Absorption* and *Dosage and Administration* sections reflects the fact that it is preferable to take the recommended dose 1 h before food or 2 h after a meal. This has been brought to the attention of the clinical Delegate.

Quality summary and conclusions

Responses from the company to the questions raised by the TGA have been evaluated and no significant pharmaceutical chemistry issues remain.

There are no objections to the registration of mirabegron 25 mg and 50 mg modified release tablets from a pharmaceutical chemistry perspective.

III. Nonclinical findings

Introduction

General comments

The sponsor has presented a comprehensive set of data to support the application. Toxicological studies were performed to good laboratory practice (GLP) standard and in accordance with relevant ICH guidelines. Drug exposure levels achieved in the toxicity studies were adequate in all species. The redacted FDA review of the pharmacology for the US application, available from the public domain[1], was consulted for the TGA nonclinical evaluation.

Pharmacology

Primary pharmacology

Mirabegron is proposed to be used in adults for the treatment of symptoms associated with OAB syndrome, including urgency, increased micturition frequency or urgency incontinence. OAB syndrome is characterised by overactivity of the detrusor muscle, through increased sensitivity to contraction-mediating neurotransmitters and mediators. Afferent signalling in OAB syndrome results in bladder sensations that are felt as urgency. Currently approved treatments for OAB are all antimuscarinic agents, which inhibit bladder detrusor muscle contractile activity during urination, when the bladder is predominantly under parasympathetic nervous control.

During the urine storage phase, the sympathetic nervous system predominates and the activation of detrusor muscle adrenergic receptors by neurally released noradrenaline produces muscle relaxation and promotes bladder filling. Both α and β-adrenoceptors are present in human detrusor muscle but relaxation-mediating β-adrenoceptors dominate functionally over contraction-mediating receptors of the α1 subtype (Nomiya and Yamaguchi, 2003[2]; Andersson and Wein, 2004[3]). The β3-adrenoceptor is the functionally dominant β-adrenoceptor mediating bladder relaxation in man, cynomolgus monkey and dog, with both β2 and β3 involved in the rat, while in cats and guinea-pigs the β1 subtype is functionally dominant, and the β2-subtype is dominant in the rabbit (Nergårdh *et al*, 1997[4]; Yamazaki *et al,* 1998[5]; Takeda *et al*, 2002[6]). Mirabegron, a first-in-class β3 adrenoceptor agonist, is proposed to suppress symptoms of OAB by inhibition of involuntary detrusor muscle contractions, and by increasing the storage capacity of the bladder.

The sponsor provided evidence that mirabegron is a selective agonist for cloned β3-adrenergic receptors *in vitro*. Using β1, β2 and β3-adrenoceptors from human and animals expressed in cell membranes from Chinese Hamster Ovary (CHO) cells, mirabegron was shown to have a relatively high affinity for the human β3-adrenoceptor

[1] <http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202611Orig1s000PharmR.pdf>
[2] Nomiya, M, Yamaguchi, O.. A quantitative analysis of mRNA expression of α1 and β-adrenoceptor subtypes and their functional roles in human normal and obstructed bladders. *The J Urol* 2003:170;649-53.
[3] Andersson, K.-E, Wein, AJ. Pharmacology of the lower urinary tract: basis for current and future treatments of urinary incontinence. *Pharmacol Rev* 2004:56;581-631.
[4] Nergårdh, A. *et al*. Characterisation of the adrenergic beta-receptor in the urinary bladder of man and cat. *Acta Pharmacologica et Toxicologica* 1977:40;14-21.
[5] Yamazaki, Y. *et al*. Species differences in the distribution of β-adrenoceptor subtypes in bladder smooth muscle. *Br J Pharmacol* 1998:124;593-599.
[6] Takeda, H. et al. Japanese Journal of Pharmacology 2002:88;108-113.

(affinity constant (K_i) = 40 nM), which was 30 and 100 times greater than the affinities for human β2 and β1 receptors, respectively. The slope of the competitive binding curve for the β3 receptor was very shallow (Hill coefficient = 0.3, compared with 0.9 and 0.6 for the β2 and β1 receptor, respectively). A Hill coefficient of less than unity (indicative of negative cooperativity at the receptor binding site) has been previously reported for the human β3-adrenoceptor, and it has been suggested that the receptor exists in at least two conformational states (Baker, 2010[7]). Thus, while the relative K_i values for human β3, β2 and β1 receptors are suggestive of a relatively high selectivity for the β3 receptor, the maximal inhibition of radioligand binding was observed at similar mirabegron concentrations for each of the three receptor subtypes.

The selectivity of an agonist is dependent on efficacy as well as affinity, and in functional studies of receptor activation (accumulation of cyclic 3', 5' adenosine monophosphate cAMP), the mirabegron 50% effective concentration (EC_{50}) for human β3 receptors expressed in CHO cells was 21 nM, approximately 1000 fold lower than the EC_{50} for activation of human β2 and β1 receptors. The intrinsic activity (IA), calculated as the proportion of maximal cAMP response evoked by isoprenaline, also indicated that mirabegron selectively activated β3 receptors. Of the nine most common human metabolites, only M13 and M14 showed measurable activation of β3 receptors, but they were approximately 1000 times less potent than the parent molecule, and activation of β2 and β1 receptors by these metabolites was negligible. Selectivity of mirabegron for β3 receptors was also demonstrated in similar experiments with rat, dog and monkey β-adrenoceptors, although some activation of β1-adrenoceptors might be anticipated in rats at high concentrations of mirabegron (IA = 0.6). The results confirmed the suitability of these species for use in nonclinical pharmacodynamic studies.

Consistent with the proposed indication, mirabegron was shown to activate β-adrenergic receptors on urinary bladder smooth muscle of rats and humans *in vitro*, leading to muscle relaxation. The effects of mirabegron on rat bladder smooth muscle were unaffected by pre-treatment with antagonists of β1 and β2-adrenoceptors, supporting the hypothesis that these effects are mediated by interaction with receptors of the β3 subtype. However, β2 (but not β1) receptor antagonists shifted the concentration-response curve for isoprenaline, indicating that there is potential for both β2 and β3-adrenoceptor dependent relaxation of bladder smooth muscle in this species. In human isolated detrusor muscle, the EC_{50} for mirabegron-mediated relaxation of carbachol-contractions was 0.78 μM. The concentrations of mirabegron showing activity in rat and human bladder smooth muscle are approximately ten-fold higher than might be anticipated based on the data obtained in single cells, which may be due mirabegron accumulation in tissues, owing to the highly lipophilic nature of the molecule.

The activity of mirabegron on the urinary bladder of rats, dogs and monkeys *in vivo* was supportive of its use for the proposed indications at clinically relevant concentrations. Mirabegron dose-dependently reduced the intravesical pressure of saline-loaded bladders in anaesthetised rats at doses ≥ 0.03 mg/kg when administered either IV or intraduodenally (ID), and reduced the frequency of distension induced rhythmic bladder contractions at doses ≥ 3 mg/kg IV, without affecting amplitude. Plasma mirabegron concentrations associated with this effect (1 h following ID administration) were ≥ 114 ng/mL (therapeutic C_{max} = 66.2 ng/mL; 178-CL-072). This effect of ID mirabegron was similar after single or repeated (14 days) doses. Overactive bladder models were studied in rats, dogs and monkeys. Mirabegron (1-3 mg/kg oral (PO)) dose-dependently increased functional bladder capacity in water loaded cerebrally infarcted rats. Carbachol-mediated increases in intravesical pressure in anaesthetised dogs were dose-dependently inhibited by mirabegron (30% effective dose (ED_{30}) = 0.00052 mg/kg IV). The functional bladder

[7] Baker, J.G. The selectivity of β-adrenoceptor agonists at human β_1-, β_2- and β_3-adrenoceptors. *Br J Pharmacol* 2010:160;1048-1061.

capacity of water loaded conscious cynomolgus monkeys was increased by mirabegron at doses of 1 and 3 mg/kg PO, with a significant reduction in micturition frequency. Mirabegron showed efficacy in a rat model for urinary urgency, bladder outlet obstructed (BOO) rats, dose-dependently reducing the frequency and amplitude of pre-micturition contractions.

Secondary pharmacodynamics and safety pharmacology

Secondary pharmacodynamic (PD) pharmacology studies indicated that mirabegron bound relatively weakly to α1-adrenoceptors and the human noradrenaline transporter, the human dopamine transporter, the muscarinic M2 receptor and the sodium channel site 2. The K_i values for mirabegron at these receptors or transporters were 1.0–11 μM, which is ≥ 30 times the unbound plasma C_{max} at the recommended therapeutic dose.[8] Of the human metabolites of mirabegron, only M5 and M16 (at a ten-fold excess compared to the radiolabelled ligand) inhibited any of the binding assays by more than 50%. M5 inhibited the dopamine transporter and opiate receptor binding, while M16 inhibited binding to the dopamine and noradrenaline transporters.

In common with other β3-adrenoceptor agonists, mirabegron was originally developed as a treatment for obesity and type 2 diabetes. Mirabegron induced lipolysis in isolated adipocytes from rats, and showed some efficacy in rodent models of type 2 diabetes. Genetically obese diabetic mice (stain kk/A^y) treated orally with mirabegron showed elevations of body temperature and energy expenditure, and reduced plasma concentrations of non-esterified fatty acids, glucose, insulin and triglycerides. Similarly, mirabegron improved glucose tolerance in fasted Zucker Fatty rats and was associated with elevations in plasma insulin levels. The lipolytic effect seen in animals was apparently not reproduced in human studies, a finding which has been observed for a number of other β3 agonists (Arch and Wilson, 1996[9]). Reduced body weight gain, which was observed in repeat-dose toxicity studies, would not be anticipated with clinical use.

Specialised safety pharmacology studies covered the central nervous system (CNS), cardiovascular and respiratory, gastrointestinal and renal systems.

Central nervous system effects in mice included prone position and slight hyperthermia at low doses, with decreased alertness and spontaneous movement and decreased muscle tone at higher doses. Rats exhibited decreased spontaneous activity at lower doses, while doses ≥ 100 mg/kg PO were associated with deep respiration, prone position, reduced activity, grip strength and muscle tone and impaired righting reflex.

Cardiovascular safety studies were conducted in rats, rabbits, dogs and monkeys. There was no evidence for any clinically relevant potential interaction of mirabegron or its five major human metabolites (M5, M11, M12, M14 and M16) with cardiac ion channels (including Human Ether-à-go-go-Related Gene (hERG) channels), and no effects on isolated guinea-pig cardiac papillary muscle action potentials or in the canine ventricular wedge preparation. Thus, the *in vitro* nonclinical data indicate that mirabegron is unlikely to prolong QT intervals[10] or have pro-arrhythmic effects in clinical use. This was generally supported by the results of *in vivo* cardiovascular safety studies. The effect of mirabegron on the QT_c interval of conscious dogs depended on the correction method used, since (as discussed below) there was a concomitant large change in heart rate. It is frequently

[8] The C_{max} for elder females in study 178-CL-072 of 43.5 ng/mL corresponds to an unbound concentration of 11.7 ng/mL (29.5 nM), assuming that mirabegron is 73% bound to plasma proteins.
[9] Arch, J.R.S, Wilson, S. Prospects for β3-adrenoceptor agonists in the treatment of obesity and diabetes. *International Journal of Obesity* 1996:20;191-199.
[10] QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A lengthened QT interval is a biomarker for ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death. QTc is the QT interval corrected for heart rate.

claimed that the use of correction formulae derived from clinical data is not appropriate for use with dog electrocardiograms (ECGs; for example, see Guth, 2007[11]). Prolongation of QT_c was seen using Van de Water's and Bazett's corrections, but there was no change in QT_c derived using Matsunga's correction following oral dosing with up to 100 mg/kg of mirabegron. Mortalities among anaesthetised dogs dosed IV with mirabegron at ≥ 10 mg/kg were due to ventricular tachycardia leading to ventricular fibrillation, and were not associated with QT prolongation. Mirabegron had no effect on QT_c (Bazett's or Friderica's correction) of conscious monkeys following oral doses up to 100 mg/kg.

Additional cardiovascular findings included elevated heart rate in anaesthetised rats after IV dosing (exposure ratios less than 2 times the maximum recommended human dose (MRHD)), in rabbits at exposure levels ≥ 9 times the MRHD, in dogs at exposures ≥ 0.1 times the MRHD and in conscious cynomolgus monkeys at exposure levels 12 times the MRHD. In the dog, IV mirabegron decreased left ventricular pressure and reduced systolic and mean blood pressure at systemic exposure levels ≥ 0.1 times the MRHD. A small, non-significant hypotensive effect was seen in rats, but mirabegron had no blood pressure effects in monkeys at exposure levels up to 52 times the MRHD (based on plasma C_{max}). Dilation of peripheral blood vessels by activation of β3-adrenoceptors has been reported to be more pronounced in the dog than in rats, and essentially absent in monkeys (Shen *et al* 1996[12]), which could account for the more pronounced hypotensive effect in canines. Studies were conducted in rats and dogs to elucidate the mechanisms underlying the chronotropic effect of mirabegron using a combination of ganglion blocking drugs and receptor antagonists. The results suggest that in dogs given low doses of mirabegron a reflex tachycardia occurs as a compensatory response to the vasodilating effects of β3 stimulation. However, higher doses of mirabegron increased heart rate in rats and dogs, most likely due to direct stimulation of β1-adrenoceptors on cardiac myocytes. The clinical implications of the cardiovascular effects observed in the nonclinical safety pharmacology studies are discussed further below under *Major Toxicities*.

Renal effects in water-loaded rats included reduced urine output and urinary electrolyte concentrations at oral doses ≥ 10 mg/kg (no observed effect level (NOEL) 3 mg/kg). Mirabegron had no effect on blood gases or electrolytes in cynomolgus monkeys at exposure levels based on AUC up to 49 times the MRHD. In dogs, the partial pressure of carbon dioxide in the blood was decreased with oral doses of 10 mg/kg, but there was no effect on respiration rate, partial pressure of oxygen or pH (acidity) of blood. Gastrointestinal transit time in mice was unaffected by single oral doses of up to 100 mg/kg. Mirabegron did not elicit contractions in guinea pig ileum *in vitro*, but it inhibited contractions mediated by histamine, barium chloride and serotonin (5-HT) at ≥ 10 nM, and acetylcholine at ≥ 100 nM. Adverse gastrointestinal effects were not observed in repeat-dose toxicity studies.

Pharmacokinetics

The main site of absorption of orally administered mirabegron in the rat was the small intestine, with a lower level of absorption from the colon, and limited absorption from the stomach. A study in dogs indicated that absorption of mirabegron was decreased by food consumption. Absorption of orally administered mirabegron was relatively rapid, with plasma T_{max} values in rats and dogs of 0.1-4.0 h. Plasma half life was 4-5 h and 4-10 h, respectively. In both species the oral bioavailability increased with increasing dose, from 23-76% in rats, and from 42-77% in dogs, which is in agreement with the clinical finding

[11] Guth, B.D. Preclinical cardiovascular risk assessment in modern drug development. *Toxicological Sciences* 2007:97**:**4-20.
[12] Shen, Y.-T. Differences in β3-adrenergic receptor cardiovascular regulation in conscious primates, rats and dogs. *J Pharmacol and Exp Ther* 1996:278;1435-1443.

of greater than dose-proportional increases in AUC. This effect could be due to saturation of either efflux ability or of first pass metabolism, but PK studies with metabolites supported the former mechanism. Mirabegron was shown to be a low affinity substrate for P-glycoprotein, an efflux transporter which is expressed in the small intestine.

Systemic exposure to mirabegron in mice, rats, rabbits and monkeys was relatively unchanged with repeated dosing in the toxicity studies. There was no notable difference in systemic exposure levels between the sexes.

Binding to proteins in plasma was relatively independent of concentration over the range 200-5000 ng/mL, and the extent of binding was similar between rodents and humans (77-78% in mice, 79-80% in rats, 87-88% in rabbits, 76-77% in Japanese and 72-73% in Caucasian humans), but somewhat lower in dogs (61-62%) and in cynomolgus monkeys (53-56%). Binding was mostly to albumin, and to a lesser extent to α1-acid glycoprotein. The *in vitro* blood: plasma radioactivity concentration ratio of ^{14}C (radiolabelled)-mirabegron was similar in rats, dogs, cynomolgus monkeys and humans, ranging from 1.2-1.6.

The volume of distribution following IV administration of mirabegron to rats and dogs was 10.3 and 14.3 L/kg, respectively. Tissue: plasma radioactivity ratios in albino rats after a single oral dose of ^{14}C-mirabegron were highest in the alimentary canal and excretory organs, adrenals, pituitary, thyroid, lungs, pancreas, spleen, submaxillary glands, bone marrow, heart, testes, skin and fat. Whole body autoradiographs also showed relatively high levels of radioactivity in brown fat and Harderian gland, and in the bladder. Elimination of radioactivity from the thyroid, kidney, testes and bone marrow was slow, with more than 40% of maximal levels detected 15 days after administration. Radioactivity levels in the CNS were low, most likely due to the presence of the P-glycoprotein efflux transporter in the brain. Tissue distribution of radioactivity was similar with repeated (21 days) daily dosing of ^{14}C-mirabegron, but the tissues showing the slowest elimination of radioactivity were kidney, thyroid, liver and adrenal gland.

Distribution of radioactivity in pigmented rats was similar to that seen in albino rats, except for the increased radioactivity in melanin-containing structures of the eye, which was predominantly due to metabolite M6, and to a lesser extent, to unchanged mirabegron. Elimination from the eye was very slow (half life = 157 days). A distribution study in cynomolgus monkeys found that the highest levels of radioactivity were present in the liver and bile, followed by the eye. However, the intraocular radioactivity levels in monkeys were considerably lower than those in pigmented rats, which may be due at least partly to interspecies differences in metabolic profile, since M6 is not found in the plasma of cynomolgus monkeys after a single oral dose of ^{14}C-mirabegron. A similar observation has been made in humans (from sponsor's clinical summaries).

Studies in pregnant rats dosed orally with ^{14}C-mirabegron showed that mirabegron and/or its metabolites cross the placenta in this species, with peak fetal radioactivity levels reaching 15% of the peak maternal plasma radioactivity level. Mirabegron-related radioactivity was detected in the milk of lactating rats at levels almost 2-fold higher than the maternal plasma concentration.

The results of *in vitro* studies with human liver microsomes indicate that mirabegron is metabolised mainly by cytochrome P450 (CYP) subtype 3A4 (CYP3A4), and to a lesser extent by CYP2D6. Mirabegron is hydrolysed by esterases in the plasma of mice, monkeys and humans, but not in rats, rabbits and dogs. In humans, this activity was mainly due to plasma butyrylcholinesterase. The major metabolic pathways for mirabegron are: (1) oxidation (or *N*-dealkylation) of the secondary amine; (2) amide hydrolysis followed by acetyl conjugation; (3) glucuronidation of the hydroxyl group or the primary amine on the thiazole ring, or carbamoyl glucuronidation of the secondary amine; (4) oxidation of the hydroxyl group to a carbonoyl group, or a combination of these four metabolic pathways.

The predominant species circulating in the plasma of humans was unchanged mirabegron, with the most abundant metabolites being the phase 2 glucuronides M11 and M12, and the phase 2 acetyl conjugate, M5. When systemic exposure to mirabegron and its human plasma metabolites was investigated, unchanged mirabegron was also the most abundant plasma species in the mouse and rat, while in the monkey the glucuronide M11 was by far the predominant metabolite, and in the rabbit it was M5. There were no unique human plasma metabolites. Based on a comparison of metabolite exposures in mice, rats, monkeys and rabbits at steady state with clinical data, all human plasma metabolites are considered to be qualified in at least one species.

Excretion of mirabegron and its metabolites was predominantly faecal in rats, with 75% eliminated by this route, and 19% in urine. Enterohepatic circulation was shown to occur in this species. In the monkey, faecal and urinary excretion were approximately equal, while in humans the renal and faecal routes accounted for 55% and 34% of administered radioactivity, respectively.

The animals used in PD and toxicity studies are appropriate models for humans based on an interspecies comparison of PK data.

Pharmacokinetic drug interactions

Mirabegron is metabolised in humans by butyrylcholinesterase, uridine diphosphate (UDP) glucuronosyltransferases (UGT), CYP3A4 and, to a lesser extent, CYP2D6. It is a substrate for P-glycoprotein, organic cation transporter type 1 (OCT1), OCT2 and OCT3. It is considered unlikely that co-administered drugs would have a major impact on the pharmacokinetics of mirabegron owing to the multiple mechanisms underlying its clearance.

In vitro studies showed that mirabegron was a strong inhibitor of human CYP2D6 and a weak inhibitor of CYP3A4 *in vitro*, and it therefore may inhibit the metabolism of substrates for these isozymes.

Toxicology

Acute toxicity

Acute oral toxicity studies were conducted in rats and dogs. Mirabegron showed low to moderate toxicity in the rat, with a maximum non-lethal dose of 500 mg/kg. Treatment related effects included salivation, lachrymation, chromodacryorrhoea and hypoactivity at ≥ 300 mg/kg/day, prone position at 500 mg/kg, and mydriasis at 800 mg/kg. Mirabegron showed a high toxicity in dogs by the oral route, with a maximum non-lethal dose in dogs of 3 mg/kg. Signs of toxicity included extreme skin reddening; increased heart rate and focal acinar dilatation or disruption of the zygomatic salivary gland at ≥ 0.3 mg/kg, while at 30 mg/kg additional treatment-related effects included vomiting, gasping, recumbence, and moderate necrosis of the zygomatic salivary gland.

An IV dose of 10 mg/kg (114 times MRHD based on C_{max}) caused salivation, pale oral mucosa, dyspnoea, loss of papillary reflex and mydriasis, ventricular tachycardia and death in a single male monkey. Intravenous doses ≥ 0.3 mg/kg were associated with ECG disturbances including increased PR or QRS wave intervals (NOEL was 0.1 mg/kg IV).

The severity of the acute oral toxicity of mirabegron appears to differ considerably between species.

Repeat-dose toxicity

Repeat dose oral toxicity studies were conducted in mice (5 day and 2 week non-pivotal studies in CD (ICR) mice, and 2 and 13 week studies in $B6C3F_1$ mice), rats (2, 13 and 26 weeks), dogs (2 weeks), and cynomolgus monkeys (2, 13 and 52 weeks). The duration of the studies, the species used (rodent and non-rodent), the group sizes and other study methods were consistent with the relevant European Medicines Agency (EMA) guidelines.[13] All repeat-dose toxicity studies were performed to GLP standards except for the two non-pivotal mouse studies. The dog appears not to have been selected as a model species for longer term studies owing to adverse ECG findings and severe effects in the salivary glands after only a few doses.

Relative exposure

Exposure ratios have been calculated based on the animal:human plasma $AUC_{0-24\,h}$. Human reference values are from clinical Study 178-CL-072, in which fasted women ≥ 55 years received the MRHD (50 mg/day). This group was selected as it represents the subpopulation with the greatest steady state exposure. Relative exposures were high in all species except the monkey, where ECG effects were dose limiting.

Table 1. Relative exposure in repeat-dose toxicity and carcinogenicity studies

Species	Study duration	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (ng·h/mL)	Exposure ratio#
Mouse (B6C3F1)	13 weeks	50	5917	12
		100	14, 271	28
		200	approximately 27,000	approximately 50
	2 years [carcinogenicity]	25	2187	4
		50	4713	9
		100	11809	23
Rat (F344/DuCrj)	3 months	10	868	2
		30	4341	8
		100	24,139	47
		300	74,201	145
	6 months	3	112	0.2
		10	976	2
		30	7268	14

[13] *Note for guidance on repeated dose toxicity;* CPMP/SWP/1042/99, and Guideline on repeated dose toxicity; CPMP/SWP/1042/99 Rev 1.

Species	Study duration	Dose (mg/kg/day)		$AUC_{0-24\,h}$ (ng·h/mL)	Exposure ratio[#]
		100		29,222	57
	2 years [carcinogenicity]	M	12.5	3519	7
			25	6168	12
			50	12,990	25
		F	25	5943	12
			50	12,261	24
			100	23,043	45
Dog (Beagle)	2 weeks	1		291	0.6
		3		1396	3
		10		7803	15
		20 (lethal)		8146	16
Monkey (Cynomolgus)	1 year	3		382	0.7
		10		1180	2
		30		4166	8
Human †(elder female)	steady state	50 mg		512	–

[#] = animal:human plasma $AUC_{0-24\,h}$ based on total plasma concentrations for mirabegron; note that relative exposure levels in the dog and monkey may be underestimated since they do not allow for interspecies differences in binding to plasma proteins; †178-CL-072. M = male, F = female.

Major toxicities

The major target organs for mirabegron were the heart and cardiovascular system, CNS and liver, with some effects also observed on the salivary and lachrymal glands. Relative exposure levels refer to plasma $AUC_{0-24\,h}$ unless stated otherwise.

- **Cardiovascular toxicity**

β-Adrenergic receptors are important regulators of human cardiac function, and although the roles of β1 and β2 subtypes are well known, a possible role for β3-adrenoceptors remains controversial (Michel *et al,* 2011[14]). The interpretation of studies is complicated by the lack of selectivity of some of the ligands used, as well as the existence of a low affinity state β1-adrenoceptor whose pharmacological profile has some overlap with that

[14] Michel, M.C *et al*. Are there functional β3-adrenoceptors in the human heart? *Br J Pharmacol* 2011:162; 817-822.

of the β3-adrenoceptor. Small, cardiostimulant effects of β3-adrenoceptor agonists in human atrial tissue are most likely mediated by activation of β1- and β-2 adrenoceptors. In contrast, β3-receptor agonists have negative inotropic effects in human ventricular tissue, which may be mediated by β3-adrenoceptors, although this is not fully established. Thus, the cardiovascular effects of a selective β3-receptor agonist cannot be confidently predicted based on the current knowledge.

As observed in the safety pharmacology studies, mirabegron increased heart rate in rats, rabbits, dogs and monkeys at exposures which were near to, or above clinical. Cardiac effects were dose limiting in dogs and monkeys, with ventricular tachycardia reported at 29 times and 37 times the MRHD (based on plasma C_{max}), respectively. More severe ventricular tachycardia was observed at higher exposure levels following IV administration. In dogs, IV doses ≥ 10 mg/kg were associated with ventricular tachycardia, which progressed to ventricular fibrillation and death within 5-10 min. The same IV dose in monkeys was associated with the development of fatal ventricular tachycardia in one male monkey. ECG effects included a trend towards prolongation of the PR interval in the 52 week monkey study at 8 times the MRHD, an effect which is suggestive of impaired conduction from atria to ventricles. However, the results of *in vitro* and *in vivo* studies do not suggest a potential for QT prolongation with clinical use.

The sponsor provided evidence that the increased heart rate observed in the nonclinical studies may partly be reflex tachycardia as a result of the vasodilating effects of β3-stimulation, and also a direct effect on β1-adrenoceptors of cardiac myocytes. Mirabegron treatment had a hypotensive effect in dogs and to a lesser extent, in rats. However, there was no reduction in blood pressure in monkeys at up to 52 times the MRHD, which is consistent with clinical observations described in the draft PI (in Phase III clinical trials, increased blood pressure was reported as an uncommon adverse reaction, with mean blood pressure changes ≤ 1 mm Hg). In a cardiovascular study in healthy male subjects, dose-dependent increases in heart rate and systolic blood pressure occurred at the supratherapeutic dose of 200 mg (Study 178-CL-053). These effects were shown to be mediated by stimulation of β1-adrenoceptors, since they were abolished by the selective β1-antagonist, bisoprolol. Dose-dependent increases in heart rate were reported in a thorough QT study over a dose range of 50-200 mg (Study 178-CL-077). Thus, the selectivity of mirabegron for β3-receptors over β1- and β2-adrenoceptors in humans, as well as in the species used in nonclinical studies, is not as great as is suggested from the *in vitro* data on recombinant receptor subtypes expressed in single cells.

- **CNS toxicity**

Mirabegron does not readily cross the blood brain barrier, and adverse CNS effects were generally associated with exposure levels well in excess of those at the MRHD. Intravenous administration to rats at 30 mg/kg resulted in mortalities that were preceded by mydriasis, tremors, bradypnoea, clonic convulsions and gasping, shallow rapid respiration. Oral administration to mice, rats and monkeys resulted in CNS effects including decreased alertness, reduced spontaneous activity and prone position at lower exposures, with higher doses in rats associated with reduced grip strength and muscle tone and impaired righting reflex. Clonic convulsions were observed in mice with oral doses of 300 mg/kg, and ptosis, staggering and vomiting were observed in monkeys. All of these effects were observed at exposure levels ≥ 8 times those anticipated at the MRHD, with the exception of observations of prone position in the 26 week rat study, which was associated with exposure levels below the exposure at the MRHD. The CNS effects of sub lethal doses of mirabegron were reversible. Adverse CNS effects are not anticipated with clinical doses of mirabegron.

· **Liver toxicity**

Liver toxicity was observed in rodents and dogs, but not in monkeys (including the 12 month study with systemic exposure levels of up to eight times the exposure at the MRHD). Liver toxicity was generally seen only at high relative systemic exposure levels.

Liver weight was increased in mice dosed for two weeks at ≥ 10 mg/kg, and in the 2, 13 and 26-week studies in rats. In rats this was accompanied by modest increases in plasma aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase (ALP) and cholesterol levels, and decreases in the serum triglyceride concentration, at relative exposures ≥ 5 times the MRHD. The lowest observed adverse effect level (LOAEL) increased with longer duration of treatment, and in the 26 week study corresponded to relative exposure levels 17-55 times the MRHD. Hepatocyte necrosis was observed in the 13 week rat study at relative exposures 145 the MRHD. However, this effect was not confirmed in the 26 week study at relative exposures 57 times the MRHD, where the only histological findings in the liver were reversible eosinophilic changes. No histopathological changes were found in the liver in the two year carcinogenicity study in rats at relative exposures 25 and 45 times the MRHD in males and females, respectively. Histopathological findings in mice included pale areas of hepatocytes at the macroscopic level, and glycogen accumulation in all treatment groups in the 13 week study (relative exposure ≥12 times based on MRHD). Adverse histopathological effects were only seen in the livers of mice at high exposure levels. Hepatocyte hypertrophy was observed at a relative exposure about 50 times based on MRHD, but was only observed at a very low frequency (1.4%) in the two year carcinogenicity study at relative exposures ≥ 5 times the MRHD.

Reversible hepatotoxic effects in a two week repeat dose study in dogs included enlarged and yellow discoloured livers, mild to moderate hepatocyte hypertrophy and hepatocyte vacuolation, slight glycogen accumulation and mild lipid deposition in peri- and centrilobular hepatocytes at systemic exposure levels 25 times the MRHD. Compared to historical control data, these effects were associated with elevated ALP and ALT levels. Liver toxicity is probably of limited clinical relevance, since it was generally observed at exposure levels in excess of ten times the MRHD.

· **Salivary and lachrymal glands**

The salivary and lachrymal glands are under autonomic control, with fluid secretion being largely under parasympathetic control, while protein secretion is mediated by sympathetic stimulation via activation of β-adrenergic receptors (Proctor and Carpenter 2007[15]; Ding *et al,* 2003[16]). Salivation with or without lachrymation was observed in rats in the 26 week study and in the two week repeat dose study in dogs at clinical exposure levels and below, which is likely to be mediated by stimulation of adrenergic receptors. The parotid glands of female mice treated with mirabegron for 13 weeks exhibited a dose-dependent atrophy at exposure levels ≥ 12 times MRHD, and there was a reduction in zymogen granules in the parotid gland of rats at similar exposure levels. These effects were reversible or showed a trend towards recovery after treatment ceased. Importantly, there were no adverse histopathological changes in the salivary glands of mice or rats treated with mirabegron for two years at relative exposures 23 times and 45 times the MRHD, respectively, nor in monkeys treated for one year at 8 times the MRHD.

Salivary gland effects were particularly severe in the zygomatic gland of dogs. In a two week study with subclinical exposure levels, toxic effects on the zygomatic salivary gland

[15] Proctor, G.B, Carpenter, G.H. Regulation of salivary gland function by autonomic nerves. *Autonomic Neuroscience* 2007:133;3-18.
[16] Ding, C, *et al*. Sympathetic control of the mouse lachrymal gland. *Investigative Ophthalmology and Visual Science* 2003:44;1513-1520.

consisted of mild to moderate oedema, haemorrhage, cellular infiltration, acinar cell necrosis and atrophy, ductal dilation and necrosis, proliferation and mineralisation of the ductal epithelium and thrombosis. These effects had mostly recovered by 13 weeks following the cessation of treatment. Adverse effects on canine salivary gland were evident even after acute treatment, including after a single oral dose of 0.3 mg/kg mirabegron in the acute toxicity study, and after three daily doses of 20 mg/kg PO (25 times the MRHD). In the latter study, moderate acinar cell atrophy was observed in the submandibular gland, and in the parotid gland this effect was accompanied by cellular infiltration of ductal epithelium and interstitial cellular infiltration. The canine salivary gland appears to be particularly sensitive to the actions of mirabegron but it does not appear to share this sensitivity with humans.

· **Metabolic effects**

As previously discussed, PD studies showed that mirabegron promoted lipolysis, increased metabolism and improved glucose tolerance in animals, an effect which was not reproduced in human studies. Similar effects were observed in the repeat dose toxicity effects, with lipolysis evident in brown and white fat of mice, rats and to a lesser extent in monkeys, and reductions in body weight gain and triglyceride levels in rats. Body weight changes were not seen clinically when mirabegron was given at doses exceeding the MRHD for 12 weeks, including a ten week period at 200 mg/day (Study 178-CL-003, 178-CL-004).

· **Renal toxicity**

In a safety pharmacology study, mirabegron administration to water-loaded rats reduced urine output and urinary electrolyte concentrations at oral doses ≥ 10 mg/kg. These findings were confirmed and extended in the repeat-dose toxicity studies in this species. In the 26 week study, urine was collected for six hours following dosing while the rats had free access to food and water. Exposure to mirabegron at levels 12-59 times the MRHD resulted in reduced urinary excretion, decreased urine pH and increased urinary concentrations of bilirubin, but the animals recovered from these effects when they were hydrated. This effect was exacerbated overnight when access to food and water was restricted, and urine became more concentrated. Renal weight tended to increase in the repeat-dose toxicity studies in rats, although not in the 26 week study. Importantly, there was no evidence of adverse histopathological changes in the kidneys of rats in the 26 week study at exposure levels 57 times the MRHD, nor in the two year carcinogenicity study at up to 25-45 times the MRHD, and no renal effects were noted in mice, dogs or monkeys.

· **Ocular toxicity**

In common with many other β-adrenoceptor agonists and antagonists, mirabegron and some of its metabolites appear to bind to melanin containing structures of the eye. As a result of this binding, mirabegron-associated radioactivity had a very long half life (157 days) in the eyes of pigmented rats, and high levels of radioactivity were detected in the eyes of monkeys following oral administration of ^{14}C-mirabegron. No ophthalmological effects were reported in the repeat dose studies in rats, dogs and monkeys, and therefore the strong melanin binding of mirabegron and its metabolites does not appear to have any toxicological consequences. Melanin binding *per se* is not predictive of ocular toxicity, and there are many examples of compounds that interact strongly with ocular tissues without causing any such effects (Leblanc *et al* 1998[17]). The design and conduct of the submitted studies is considered to have been adequate to address the potential for mirabegron and its metabolites to induce ocular toxicity.

[17] Leblanc, B. *et al*. Binding of drugs to eye melanin is not predictive of ocular toxicity. *Regulatory Toxicology and Pharmacology* 1998:28;124-132.

- **Reproductive organ findings**

Distribution studies in rats showed a tendency for mirabegron and/or its metabolites to accumulate in the testes. However, there were no histological correlates of reduced prostate and seminal vesicle weights seen at high levels of systemic exposure in the two and 13 week studies in this species, and no adverse effects on the reproductive system of male rats in the 26 week study at relative exposures of 55 times the MRHD, nor in the two year carcinogenicity study at 25 times MRHD.

Evidence of potential toxicity to the reproductive system of female rats included decreased ovarian and uterine weights and uterine atrophy at high relative exposure levels in the two and 13 week studies. These effects were not reproduced in the 26 week repeat dose toxicity study or in the two year carcinogenicity study at relative exposure levels 59 times and 45 times the MRHD, respectively.

There were no adverse effects on the male or female reproductive system of mice, dogs or monkeys in the repeat dose toxicity studies. The potential for adverse reproductive effects with clinical appears to be low.

Genotoxicity

The genotoxicity of mirabegron was examined in a standard battery of genotoxicity studies which included a bacterial reverse mutation assay, a human peripheral blood lymphocyte chromosome aberration assay, and a rat bone marrow micronucleus test. These three assays were conducted in accordance with ICH guidelines and under GLP conditions. Concentrations or doses used were appropriate and limited by cytotoxicity, solubility or mortality. The bacterial assay used a suitable set of tester strains of *Salmonella typhimurium* and *Escherichia coli*. All three assays were validated with appropriate negative and positive controls, and did not provide evidence of genotoxicity for mirabegron.

Carcinogenicity

The carcinogenic potential of mirabegron was examined in two-year studies in mice and rats given daily doses of mirabegron by the oral route. The studies were conducted in accordance with ICH guidelines[18] and the doses selected were appropriate, with relative systemic exposure levels being adequate multiples of the clinical exposure, as indicated above (see *Relative exposure* above). In the mouse study, reductions in body weight gain were in keeping with the pharmacological action of β3-receptor stimulation. Reduced body weight gain was seen in the face of increased food consumption, reflecting exaggerated pharmacological activity rather than toxicity. This effect was unlikely to influence tumour incidences as there was no notable difference in survival between groups.

In the mouse carcinogenicity study, the incidences of benign hepatocellular adenomas from the control and ascending dosage groups were 1.4, 16, 10 and 4%, respectively, for female mice (historical control rate for the conducting laboratory 0.6%, range 0-1.4%), and 10, 16, 19 and 14%, respectively for male mice (historical control rate 8%, range 0-12%). A statistically significant increase in tumour incidence was only found for female mice at the lowest dose (p= 0.0017). The benign hepatocellular adenomas in female mice are not considered treatment related because the effect showed no dose-dependence and was not observed in male mice. The incidence of combined adenoma and carcinoma was not increased in either sex. The historical control incidence of hepatocellular adenomas in

[18]ICH Topic S1C(R2) *Dose Selection for Carcinogenicity Studies of Pharmaceuticals*, EMEA/CHMP/ICH/383/1995; and *Note for Guidance on Carcinogenic Potential, CPMP/SWP/2877/00*

mice of this strain appears to vary considerably with the conducting laboratory, and the incidences of hepatocellular adenoma in female mice observed in this study are within historical control limits of 26-28% reported by the National Toxicology Program.

Benign renal tubular adenomas were observed in one mid dose (MD) male mouse and in two male mice at the high dose (HD) level. It is not possible to establish whether this is treatment related, but there was no treatment-related histopathological change in the kidney, except for tubular vacuolation, which was seen in the same treatment groups (but not in the animals having tubular adenomas). An examination of the overall tumour incidence showed no treatment related trend (Peto trend test).

In the two year carcinogenicity study in rats the survival of females rats at the HD level was reduced (40%, compared with 70% for the control group). A lower dose had been selected for male rats in this study in order to limit the extent of reduced body weight gain, and the reduced survival of female rats at the HD level may indicate that the maximum tolerated dose had been exceeded in this sex. There was an increase in the incidence of endometrial stromal polyps of the uterus and cervix in the low dose (LD) group (22%, compared with a control incidence of 12%), but the lack of dose-dependence suggests that this was not an effect of treatment. An increase in benign thyroid follicular cell adenomas in MD (3/60) and HD males (2/60) and females (1/59) is not considered to be of toxicological significance. Overall, there was no evidence of a positive dose related trend or increase tumour incidence in HD animals compared with controls.

The nonclinical data do not indicate that mirabegron is genotoxic or carcinogenic. However, an increased incidence of neoplasia was observed in a clinical study in subjects dosed for 12 months with mirabegron at 100 mg (11/820) compared with those treated with 50 mg (1/812) and an active comparator group (4/812); Study 178-CL-049. There is evidence from animal studies that stimulation of β-adrenoceptors may promote growth and metastasis of neoplasms. However, the nonclinical data submitted by the sponsor do not provide any evidence that mirabegron treatment is associated with an earlier onset or more rapid progression of neoplasia. According to the FDA pharmacology review of the US application for this drug (available on the FDA website[19]), an FDA Executive Carcinogenesis Assessment Committee met to review the mouse and rat carcinogenicity data. The committee concluded that both studies were adequate, and there was no evidence that mirabegron increased the incidence of neoplasms in either species. The nonclinical evaluator is in agreement with these conclusions.

Reproductive toxicity

The sponsor submitted fertility and early embryonic development studies in male and female rats (dosing for two weeks prior to mating and until gestation day (GD) 14 and GD 7 in males and females, respectively), embryofetal development studies in rats and rabbits with maternal dosing during the period of organogenesis, and a prenatal and postnatal development study in rats in which dams were dosed from implantation to weaning. The studies were conducted in accordance with ICH guidelines and are considered adequate with respect to study design, species, group sizes and timing and duration of treatment. Relative exposure levels encompassed large multiples of the anticipated clinical exposure, as shown below.

[19] <http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202611Orig1s000PharmR.pdf>

Table 2. Relative exposure in reproductive toxicity studies

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (ng·h/mL)	Exposure ratio[#]
Rat (SD)	[†]Fertility	30	14,100	34
		100	31,800	77
		300	70,800	171
	[*]Embryofetal development	10	457	0.9
		30	3,166	6.2
		100	11,015	22
		300	48,948	96
Rabbit (NZW)	Embryofetal development GD 20	3	364	0.7
		10	7230	14
		30	18,277	36
Human (healthy volunteers)	steady state	50 mg	Male: 413 Female: 512	–

[#] = animal:human plasma $AUC_{0-24\,h;}$ [†]data are based on day 15 AUC data from male fertility study (178-TX-039), except for the HD where day 1 data were used, and exposure ratio is based on AUC data from Study 178-CL-072; [*]based on GD17 AUC data

Mirabegron is not anticipated to have adverse effects on male or female fertility with clinical use, based on the results of studies in rats. There was no effect on female fertility at exposure levels approximately 22 times those anticipated at the MRHD (using the toxicokinetic data from pregnant rats in the embryofetal toxicity study). Adverse effects at 96 times the MRHD included prolongation of the dioestrous period and slight reductions in mean numbers of corpora lutea, implantations and live fetuses, but these effects are likely to be secondary to maternal toxicity (decreased body weight and food consumption). The fertility of male rats was unimpaired at relative exposures 77 times the MRHD. Male fertility was reduced at doses that were associated with mortality (171 times the MRHD, mortality rate 14/20).

Mirabegron was shown to cross the placenta of pregnant rats, resulting in fetal exposure. Reversible delays in skeletal ossification and wavy ribs were associated with relative exposure levels ≥ 22 times MRHD, which were not associated with maternal toxicity. At higher doses (96 times the MRHD, and associated with marked maternal toxicity), delayed ossification was more extensive, and was accompanied by decreased fetal weight and bone malformations. The NOEL for embryofetal toxicity in this study was equivalent to ≤ 6 times the MRHD.

The relative systemic exposure associated with embryofetal NOEL in the rabbit was 0.7 times the MRHD. At a relative exposure of 14 times the MRHD, fetal weight was reduced by 10-12%, but no other toxic effects were reported. At a relative exposure level of 36 times the MRHD, post-implantation loss, fetal death, reduced fetal weight, cardiomegaly, dilated aorta, fusion of the sternebrae and a slight delay in the ossification of some digits were

observed. This dose was also maternally toxic, with reductions in food consumption and body weight observed. Toxicokinetic studies in pregnant and non-pregnant rabbits showed an approximately two-fold increase in mirabegron exposure during pregnancy, but this was not observed in rats. The effect of pregnancy on mirabegron pharmacokinetics human is unknown.

Mirabegron was excreted in the milk of lactating rats. In the peri- and postnatal development study in this species, there were no adverse effects on pup survival or development at doses corresponding to relative exposures 6 times the MRHD. At relative exposures corresponding to 22 times the MRHD there was an increase in postnatal mortality in the first four days after birth, and pup weight post-weaning was reversibly reduced. Surviving pups showed no adverse behavioural or developmental effects, and their reproductive performance was unimpaired.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3[20], which is acceptable based on the adverse effects seen in the embryofetal toxicity studies.

Local tolerance

Mirabegron did not cause skin irritation when applied topically to rabbit skin. It was a mild ocular irritant.

Antigenicity

Mirabegron showed a moderate skin sensitising potential in the adjuvant/patch test and in the Buehler test in guinea-pigs. The draft PI document lists urticaria, rash and pruritus as uncommon adverse reactions in the three 12-week Phase III clinical trials with mirabegron while leucocytoclastic vasculitis and purpure were classified as “rare” reactions.

Interference with detection of protein in urine

An apparent increase in urinary protein concentration was detected in the 2- and 13-week repeat dose toxicity studies in rats at a dose of 300 mg/kg. It was established that mirabegron gave false positive readings for protein using some commercially available dipstick assays. A study evaluated by the FDA but not submitted to the TGA (178-TX-058) showed false positive readings for protein when human urine was spiked with mirabegron at concentrations of 0.1-1.0 mg/mL. Based on the data submitted to the FDA, mirabegron and its two major urinary metabolites M11 and M12 are not expected to interfere with urinalysis tests with normal clinical use.

Impurities

The proposed specifications for impurities in the drug substance and product are below ICH qualification thresholds or have been adequately qualified.

Paediatric use

Mirabegron is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

[20] The definition of use in pregnancy Category B3 is: *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.*

Comments on the safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for mirabegron detailed in the sponsor's draft Risk Management Plan (RMP) are in general concordance with those of the nonclinical evaluator.

Nonclinical summary and conclusions

- Mirabegron is a first-in-class β3-adrenoceptor agonist for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in patients with OAB syndrome. The proposed dose is 50 mg/day PO (25 mg/day for patients with severe renal impairment).
- The sponsor has submitted a comprehensive set of data to support the application, including general and safety pharmacology, PK, single and repeat dose toxicity, genotoxicity, carcinogenicity, reproductive toxicity, local tolerance and sensitisation studies. The pivotal toxicity studies were conducted in accordance with ICH guidelines and in compliance with GLP.
- Mirabegron had a relatively high affinity for cloned human β3-adrenergic receptors, and its intrinsic activity at these receptors was high (determined by the maximum stimulation of cAMP production relative to isoprenaline). Studies with cloned rat, dog and monkey β-adrenoceptors confirmed that these species were suitable models. Mirabegron had a relatively low affinity and intrinsic activity at cloned β1- and β2-adrenoceptors, and its metabolites showed negligible activity at any of the three β receptor subtypes. Activation of β3-adrenoceptors on urinary bladder smooth muscle by mirabegron *in vitro* produced relaxation of contracted tissue, with an EC_{50} in human isolated detrusor muscle of 0.78 μM. The activity of mirabegron on the urinary bladder of rats, dogs and monkeys *in vivo,* including in models of OAB and urinary urgency, was supportive of its use for the proposed indications at clinically relevant concentrations. Mirabegron increased functional bladder capacity and decreased voiding frequency in these studies, but did not affect voiding pressure or residual volume.
- Mirabegron increased heart rate in rats, rabbits, dogs and monkeys, which at high doses resulted in fatal ventricular tachycardia (exposure levels 29 and 37 times the clinical plasma C_{max}). In all species (including humans) tachycardia appears to result from stimulation of β1-adrenoceptors by mirabegron, which contrasts with the apparent selectivity for β3-adrenoceptors over β1- and β2-adrenoceptors observed with cloned receptors *in vitro*. In dogs, the tachycardic response may in part be a reflex response to vasodilation, since blood pressure was reduced in this species, and to a lesser extent in rats, but not in monkeys. Mirabegron and its metabolites did not show any potential for QT prolongation.
- Mirabegron induced lipolysis in isolated adipocytes, increased metabolic rate and showed some efficacy in rodent models of type 2 diabetes, including elevation of body temperature and energy expenditure, and reduced plasma concentrations of non-esterified fatty acids, glucose, insulin and triglycerides in genetically obese diabetic mice (strain kk/A^y), and improved glucose tolerance in fasted Zucker Fatty rats. In common with a number of other β3 agonists, the lipolytic effect was apparently not reproduced in human studies. Reduced body weight gain, which was observed in repeat-dose toxicity studies, is not anticipated with clinical use.
- Mirabegron absorption (predominantly from the small intestine) was extensive and relatively rapid following oral administration, and extensively distributed. Bioavailability increased with dose in rats (23-76%), dogs (42-77%) and humans (24-45%), possibly due to saturation of P-glycoprotein mediated intestinal efflux. In rabbits, systemic exposure to mirabegron was increased 1.5 to 2-fold during

pregnancy, but this did not occur in rats. Mirabegron binds to plasma proteins (72-80%) in mice, rats and humans. Tissue distribution studies showed negligible passage of mirabegron and its metabolites across the blood-brain barrier, and indicated that elimination from thyroid, kidney, testes and bone marrow was slow, but this did not appear to have any toxicological consequences. Mirabegron and its metabolites accumulated in melanin-containing tissues, again without adverse toxicological effects. Placental and lactational transfer was demonstrated in rats.

- Mirabegron is metabolised by multiple pathways involving dealkylation, oxidation, amide hydrolysis and glucuronidation. Responsible enzymes include CYP2D6 and CYP3A4, plasma butyrylcholinesterase and UGT. When systemic exposure to mirabegron and its human plasma metabolites was investigated, unchanged mirabegron was the most abundant plasma species in the mouse, rat and human, while in the monkey and rabbit, respectively, M11 (glucuronide) and M5 (phase 2 acetyl conjugate) were the most abundant. There were no unique human plasma metabolites. Mirabegron and its metabolites were excreted by the renal and faecal routes in all species, being approximately equal in monkeys, more renal in humans and more faecal in rats. Enterohepatic circulation was demonstrated in rats.
- Based on *in vitro* nonclinical data, mirabegron may potentially inhibit the metabolism of substrates for CYP2D6 and CYP3A4. Owing to the multiple mechanisms underlying its clearance, the PK of mirabegron are unlikely to be markedly altered by co-administered drugs, although the nonclinical data indicate that it is a substrate for P-glycoprotein, OCT1, OCT2, OCT3, butyrylcholinesterase, UGT, CYP3A4 and, CYP2D6.
- Mirabegron showed low to moderate acute oral toxicity in the rat, and high acute oral toxicity in the dog, generally due to exaggerated pharmacological effects. Intravenous administration to a single monkey (at a dose more than 100 times the recommended therapeutic dose based on C_{max}) induced salivation, pale oral mucosa, dyspnoea, loss of papillary reflex and mydriasis, ventricular tachycardia and death.
- The major targets of toxicity were the CNS, liver, kidney and lachrymal and salivary glands, as well as the cardiovascular system, which essentially confirmed and extended the findings from the safety pharmacology study. In the 52 week monkey study, mirabegron prolonged the cardiac PR interval at systemic exposure levels eight times higher than therapeutic levels, an effect which is suggestive of impaired conduction from atria to ventricles.
- Mirabegron does not readily cross the blood brain barrier, and severe adverse CNS effects were generally associated with exposure levels well above therapeutic. Decreased alertness, reduced spontaneous activity and prone position were seen in mice, rats and monkeys at exposure levels similar to that expected clinically.
- Hepatic enzymes were moderately elevated in rats (50-70% increases in AST for males, up to 10-fold increases in ALT for males, and 60% for females) and dogs (2-3.5 times historical control values) at high doses (exposure levels 12-25 times the MRHD). Adverse histopathological changes in rats were only seen at systemic exposure levels 12-17 times those anticipated clinically. Adverse hepatic effects were generally reversible. No adverse hepatic effects were seen in monkeys exposed to mirabegron at up to eight times the therapeutic level for 52 weeks.
- Systemic exposure of rats to mirabegron at 12-59 times therapeutic levels in the 26-week study in rats resulted in reduced urinary excretion, decreased urine pH and increased urinary concentrations of bilirubin, but no adverse histological findings were reported in this study, nor in the two year carcinogenicity studies in mice or rats at higher exposure levels. No adverse renal effects were noted in the 52 week monkey study.

- Salivation and lacrimation, observed in rats and dogs at near to clinical exposure levels, are anticipated effects based on the pharmacology of mirabegron. Treatment-related effects in the zygomatic salivary glands of dogs at subclinical exposure levels included oedema, haemorrhage, necrosis and atrophy of acinar and ductal cells. These findings were generally reversible. Parotid gland atrophy and reduced zymogen granules were seen in the 13 and 26 week studies in mice and rats, respectively at more than ten times the clinical exposure level, but no salivary gland changes were seen in the mouse or rat carcinogenicity studies at considerably higher exposures, nor in monkeys treated for one year at eight times the therapeutic exposure level.
- Mirabegron is not considered to be genotoxic based on the results of a bacterial reverse mutation assay, a human peripheral blood lymphocyte chromosome aberration assay, and a rat bone marrow micronucleus test. The results of two year carcinogenicity assays in rats and mice did not indicate carcinogenic potential.
- Mirabegron did not adversely affect fertility in male and female rats. There was no embryofetal toxicity evident in rats whose dams were exposed to mirabegron levels less than or equal to six times the human therapeutic exposure level. The embryofetal NOAEL (rabbits and rats) and peri-postnatal NOAEL (rats) were established at relative exposures levels of approximately one and six in rabbits and rats, respectively. Reversible adverse developmental findings consisting of delayed ossification and wavy ribs in rats and decreased fetal body weights in rabbits occurred at relative exposures greater than or equal to 22 and 14, respectively. At maternally toxic exposures decreased fetal weights were observed in rats and rabbits, with the additional findings in the rabbit (at a relative exposure level of 36)of 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.
- Mirabegron showed a moderate skin sensitising potential in the adjuvant/patch test and in the Buehler test in guinea-pigs. It is noted that urticaria, rash, pruritus, leucocytoclastic vasculitis and purpure were observed in Phase 3 clinical trials with mirabegron.
- Mirabegron interfered with the measurement of urinary protein concentrations in nonclinical studies but this is unlikely to be of clinical relevance.

Recommendation

There are no nonclinical objections to the registration of mirabegron.

Recommendations regarding revisions to nonclinical statements in the draft PI are beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Mirabegron is a new chemical entity, a first-in-class compound with a different mechanism of action than the current agents used to treat OAB. The proposed indication is:

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

The *standard* recommended dose for mirabegron is one 50 mg tablet once daily, with or without food. In patients with severe renal or moderate hepatic impairment, the recommended dose is one 25 mg tablet once daily.

Clinical rationale

The urinary bladder has two main roles: the storage of urine produced by the kidneys and the release of that stored urine during voluntary voiding at a convenient time. The neurophysiological control of these two opposing functions is complex. At the simplest level, voiding is triggered by a stretch reflex initiated in the bladder wall, leading to relaxation of the urinary sphincter and contraction of the main bladder muscle, the detrusor. In a normal toilet-trained subject, this reflex is inhibited by higher centres, so that the subject experiences a desire to void but can post-pone the void, often for prolonged periods. In a variety of conditions, including cerebral and spinal cord disease, bladder damage, or more subtle idiopathic disturbances, the balance between storage and voiding, and the central inhibition of the stretch reflex, can be disturbed. A common syndrome of bladder dysfunction is over-active bladder (OAB), in which subjects have the urge to void at relatively low bladder volumes, have difficulty postponing voiding, may be excessively aware of the need to void, or may lose urine involuntarily because of active detrusor contraction. A hallmark of this syndrome is *urgency*, in which patients experience a rapid escalation from initial awareness of bladder fullness to a strong desire to void, have difficulty postponing voiding, and may be incontinent if they do not get to a toilet in time.

The main two arms of the autonomic nervous system, the parasympathetic and sympathetic systems, exert opposing influences on bladder function. Contractions of the detrusor are enhanced by parasympathetic activity, mediated by muscarinic acetylcholine receptors, and traditional approaches to OAB have involved the use of antimuscarinic (anticholinergic) agents. Problems with such agents include lack of efficacy, constipation, dry eyes, dry mouth, and sedation. Many patients abandon antimuscarinic therapy because of these side effects, or because efficacy is inadequate. Others continue antimuscarinic agents but suffer continued symptoms of OAB. These symptoms may include urinary frequency, urgency, incontinence, social isolation and low self esteem. Many patients can only avoid incontinence by planning each trip around the location of toilets, or by frequent pre-emptive voiding.

Mirabegron is a new agent that works by stimulating a subclass of sympathetic receptors in the bladder, the β3-adrenergic receptors. Whereas stimulation of muscarinic receptors facilitates detrusor contraction, activation of β3-adrenergic receptors in the bladder's triangular base (the trigone) facilitates urine storage by flattening and lengthening the bladder base (Yamanishi *et al*, 2003[21]). The dominant β-adrenergic receptor subtype in the human detrusor muscle is the β3-adrenergic receptor, and activation of β3-adrenergic receptors has been shown to promote urine storage in the bladder (Kumar *et al*, 2003[22]; Yamaguchi, 2002[23]).

A range of animal studies have supported the idea that a β3-adrenergic receptor agonist might be useful in promoting urine storage. Using the β3-adrenergic receptor agonists FK175 and CL-316243, it has been shown that activation of β3-adrenergic receptors

[21] Yamanishi T *et al*. Role of β-Adrenoceptor Subtypes in Mediating Relaxation of the Pig Bladder Trigonal Muscle *In Vitro*. *Neurourology and Urodynamics* 2003:22;338-342.
[22] Kumar V et al. Recent developments in the management of detrusor overactivity. *Curr Opin Urol.* 2003;13:285-91.
[23] Yamaguchi T. Beta 3-adrenoceptors in human detrusor muscle. *Urology*. 2002;59(5 Suppl 1):25-9

promoted urine storage in rats by increasing bladder capacity (Fujimura et al, 1999[24]; Takeda *et al*, 2000[25]). Also, CL-316243 increased urinary bladder capacity in OAB models in rats (Woods *et al*, 2001[26]; Takeda *et al*, 2002[27]; Leon *et al*, 2008[28]), leading some authors to propose use of beta 3-AR agonists as bladder relaxant drugs for treatment of OAB (Yamaguchi, 2002[29]).

The sponsor reports that preclinical work with mirabegron showed it to be a selective β3-adrenergic receptor agonist. Mirabegron reportedly showed selective agonistic activity and high affinity for human β3-adrenergic receptor as compared with β1- and β2-adrenergic receptors, and it had little affinity for a wide panel of other receptors, ion channels, and transporters. It did not have any inhibitory effects on the activity of a panel of enzymes. Mirabegron increased cAMP concentrations in bladder tissues isolated from rats and it showed a potent relaxant effect in isolated rat and human bladder strips precontracted with carbachol. It also decreased the resting intravesical (intra-bladder) pressure in rats. It decreased the frequency of rhythmic bladder contractions in anaesthetised rats, without affecting the force of the contractions. In water-loaded conscious cynomolgus monkeys, it increased the volume voided per micturition and decreased the voiding frequency. In a cerebral infarction (stroke) model of OAB in rats, mirabegron increased the mean voided volume per micturition. In rats with partial urethral obstruction, it decreased the frequency of non-voiding contractions without affecting the voided volume per micturition, voiding pressure, or residual urine volume. Overall, this evidence suggests that mirabegron enhances urine storage function by stimulating β3-adrenergic receptors in the bladder, without affecting voiding contractions.

Evaluator comment: Overactive bladder is a common and distressing condition so the prospect of a new agent for relieving OAB symptoms is welcome. The main question raised by the proposed mechanism of action is whether the β3-adrenergic receptors play a sufficiently potent role in modifying urine storage to allow a meaningful improvement of OAB symptoms with this approach, and whether stimulation of adrenergic receptors can be achieved without causing systemic adrenergic side effects, such as hypertension.

Guidance

The European Medicines Agency (EMA) for the evaluation of medicinal products has produced guidelines for the clinical investigation of products intended to treat urinary incontinence[30], which the TGA has adopted. Those guidelines suggest that the primary aim of incontinence treatment is to provide a subjective improvement, so subjective response should be a major clinical outcome measure. The guidelines argue that quantification of symptoms in terms of frequency of incontinence or micturition is worthwhile but cannot be used as a surrogate for subjective improvement. The sponsor's pivotal studies partially conform to these general principles; the co-primary endpoints of all three pivotal studies were the same, and consisted of a quantification of urinary frequency and incontinence.

[24] Fujimura T *et al*. Expression and possible functional role of the beta3-adrenoceptor in human and rat detrusor muscle. *J Urol*. 1999 Feb;161(2):680-5.
[25] Takeda H. *et al*. Role of the β3-adrenoceptor in urine storage in the rat: comparison between the selective β3-adrenoceptor agonist, CL316, 243, and various smooth muscle relaxants. *J Pharmacol Exp Ther* 2000; 293:939-45.
[26] Woods M *et al*. Efficacy of the β3-adrenergic receptor agonist CL-316243 on experimental bladder hyperreflexia and detrusor instability in the rat. *J Urol* 2001;166:1142-7.
[27] Takeda *et al*. Effects of beta(3)-adrenoceptor stimulation on prostaglandin E(2)-induced bladder hyperactivity and on the cardiovascular system in conscious rats. *Neurourol Urodyn*. 2002;21(6):558-65.
[28] Leon LA *et al*. Effects of the beta 3-adrenergic receptor agonist disodium 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,3-benzodioxole-2,2-dicarboxylate (CL-316243) on bladder micturition reflex in spontaneously hypertensive rats. *J Pharmacol Exp Ther*. 2008 Jul;326(1):178-85.
[29] Yamaguchi O. Beta 3-adrenoceptors in human detrusor muscle. *Urology*. 2002;59(5 Suppl 1):25-9.
[30] *"Note for Guidance on the Clinical Investigation of Medicinal Products for the Treatment of Urinary Incontinence."* CPMP, December 2002.

Subjective endpoints were included, but were secondary or tertiary in importance. Because these subjective endpoints were positive in most cases, with mirabegron achieving statistically significant superiority over placebo, the sponsor's initial ranking of these endpoints ranking is not critical.

In other respects, the sponsor's submission conforms to suggestions in the EMA guidelines, such as the use of a parallel, placebo-controlled design, and pivotal study durations of at least 3 months.

Contents of the clinical dossier

The contents of the clinical submission are as follows:

- Module 5: 41 clinical studies, as shown in Table 3.
- Literature references
- *Integrated Summary of Efficacy, Integrated Summary of Safety*
- Module 2: Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety.

The clinical studies included 29 clinical pharmacology studies, 3 Phase II OAB studies and 6 Phase III OAB studies, three of which are considered pivotal. Three Phase II studies for other indications (diabetes and bladder outlet obstruction) contributed safety data.

Table 3. Overview of the clinical development program for mirabegron

	IR Formulation		OCAS Formulation	
Phase	**Single Dose**	**Multiple Dose**	**Single Dose**	**Multiple Dose**
Phase 1	178-CL-001 SAD 178-CL-007 MB†	178-CL-002 MAD 178-CL-005 DDI § 178-CL-006 DDI	178-CL-033BA¶ 178-CL-036 DDI 178-CL-038 Renal 178-CL-039 Hepatic 178-CL-041 FE 178-CL-053 CI 178-CL-064 FE‡ 178-CL-066 DP‡ 178-CL-070 DDI 178-CL-076§ PK¶ 178-CL-078 FE‡	178-CL-030 PK† 178-CL-031 PK 178-CL-034 PK‡§ 178-CL-037 TQT 178-CL-040 DDI 178-CL-058 DDI 178-CL-059 DDI 178-CL-068 DDI 178-CL-069 DDI§ 178-CL-072 A/G 178-CL-077 TQT 178-CL-080 DDI 178-CL-081 IOP
Phase 2 (Other)		178-CL-003 POC DM 12-weeks 178-CL-004 POC DM 12-weeks		178-CL-060 Urodynamics LUTS/BOO
Phase 2 (OAB)		178-CL-008 POC 4-weeks		178-CL-044 DF 12-weeks 178-CL-045‡ DF 12-weeks
Phase 3 (OAB)				178-CL-046 E/S, 12-weeks 178-CL-047 E/S, 12-weeks 178-CL-074 E/S, 12-weeks 178-CL-048 ‡ E/S, 12-weeks 178-CL-049 E/S, 52-weeks 178-CL-051‡ E/S, 52-weeks

A/G: age and gender; BA: bioavailability; CI: cardiac impedance; DDI: drug-drug interaction; DF: dose finding; DM: type 2 diabetes mellitus; DP: dose proportionality; E/S: efficacy and safety; FE: food effect; IOP: intraocular pressure; IR: immediate release; LUTS/BOO: lower urinary tract symptoms/bladder outlet obstruction; MB: mass balance; MAD: multiple ascending dose; OAB: overactive bladder; OCAS: oral controlled absorption system; PK: pharmacokinetics; POC: proof of concept; SAD: single ascending dose; TQT: thorough QT.

† Study 178-CL-030 also included the IR formulation and Study 178-CL-007 used an oral solution of radiolabeled mirabegron.

‡ Studies conducted in Japan.

§ Studies 178-CL-005, 178-CL-034 and 178-CL-069 also included single doses.

¶ Used an intravenous formulation.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

All submitted studies included an assurance that they were conducted in keeping with current guidelines on Good Clinical Practice.

Pharmacokinetics

Studies providing pharmacokinetics data

The table below shows the studies relating to each PK (and PD) topic.

Table 4. Overview of mirabegron Phase I Studies.

Study No./ Region	Type of Study	Dose (mg)	No. E/C	Subject Type/ Diagnosis	Design
MIRABEGRON BIOPHARMACEUTIC STUDIES					
178-CL-030 (EU)	OCAS Selection	200 qd OCAS-F, OCAS-S and OCAS-M 100 bid IR tablet	36/34	HV	OL, XO
178-CL-033 (EU)	Absolute BA	50, 150 sd OCAS; 15, 50 sd iv over 2 hrs	12/12	HV	OL, XO
178-CL-076 (US)	IVIVC, Absolute BA	25, 50, 100 sd OCAS-H, OCAS-L, OCAS-M, OCAS-M other batch; 7.5 15, 30 sd iv over 2 hrs	91/75	HV	OL, XO
178-CL-041 (US)	Effect of Food; Pivotal	50, 100 sd OCAS	76/64	HV	OL, XO
178-CL-064 (JP)	Effect of Food	50 sd OCAS	24/23	Male HV	OL, XO
178-CL-078 (JP)	Effect of Food; Pivotal	50, 100 sd OCAS	72/70	HV	OL, XO
MIRABEGRON HEALTHY SUBJECT PK AND INITIAL TOLERABILITY STUDIES					
Studies using Oral Solution and IR (Immediate-Release) Capsule					
178-CL-001 (EU)	Single-dose PK and Food Effect	0.1, 0.3, 1, 3, 10, 30, 100, 160, 240, 340 sd capsule	85/85	Male HV	DB, PC
		160 sd capsule	12/12		OL, XO
178-CL-002 (EU)	Multiple-dose PK and Food Effect	40, 80, 160, 240 qd for 7 days capsule	40/38	Male HV	DB, PC
178-CL-007 (EU)	Mass Balance	^{14}C-mirabegron 160 sd drinking solution	4/4	Male HV	OL
Studies using OCAS Formulation					
178-CL-031 (EU)	Single- and Multiple-dose PK in Young and Elderly	50, 100, 200, 300 sd followed by 50, 100, 200, 300 qd for 10 days	96/96	HV (18-55 yrs and 65-80 yrs)	DB, PC
178-CL-066 (JP)	Dose Proportionality	25, 50, 100 sd	12/12	Male HV	OL
178-CL-034 (JP)	Single- and Multiple-dose PK in Japanese Subjects	0, 50, 100, 200, 300, 400 sd 0, 100, 200 qd	40/40 24/24	Male HV	SB, PC
MIRABEGRON STUDIES IN SPECIAL POPULATIONS (INTRINSIC FACTORS)					
Studies using OCAS Formulation					
178-CL-072 (EU)	Age and Sex	25, 50, 100 qd	75/67	HV (18-45 yrs and ≥ 55 yrs)	OL, XO
178-CL-038 (US)	Renal Impairment	100 sd	33/32	Normal, mild, moderate, severe renal impairment (eGFR-MDRD)	OL
178-CL-039 (EU)	Hepatic Impairment	100 sd	32/32	Normal, mild, moderate hepatic impairment (Child-Pugh A, B)	OL

Table 4 continued. Overview of mirabegron Phase I Studies.

Study No./ Region	Type of Study	Dose (mg)	No. E/C	Subject Type/ Diagnosis	Design
MIRABEGRON STUDIES OF DRUG-DRUG INTERACTION (EXTRINSIC FACTORS)					
Studies using IR Capsule or Tablet					
178-CL-005 (EU)	CYP2D6 Genotype, Metoprolol PK Interaction	160 sd capsule	16/16	Male HV; CYP2D6 PM and EM	OL
		160 qd capsule; metoprolol 100 sd	12/12	Male HV; CYP2D6 EM	
178-CL-006 (EU)	Metformin PK Interaction	160 qd tablet; metformin 500 bid	32/31	Male HV	OL
Studies using OCAS Formulation					
178-CL-036 (US)	Ketoconazole PK Interaction	100 sd; ketoconazole 400 qd	24/23	HV	OL, XO
178-CL-040 (EU)	Warfarin PK and PD Interaction	100 qd; warfarin 25 sd	24/24	HV	OL
178-CL-058 (EU)	Desipramine PK Interaction	100 qd; desipramine 50 sd	28/27	HV	OL
178-CL-068 (EU)	COC PK Interaction	100 or placebo qd; COC (EE 30 mcg + LNG 150 mcg) qd	30/23	Female HV	DB, PC
178-CL-059 (EU)	Digoxin PK Interaction	100 qd; digoxin 0.250 sd	25/23	HV	OL
178-CL-069 (EU)	Solifenacin PK Interaction	100 sd; solifenacin 10 qd 100 qd; solifenacin 10 sd	41/40	HV	OL
178-CL-070 (US)	Rifampin PK Interaction	100 sd; rifampin 600 qd	24/24	HV	OL
178-CL-080 (EU)	Tamsulosin Cardiovascular PD Interaction	100 qd; tamsulosin 0.4 sd (prolonged release) 100 sd; tamsulosin 0.4 qd (prolonged release)	48/46	Male HV	OL, XO
MIRABEGRON PD STUDIES					
Studies using OCAS Formulation					
178-CL-053 (EU)	Mechanism of Cardiovascular Responses	200 sd; bisoprolol 10 sd; propranolol 160 sd (prolonged release)	12/12	Male HV	SB, XO
178-CL-037 (US)	Thorough QT	100, 200 qd for 7 days; moxifloxacin 400 sd	49/43	HV	DB, XO PC/AC
178-CL-077 (US)	Thorough QT	50, 100, 200 qd for 10 days; moxifloxacin 400 qd for 10 days	352/319	HV	DB, XO, PC/AC
178-CL-081 (US)	Intraocular Pressure	100 qd	321/305	HV or adults with OAB	DB, PG, PC

EU: Europe; JP: Japan; US: United States; E/C: enrolled/completed; sd: single dose; DB: double-blind; SB: single-blind; OL: open-label; PC: placebo-controlled; PG: parallel group; AC: active-controlled; XO: crossover; HV: healthy volunteers (male and female unless indicated otherwise); qd: once a day; bid: twice a day; OCAS: oral-controlled absorption system (-F [fast], -M [medium], -S [slow], -H [high], -L [low]); IR: immediate release; iv: intravenous; PK: pharmacokinetic(s); PD: pharmacodynamic(s); BA: bioavailability; IVIVC: in-vitro-in-vivo correlation; eGFR-MDRD: estimated glomerular filtration rate using abbreviated modification of diet in renal disease formula; PM: poor metabolizer; EM: extensive metabolizer; COC: combined oral contraceptive (containing ethinyl estradiol and levonorgestrel); EE: ethinyl estradiol; LNG: levonorgestrel; OAB: overactive bladder.

Evaluator's summary and overall conclusions on pharmacokinetics

The PK of mirabegron have been well characterised. They are adequately described in the sponsor's proposed PI. Important features are a pronounced food effect, with lower exposure when combined with food, a large volume of distribution, and moderate increases in exposure in the setting of renal or hepatic impairment. Several minor drug interactions were observed with mirabegron, but dose adjustment of mirabegron is generally not required. Drugs that are substrates for CYP2D6 may need dose adjustment when combined with mirabegron, and digoxin should be introduced slowly and titrated with the assistance of drug levels when combined with mirabegron.

Pharmacodynamics

Primary pharmacodynamics

No primary PD studies directly assessing bladder physiology in response to mirabegron were submitted.

The sponsor submitted some PD population modelling, based on the major Phase II and III efficacy studies (178-CL-044, 178-CL-046, 178-CL-047 and 178-CL-074), using a Poisson-Normal mixed effect model. This modelling attempted to create a dose response curve, despite very noisy underlying data. Such modelling does not provide new information beyond a direct assessment of the contributory studies, and inevitably imports a range of assumptions into the model.

The table below shows the placebo-subtracted changes in micturition frequency and volume voided expected from the model across the dose range 25 mg to 200 mg. Similar information is displayed graphically in the subsequent pair of figures, where each curve represents an individual model run that attempts to capture the variability between patients. The idealised model is shown in Figure 3.

The model predicts that 25 mg produces 52% (29% to 70%) of the maximum effect, 50 mg produces 85% (68% to 97%) of the maximum effect, and 100 mg produces 98% (86% to 100%).

Table 5. Pharmacodynamic model of mirabegron effect from 25 mg to 200 mg

Dose (mg)	Micturition frequency	Mean volume voided (mL)
	Estimate (95% prediction interval)	Estimate (95% prediction interval)
25	-0.31 (-0.15 , -0.48)	6.74 (3.41 , 9.83)
30	-0.38 (-0.22 , -0.55)	8.24 (5.03 , 11.30)
35	-0.43 (-0.28 , -0.61)	9.47 (6.41 , 12.50)
40	-0.47 (-0.34 , -0.65)	10.43 (7.53 , 13.40)
50	-0.53 (-0.40 , -0.71)	11.75 (9.04 , 14.64)
60	-0.57 (-0.43 , -0.74)	12.57 (9.79 , 15.45)
70	-0.59 (-0.45 , -0.77)	13.07 (10.18 , 16.01)
75	-0.60 (-0.46 , -0.78)	13.24 (10.33 , 16.20)
80	-0.61 (-0.47 , -0.79)	13.38 (10.40 , 16.40)
100	-0.63 (-0.48 , -0.81)	13.74 (10.67 , 16.90)
125	-0.64 (-0.48 , -0.82)	13.97 (10.78 , 17.29)
150	-0.64 (-0.49 , -0.83)	14.06 (10.82 , 17.53)
200	-0.65 (-0.49 , -0.85)	14.13 (10.86 , 17.78)

Figure 2. First 50 predicted dose-response relationships for micturition frequency (left) and mean volume voided (right)

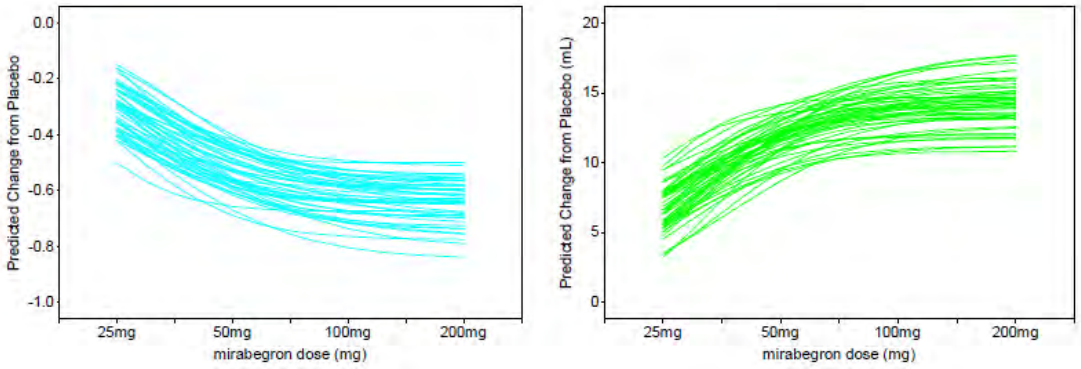
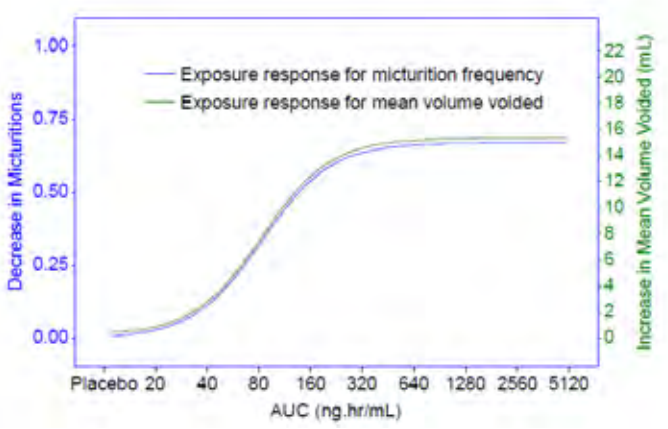


Figure 3. Idealised dose-response curve for mirabegron.



Secondary pharmacodynamic studies

The sponsor submitted three secondary PD studies related to potential tolerability issues with a systemic beta agonist. One of these assessed the cardiovascular response to mirabegron in the presence or absence of beta blockers, confirming that mirabegron exerts a minor cardiovascular effect that is partially blocked by β1-adrenergic receptor selective and non-selective antagonists. This result is consistent with a low degree of β1-adrenergic receptor agonist activity, and shows that selectivity for the β3-adrenergic receptor is only relative, but the clinical consequences of the minor β1-adrenergic receptor agonism are minimal. A similar result was obtained in the mirabegron monotherapy arm of the tamsulosin interaction study (178-CL-080).

Another study looked for changes in intraocular pressure with continued use, finding no evidence of this. Two studies assessed the potential QT effects of mirabegron [Thorough QT Studies 178-CL-037 and 178-CL-077]; these are summarised in the *Safety* section below.

Dosage selection for the pivotal studies

Dosage selection for the pivotal studies was largely based on the Phase IIb study, Study 044, which assessed once daily mirabegron OCAS 25, 50, 100 and 200 mg.

Active treatment with mirabegron in this study was associated with a placebo-subtracted improvement in micturition frequency of 0.45, 0.64, 0.68, and 0.80 episodes per 24 h in the 25 mg, 50 mg, 100 mg and 200 mg groups, respectively. There was a dose trend across the range 25 mg to 200 mg, suggesting that 200 mg might be more effective than lower doses, but mild QT prolongation has been observed at this dose. The results in the 25 mg group were not significantly different from placebo, suggesting that 25 mg is likely to be an ineffective dose in most OAB patients. The proposed dose of 50 mg showed a significant treatment effect, as did 100 mg, but the difference between 50 mg and 100 mg was minor. The sponsor chose 50 mg and 100 mg for further evaluation, and assessed both of these doses in two pivotal studies (Study 046 and Study 047). According to the sponsor, the FDA suggested another assessment of the 25 mg dose, so the third pivotal study (Study 074) assessed 25 mg as well as 50 mg (subsequently showing that 25 mg achieved some, but nor all efficacy endpoints, and was generally inferior to the 50 mg dose).

The population-PD modelling described above (under *Pharmacodynamics*) was performed after the pivotal studies were complete, but provides some retrospective justification of the doses chosen. The proposed 50 mg dose appears to offer most of the efficacy available

from mirabegron, while avoiding the increased risks expected from higher doses. It also provides a greater safety margin compared to the QT-prolonging dose of 200 mg.

Efficacy

Studies providing efficacy data

The sponsor performed three pivotal efficacy studies, which shared most design features including entry criteria, primary endpoints and statistical methods. All studies included multiple secondary endpoints. The studies differed in the doses assessed and only one of them employed an active control.

Pivotal Study 046 was a large (n=1987), randomised, parallel-group, international study comparing mirabegron 50 mg (the proposed dose), mirabegron 100 mg, tolterodine 4 mg and placebo in the treatment of patients of either gender ≥ 18 years of age with OAB. It had a single-blind placebo run-in period of two weeks followed by a randomised, double-blind, active and placebo-controlled main study period of 12 weeks.

The main efficacy variables were:

- Mean number of micturitions in 24 h based on a 3-day micturition diary
- Mean number of incontinence episodes in 24 h based on a 3-day micturition diary

The co-primary efficacy outcomes were:

- Change from baseline to end of treatment in mean number of micturitions in 24 h
- Change from baseline to end of treatment in mean number of incontinence episodes in 24 h

Pivotal Study 047 was a Phase III, randomised, parallel-group, placebo-controlled, double-blind, multinational study assessing the efficacy of placebo, mirabegron 50 mg or mirabegron 100 mg in female and male adults (≥ 18 years) with symptoms of OAB (urinary frequency and urgency with or without incontinence) present for at least 3 months.

As in Study 046, all subjects completed a single-blind placebo run-in period of 2 weeks. Eligible patients were then randomised to receive placebo, mirabegron 50 mg or mirabegron 100 mg orally once daily for 12 weeks. Unlike Study 046, there was no active control.

The two co-primary endpoints were identical to Study 046.

Pivotal Study 074 was a Phase III, randomised, parallel-group, placebo-controlled, double-blind, multinational study conducted in female and male adults with symptoms of OAB (urinary frequency and urgency with or without incontinence) present for at least 3 months. The inclusion criteria were the same as the other pivotal studies.

Study 074, like the other pivotal studies, used a single-blind placebo run-in period of 2 weeks. Following this, eligible patients were randomized in a 1:1:1 ratio to receive placebo, mirabegron 25 mg or mirabegron 50 mg orally daily for 12 weeks. Note that the proposed mirabegron dose of 50 mg was the higher dose assessed in this study, but it was the lower dose of Studies 046 and 047, and that this study was the only pivotal study to assess a dose of 25 mg.

The study used the same two co-primary endpoints assessed in the other pivotal studies.

A pooled analysis of all three of the 3 pivotal Phase III studies (Studies 046, 047 and 074) was also conducted.

In addition to the pivotal studies, the sponsor performed a number of supportive studies, as follows:

- 1 supportive Phase III study (178-CL-048),
- 2 supportive Phase IIb studies (178-CL-045 and 178-CL-044),
- 1 Phase IIa proof-of-concept study (178-CL-008),
- 1 Phase III active-controlled long-term safety study (178-CL-049), and
- 1 Phase III open label, long-term safety study (178-CL-051).

Summary of findings from the pivotal trials

Because the three pivotal studies shared entry criteria and endpoints, they were suitable for a pooled analysis. The results from the individual and pooled analyses are shown in Table 6. Note that the studies were all slightly different in terms of the treatments being assessed, with Study 046 using a tolterodine control group as well assessing mirabegron 50 mg and 100 mg, Study 047 just assessing mirabegron 50 mg and 100 mg, and Study 074 assessing 50 mg and 25 mg, but not 100 mg. The pooled results therefore involve all three studies, for the proposed 50 mg dose, but only Studies 046 and 047 for the 100 mg dose.

In general, the results for the proposed 50 mg dose in the pooled analysis were consistent with the individual studies. The results in the 25 mg group were derived from only one study, so the confidence intervals were broader. The magnitude of the effects at this dose also appeared inferior to the pooled 50 mg results.

Table 6. Overview of efficacy results, individual and pooled pivotal studies

	Study 178-CL-046			Study 178-CL-047		Study 178-CL-074		Pooled Primary Studies	
	Mirabegron 50 mg	Mirabegron 100 mg	Tolterodine ER 4 mg	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron 25 mg	Mirabegron 50 mg	Mirabegron 50 mg	Mirabegron 100 mg
Co-Primary Efficacy Results									
Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 hours (FAS-I)									
n	293	281	300	312	296	254	257	862	577
Adjusted mean difference vs placebo (SE)	-0.41 (0.160)	-0.29 (0.162)	-0.10 (0.159)	-0.34 (0.160)	-0.50 (0.162)	-0.40 (0.17)	-0.42 (0.17)	-0.40 (0.09)	-0.41 (0.11)
95% 2-sided CI	(-0.72, -0.09)	(-0.61, 0.03)	(-0.42, 0.21)	(-0.66, -0.03)	(-0.82, -0.18)	(-0.74, -0.06)	(-0.76, -0.08)	(-0.58, -0.21)	(-0.62, -0.19)
P value ‡	0.003#	0.010#	0.11	0.026#	< 0.001#	0.005#	0.001#	<0.001#	<0.001#
Change from Baseline to Final Visit in Mean Number of Micturitions per 24 hours (FAS)									
n	473	478	475	425	412	410	426	1324	890
Adjusted mean difference vs placebo (SE)	-0.60 (0.156)	-0.44 (0.156)	-0.25 (0.156)	-0.61 (0.188)	-0.70 (0.189)	-0.47 (0.18)	-0.42 (0.17)	-0.55 (0.10)	-0.54 (0.12)
95% 2-sided CI	(-0.90, -0.29)	(-0.74, -0.13)	(-0.55, 0.06)	(-0.98, -0.24)	(-1.07, -0.33)	(-0.82, -0.13)	(-0.76, -0.08)	(-0.75, -0.36)	(-0.77, -0.31)
P value †	< 0.001#	0.005#	0.11	0.001#	< 0.001#	0.007#	0.015#	<0.001#	<0.001#
Key Secondary Efficacy Results									
Change from Baseline to Final Visit in Mean Volume Voided (mL) per Micturition (FAS)									
n	472	478	475	424	412	410	426	1322	890
Adjusted mean difference vs placebo (SE)	11.9 (2.83)	13.2 (2.82)	12.6 (2.83)	11.1 (3.43)	11.0 (3.45)	4.6 (3.16)	12.4 (3.13)	11.9 (1.82)	12.3 (2.12)
95% 2-sided CI	(6.3, 17.4)	(7.7, 18.7)	(7.1, 18.2)	(4.4, 17.9)	(4.2, 17.7)	(-1.6, 10.8)	(6.3, 18.6)	(8.3, 15.5)	(8.1, 16.5)
P value †	< 0.001#	< 0.001#	< 0.001*	0.001#	0.002#	0.15§	<0.001#§	<0.001#	<0.001#
Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 hours (FAS-I)									
n	293	281	299	309	293	254	255	857	574
Adjusted mean difference vs placebo (SE)	-0.39 (0.167)	-0.38 (0.169)	-0.35 (0.166)	-0.48 (0.166)	-0.46 (0.168)	-0.34 (0.17)	-0.51 (0.17)	-0.45 (0.10)	-0.42 (0.12)
95% 2-sided CI	(-0.71, -0.06)	(-0.71, -0.05)	(-0.68, -0.03)	(-0.80, -0.15)	(-0.79, -0.13)	(-0.68, -0.01)	(-0.85, -0.17)	(-0.64, -0.26)	(-0.65, -0.20)
P value ‡	0.002#	0.002#	0.019*	0.003#	< 0.001#	0.039§	<0.001#§	<0.001#	<0.001#
Change from Baseline to Week 4 in Mean Number of Micturitions per 24 hours (FAS)									
n	471	477	474	422	409	410	424	1317	886
Adjusted mean difference vs placebo (SE)	-0.40 (0.136)	-0.52 (0.136)	-0.33 (0.136)	-0.42 (0.182)	-0.60 (0.183)	-0.18 (0.176)	-0.37 (0.17)	-0.40 (0.09)	-0.56 (0.11)
95% 2-sided CI	(-0.66, -0.13)	(-0.79, -0.26)	(-0.60, -0.06)	(-0.77, -0.06)	(-0.96, -0.24)	(-0.53, 0.16)	(-0.71, -0.03)	(-0.59,-0.22)	(-0.78, -0.35)
P value †	0.004#	<0.001#	0.016*	0.022#	0.001#	0.30§	0.035§	<0.001#	<0.001#
Key Secondary Efficacy Results for Study 178-CL-074 and Pooled Primary Studies; Additional Secondary Efficacy Results for Studies 178-CL-046 and 178-CL-047									
Change from Baseline to Final Visit in Mean Level of Urgency (FAS)									
n	472	475	473	425	411	410	426	1323	886
Adjusted mean difference vs placebo (SE)	-0.09 (0.040)	-0.08 (0.040)	-0.07 (0.040)	-0.11 (0.037)	-0.13 (0.037)	-0.07 (0.04)	-0.14 (0.04)	-0.11 (0.02)	-0.11 (0.03)
95% 2-sided CI	(-0.17, -0.02)	(-0.16, -0.01)	(-0.15, 0.01)	(-0.18, -0.04)	(-0.20, -0.05)	(-0.15, 0.01)	(-0.22, -0.06)	(-0.16, -0.07)	(-0.16, -0.06)
P value †	0.018*	0.037*	0.085	0.004*	< 0.001*	0.083§	<0.001§	<0.001#	<0.001#
Change from Baseline to Final Visit in Mean Number of Urgency Incontinence Episodes per 24 hours (FAS-I)									
n	286	276	289	297	291	247	251	834	567
Adjusted mean difference vs placebo (SE)	-0.35 (0.155)	-0.22 (0.156)	-0.07 (0.154)	-0.43 (0.145)	-0.56 (0.145)	-0.36 (0.16)	-0.39 (0.16)	-0.40 (0.09)	-0.40 (0.10)
95% 2-sided CI	(-0.65, -0.05)	(-0.53, 0.09)	(-0.38, 0.23)	(-0.72, -0.15)	(-0.85, -0.28)	(-0.67, -0.05)	(-0.69, -0.08)	(-0.57, -0.23)	(-0.60, -0.20)
P value ‡	0.003*	0.024*	0.26	0.005*	< 0.001*	0.004§	0.002§	<0.001#	<0.001#
Change from Baseline to Final Visit in Mean Number of Urgency Episodes (Grade 3 or 4) per 24 hours (FAS)									
n	470	474	472	424	411	410	426	1320	885
Adjusted mean difference vs placebo (SE)	-0.60 (0.214)	-0.31 (0.214)	-0.42 (0.214)	-0.75 (0.228)	-0.94 (0.230)	-0.33 (0.22)	-0.59 (0.22)	-0.64 (0.13)	-0.60 (0.15)
95% 2-sided CI	(-1.02, -0.18)	(-0.73, 0.11)	(-0.84, -0.00)	(-1.20, -0.30)	(-1.40, -0.49)	(-0.76, 0.10)	(-1.01, -0.16)	(-0.89, -0.39)	(-0.89, -0.31)
P value †	0.005*	0.14	0.050*	0.001*	< 0.001*	0.13§	0.007§	<0.001#	<0.001#

Table 6 legend: Pooled primary studies include 178-CL-046, 178-CL-047, and 178-CL-074. All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All randomized patients who took at least one dose of double-

blind study drug and who had a micturition measurement and at least one incontinence episode in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set-Incontinence [FAS-I]). ER: extended release. For the pooled primary studies and Studies 178-CL-046, 178-CL-047 and 178-CL-074 individually, a stepwise parallel gate keeping procedure was performed to control the Type I error rate at the 0.05 significance level for the coprimary and key secondary efficacy endpoints. Since 2 mirabegron treatment groups were compared with placebo, the Hochberg procedure was used to adjust for multiplicity within each stage. Since the comparison between tolterodine and placebo was a secondary analysis in Study 178-CL-046, no adjustment for multiplicity was necessary. In the pooled primary studies, the adjusted mean difference versus placebo for change from baseline and corresponding 95% confidence interval (CI) were generated from an ANCOVA model with treatment group, gender and study as fixed factors and baseline as a covariate. In Studies 178-CL-046, 178-CL-047, and 178-CL-074, the adjusted mean difference versus placebo for change from baseline and corresponding 95% CI were generated from an analysis of covariance (ANCOVA) model with treatment group, gender and geographical region as fixed factors and baseline as a covariate. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from that of treatment groups.
† Nominal P values are from pairwise comparisons versus placebo within the ANCOVA model, a parametric analysis.
‡ Nominal P values are from pairwise comparison versus placebo within the stratified rank ANCOVA, a nonparametric analysis.
# Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.
* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.
§ Study 178-CL-074 only: Since the mirabegron 25 mg group did not meet statistical significance with multiplicity adjustment for mean volume voided (P=0.15), subsequent key secondary efficacy endpoints for the mirabegron 25 mg group were excluded from further hypothesis testing as part of the gatekeeping procedure. Mean volume voided per micturition and subsequent key secondary efficacy endpoints for the mirabegron 50 mg group were evaluated at the 0.025 significance level. Since the mirabegron 50 mg group did not meet statistical significance with multiplicity adjustment for change from baseline to Week 4 in mean number of micturitions per 24 hours (P=0.035), subsequent key secondary efficacy endpoints for the mirabegron 50 mg group were excluded from further hypothesis testing as part of the gatekeeping procedure.

Evaluator's conclusions on clinical efficacy

Overall, the submitted efficacy data shows that mirabegron has a minor beneficial effect on the symptoms of OAB. The statistical evidence in support of the efficacy of mirabegron 50 mg is robust and consistent: all three pivotal studies and the pooled analysis showed a statistically significant treatment effect for both of the co-primary endpoints, micturition frequency and incontinence frequency. Secondary endpoints were also achieved with statistical significance in most cases, including a number of subjective endpoints, such as the Treatment Satisfaction Visual Analog Scale (TS-VAS).

There were no major methodological flaws compromising the statistical interpretation of the major endpoints, but there was a pronounced placebo response for both co-primary endpoints and most secondary endpoints. The placebo-subtracted treatment effect was relatively small compared to this placebo response.

The magnitude of the placebo-subtracted treatment effect was disappointing. In the pooled analysis of the pivotal studies, the number of voluntary micturitions avoided per 24 h was 0.55 episodes for the proposed 50 mg dose and 0.54 for the 100 mg dose, from a baseline of 11 to 12 episodes. This hardly seems worth pursuing. The mean number of incontinence episodes was reduced with mirabegron 50 mg by 0.40 episodes, from a baseline of about two and a half episodes across the various treatment groups. The reduction with mirabegron 100 mg was 0.41 episodes.

This modest quantitative improvement was associated with a statistically significant improvement in the subjective TS-VAS, which showed a placebo-subtracted improvement of 0.76 for mirabegron 50 mg and 1.08 for mirabegron 100 mg, in a scale ranging from 0 to

10 and baseline values of about 4. The improvement in the placebo group was 1.89, 0.7, 1.05 across the three studies. A fully effective drug would potentially produce a rating of 10 (complete satisfaction with treatment), giving an overall improvement of 6 points, and a placebo-subtracted improvement of 4-5 points.

Results in the 50 mg and 100 mg groups were generally similar to each other. The lower dose of 25 mg was only assessed in one pivotal study, and although this dose achieved significance for many endpoints, it was inferior to 50 mg and did not achieve all of its secondary endpoints.

The efficacy of mirabegron was broadly similar to that seen with the active control, tolterodine.

Thus, overall, mirabegron has modest efficacy, which some patients might find useful, and is comparable to another agent already used for OAB.

Safety

The studies listed below are the major source of evaluable safety data. The sponsor defined 5 different study populations, as indicated by the last 5 columns of the table below. The most important of these were the global Phase II/III population and the 12-week (placebo-controlled) global Phase II/III population. Patient disposition in the Phase II/III population is listed in Table 8.Most subjects (85.6%) completed treatment with mirabegron, but some patients withdrew for a variety of reasons. Adverse events (AEs) caused withdrawals in 5% of the global Phase II/III population.

Table 7. Overview of Phase II/II study populations

Study	Phase	Mirabegron Formulation	Population	Duration of Treatment	Global Phase 2/3	Global OAB 12-week Phase 2/3	EU/NA OAB 12-week Phase 3	EU/NA Long-term Controlled	Japan Long-term Uncontrolled
178-CL-044	2	OCAS	OAB	12 weeks	X	X			
178-CL-045	2	OCAS	OAB	12 weeks	X	X			
178-CL-046	3	OCAS	OAB	12 weeks	X	X	X		
178-CL-047	3	OCAS	OAB	12 weeks	X	X	X		
178-CL-074	3	OCAS	OAB	12 weeks	X	X	X		
178-CL-048	3	OCAS	OAB	12 weeks	X	X			
178-CL-049	3	OCAS	OAB	52 weeks (12 months)	X			X	
178-CL-051	3	OCAS	OAB	52 weeks (12 months)	X				X
178-CL-008	2	IR	OAB	4 weeks	X				
178-CL-060	2	OCAS	LUTS/BOO	12 weeks	X				
178-CL-003	2	IR	Type 2 diabetes mellitus	12 weeks	X				
178-CL-004	2	IR	Type 2 diabetes mellitus	12 weeks	X				

BOO: bladder outlet obstruction; IR: immediate release; ISS: integrated summary of safety; LUTS: lower urinary tract symptoms; OAB: overactive bladder; OCAS: oral controlled absorption system.

Table 8. Patient disposition, global Phase II/III population

n (%) of Patients	Total Mirabegron
Received at least one dose of mirabegron	5863
Completed treatment with mirabegron	5016 (85.6%)
Discontinued from mirabegron	847 (14.4%)
Primary reason for discontinuation	
AE	296 (5.0%)
Withdrawal of consent	256 (4.4%)
Lack of efficacy	96 (1.6%)
Protocol violation	64 (1.1%)
Patient lost to follow up	50 (0.9%)
Not fulfilling inclusion or exclusion criteria	21 (0.4%)
Worsening of disease	1 (< 0.1%)
Other	63 (1.1%)

Patient exposure

Exposure to mirabegron has been fairly extensive, with 10,552 subjects exposed in the clinical study program: this includes 1800 healthy volunteers and 8752 patients. Most patients (8433) have had OAB; the remainder (319) consists of male patients with lower urinary tract symptoms/bladder outlet obstruction (LUTS/BOO) and some patients with type 2 diabetes mellitus.

Not all exposed subjects were in studies that contributed to the integrated safety data set. The safety data set is based on 29 Phase I studies and 9 Phase II/III studies in OAB, and 3 studies in other conditions (one study in patients with LUTS/BOO and two studies in patients with type 2 diabetes mellitus). Detailed safety data thus comes from 1462 volunteers in Phase I studies and 5863 patients (5648 patients with OAB) in the Phase II/III studies.

Summary of findings

Treatment emergent adverse events

In the pooled 12-week Phase II/III population (involving subjects followed for 12 weeks, but excluding subjects from the non-placebo-controlled long-term studies), the incidence of treatment emergent adverse events (TEAEs) in the total mirabegron population (53.4%) was similar to that in the placebo group (55.2%), and there was actually a trend to reduced incidence of TEAEs at higher mirabegron doses, as shown in the table below.

Table 9. Serious AEs, TEAEs and TEAEs leading to discontinuation of study drug, Global OAB 12-Week Phase II/III Population

n (%) of Patients	Placebo (n = 2142)	Mirabegron					Tolt ER 4 mg (n = 958)
		25 mg (n = 811)	50 mg (n = 2131)	100 mg (n = 1305)	200 mg (n = 167)	Total Mira (n = 4414)	
SAE	38 (1.8%)	11 (1.4%)	34 (1.6%)	29 (2.2%)	3 (1.8%)	77 (1.7%)	16 (1.7%)
Drug-related SAE†	8 (0.4%)	4 (0.5%)	8 (0.4%)	5 (0.4%)	0	17 (0.4%)	7 (0.7%)
TEAE	1182 (55.2%)	452 (55.7%)	1173 (55.0%)	654 (50.1%)	80 (47.9%)	2359 (53.4%)	577 (60.2%)
Drug-related TEAE†	389 (18.2%)	169 (20.8%)	438 (20.6%)	262 (20.1%)	37 (22.2%)	906 (20.5%)	275 (28.7%)
TEAE leading to permanent d/c of study drug	63 (2.9%)	31 (3.8%)	75 (3.5%)	47 (3.6%)	7 (4.2%)	160 (3.6%)	36 (3.8%)
Drug-related TEAE leading to permanent d/c of study drug†	36 (1.7%)	19 (2.3%)	48 (2.3%)	32 (2.5%)	5 (3.0%)	104 (2.4%)	28 (2.9%)

Considering specific AEs, the most common AEs reported in the mirabegron group were: nasopharyngitis, hypertension, increased blood glucose, headache, urinary tract infection (UTI), increased gamma glutamyl transferase, and abnormal urinary sediment, with incidences as shown in the table below.

Table 10. TEAEs by Preferred Term (Reported by ≥ 3.0% in the total mirabegron group), Global Phase II/III Population

MedDRA v12.1 PT†, n (%) of Patients	Total Mirabegron (n = 5863)				
	TEAE	Mild	Moderate	Severe‡	Drug-related
Overall	3473 (59.2%)	2165 (36.9%)	1053 (18.0%)	255 (4.3%)	1397 (23.8%)
Nasopharyngitis	438 (7.5%)	364 (6.2%)	64 (1.1%)	10 (0.2%)	3 (0.1%)
Hypertension	377 (6.4%)	287 (4.9%)	86 (1.5%)	4 (0.1%)	234 (4.0%)
Blood glucose increased	275 (4.7%)	271 (4.6%)	3 (0.1%)	1 (< 0.1%)	17 (0.3%)
Headache	214 (3.7%)	139 (2.4%)	62 (1.1%)	13 (0.2%)	109 (1.9%)
UTI	199 (3.4%)	133 (2.3%)	63 (1.1%)	3 (0.1%)	25 (0.4%)
GGT increased	175 (3.0%)	150 (2.6%)	22 (0.4%)	3 (0.1%)	77 (1.3%)
Urinary sediment abnormal	175 (3.0%)	175 (3.0%)	0	0	11 (0.2%)

Many of these reflect intercurrent illnesses present in any population studied for a prolonged period. When compared with the incidence of the same AEs in the placebo population there was no substantial difference between active treatment and placebo. The overall incidence of each AE was similar with active treatment and placebo, as was the distribution amongst the mild, moderate and severe categories.

Treatment related adverse events

The incidence of serious AEs (SAEs) in the global 12-week Phase II/III population is shown in Table 9 above. There was no notable overall difference between the incidence of SAEs in

the placebo group (1.8%) versus the pooled mirabegron group (1.7%). Considering the subgroup of SAEs that were considered potentially 'drug-related', the incidence was similar across the placebo group (0.4%), the pooled mirabegron group (0.4%) and the individual dose groups (0.5%, 0.4%, 0.4% and 0% across the 25 mg, 50 mg, 100 mg and 200 mg dose groups, respectively).

The individual SAEs reported by two or more patients in the pooled mirabegron group of the 12-week Phase II/III population are summarised in Table 11. There was no overall pattern in the distribution of SAEs.

Table 11. SAEs (reported by ≥ 2 patients in the total mirabegron group), global OAB 12-Week Phase II/III Population

MedDRA v12.1 SOC PT†, n (%) of Patients	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Mirabegron Total Mirabegron (n = 4414)	Tolt ER 4 mg (n = 958)
Overall	38 (1.8%)	11 (1.4%)	34 (1.6%)	29 (2.2%)	3 (1.8%)	77 (1.7%)	16 (1.7%)
Cardiac disorders	6 (0.3%)	1 (0.1%)	5 (0.2%)	4 (0.3%)	0	10 (0.2%)	1 (0.1%)
Atrial fibrillation	1 (< 0.1%)	0	3 (0.1%)	2 (0.2%)	0	5 (0.1%)	0
Cardiac failure	0	1 (0.1%)	0	1 (0.1%)	0	2 (< 0.1%)	0
General disorders and administration site conditions	3 (0.1%)	1 (0.1%)	0	3 (0.2%)	0	4 (0.1%)	0
Chest pain	2 (0.1%)	1 (0.1%)	0	3 (0.2%)	0	4 (0.1%)	0
Infections and infestations	6 (0.3%)	2 (0.2%)	9 (0.4%)	3 (0.2%)	2 (1.2%)	16 (0.4%)	2 (0.2%)
Pneumonia	1 (< 0.1%)	0	2 (0.1%)	0	2 (1.2%)	4 (0.1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.1%)	1 (0.1%)	4 (0.2%)	3 (0.2%)	0	8 (0.2%)	1 (0.1%)
Prostate cancer	0	0	2 (0.1%)	0	0	2 (< 0.1%)	0
Surgical and medical procedures	3 (0.1%)	0	2 (0.1%)	2 (0.2%)	0	4 (0.1%)	1 (0.1%)
Bunion operation	0	0	0	2 (0.2%)	0	2 (< 0.1%)	0

Safety issues with the potential for major regulatory impact

· Liver toxicity

There is no evidence in the current submission that mirabegron produces significant liver toxicity.

· Haematological toxicity

Mirabegron was associated with a minor reduction in mean leukocyte counts, but there was no evidence of clinically significant haematological toxicity.

· Serious skin reactions and unwanted immunological events

Considering all AEs grouped under "Skin and subcutaneous tissue disorders", there was a slight increase in skin reactions in the active groups compared to placebo, and this increased with increasing doses. The incidence of skin-related AEs leading to discontinuation in the 12-week phase 2/3 population was for each treatment group: placebo 0.1%, mirabegron 25 mg 0.2%, mirabegron 50 mg 0.4%, mirabegron 100 mg 0.6%, mirabegron 200 mg 1.2%, total mirabegron 0.5% and tolterodine 0.2%.

Over the whole clinical program, two events were suggestive of moderate skin reactions, reported as Stevens-Johnson syndrome and leukocytoclastic vasculitis (see Attachment 2 of this AusPAR for details).

Overall, there appears to be a risk of serious skin reactions and hypersensitivity in some susceptible individuals, but the incidence is low, and patients recovered when study drug was ceased.

· Cardiovascular safety

Treatment with mirabegron was associated with mild changes in mean pulse rate and blood pressure. Despite this, mirabegron treatment was not associated with an increased risk of clinically significant hypertension, as reflected in the incidence of 'hypertension' AEs in the 12-week Phase II/III population, which was similar in the placebo and mirabegron groups.

The sponsor submitted a specific assessment of the cardiovascular risk of mirabegron which included a detailed review of all cardiovascular events. Hypertensive events identified in that report do not suggest a clinically significant impact on the risk of hypertension.

Postural hypotension and falls also occurred with a similar incidence in the mirabegron and placebo groups.

In the 12-week Phase II/III population, SAEs listed under 'Cardiac disorders' occurred with similar incidence in the pooled mirabegron (0.2%) and placebo (0.3%) groups.

The sponsor performed two QT studies, which suggested that mirabegron may mildly prolong the QT interval, especially at higher doses and in women, who experience greater exposure than men for the same dose.

Despite the mildly concerning results in the QT studies, clinically relevant arrhythmias were not observed at a higher frequency with mirabegron.

In the long-term Europe, North America and Australia (EU/NA) population, there was no placebo comparator, but the incidence of arrhythmias with mirabegron compared favourably with the incidence of arrhythmias observed with tolterodine treatment.

Overall, mirabegron appears to pose a minimal cardiovascular risk. Given the results of the QT studies, which showed mild QT prolongation at supra-therapeutic doses, mirabegron should be avoided in patients with long QT syndrome, and in combinations involving other QT-prolonging drugs.

Evaluator's overall conclusions on clinical safety

The safety and tolerability of mirabegron was acceptable in the pooled Phase II/III population, with an incidence of adverse events only slightly in excess of placebo, as summarised in Table 9 above. The distribution of individual AE types, including cardiovascular and urological AEs, did not raise specific concerns.

Potential safety issues with mirabegron arise from the mild QT-prolonging effect observed at the supratherapeutic dose of 200 mg, a low incidence of skin reactions, and the possibility of drug interactions. Although mirabegron does not require dose adjustment when combined with other drugs, it may modify the pharmacokinetics of drugs metabolised CYP2D6, increasing their levels, which could be relevant for drugs with narrow therapeutic indices. Mirabegron also increases exposure to digoxin when the two are co-administered, so digoxin should be introduced at a low dose and titrated according to blood levels.

The systemic beta agonist effects of mirabegron are minimal, but minor increases in pulse rate and blood pressure have been observed. The incidence of clinically relevant hypertension was not increased with mirabegron. Falls, syncope and hypotension did not occur with increased incidence in mirabegron recipients.

The proposed PI contains appropriate warnings about these few safety issues.

Exposure to mirabegron is increased (approximately doubled) in the setting of severe renal impairment. The PI therefore recommends halving the dose to 25 mg once daily in patients with severe renal impairment, but no adjustment in patients with mild to moderate renal impairment. Given that the proposed dose (50 mg) is half the maximum dose tested in the pivotal studies (100 mg), patients with severe renal impairment would experience an exposure that has been shown to have an acceptable safety profile. Similarly, a reduction of the dose to 25 mg once daily in patients with moderate hepatic impairment is recommended in the PI, and would be expected to produce an exposure similar to that experienced by normal subjects receiving a standard dose.

Mirabegron has not been studied at all in patients with severe hepatic impairment (Child-Pugh Class C[31]) or in patients with End-Stage Renal Failure (ESRF). The proposed PI includes appropriate warnings against use in these two populations, under *Precautions.*

First round benefit-risk assessment

First round assessment of benefits

The benefits of mirabegron in the proposed usage are:

- A slightly lower micturition frequency (one less void every two days)
- A slightly lower rate of incontinence (approximately 0.4 episodes prevented per day)
- Marginally improved quality of life

First round assessment of risks

The risks of mirabegron in the proposed usage are:

- A slight risk of QT prolongation in the event of accidental supratherapeuic exposure
- A slight risk of hypersensitivity reactions that would be expected to resolve with discontinuation
- Minor increases in blood pressure in susceptible subjects

First round assessment of benefit-risk balance

The benefit-risk balance of mirabegron, given the proposed usage, is favourable. It is expected that many patients will find the efficacy of mirabegron unacceptably low, but those who fail to show an adequate response could discontinue the drug, and a therapeutic trial of mirabegron is likely to be a worthwhile exercise in patients distressed by OAB symptoms.

First round recommendation regarding authorisation

Mirabegron should be approved for use in patients with overactive bladder.

[31] The Child-Pugh score is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement. Chronic liver disease is classified into Child-Pugh class A to C based on the total score.

Clinical questions

Efficacy

The sponsor was asked to confirm that Study 074 produced identical placebo-subtracted differences and 95% confidence intervals (CIs; -0.42; 95%CI -0.76 to -0.08) for the two co-primary endpoints in the 50 mg group.

Second round evaluation of clinical data submitted in response to questions

The sponsor confirmed that the results are correct.

Second round benefit-risk assessment

Assessment remains unchanged from that in the First round assessment, above.

Second round recommendation regarding authorisation

It is recommended that mirabegron should be approved for use in patients with overactive bladder.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (AU-RMP Version: 1.0, dated August 2012, comprising the EU-RMP Version: 1.0, dated 4 August 2011, with an Australian Specific Annex (ASA)) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the non-clinical aspects of the Safety Specification (SS) by the Toxicology area of the Office of Scientific Evaluation (OSE) and the clinical aspects of the SS by the Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (Table 12.):

Table 12. Summary of the Ongoing Safety Concerns

Important *identified* risks	None
Important *potential* risk	QT prolongation; Increased heart rate; Increased blood pressure; Nonimmediate cutaneous hypersensitivity reactions; Exposure in utero.
Important *missing* information	End-stage renal disease Severe hepatic impairment Pediatric use

Pharmacovigilance plan

Proposed pharmacovigilance activities

The sponsor states that routine pharmacovigilance activities, consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03),* are proposed to monitor all the specified ongoing safety concerns. This includes the use of Targeted Data questionnaires for all the specified important potential risks.

The evaluator noted that the FDA approval letter for mirabegron (trade name Myrbetriq) in the US included the following:

> *We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of serious risk related to: 1) observed increases in mean systolic and diastolic blood pressure and 2) increased reporting of new malignant events in the long-term clinical trial of Myrbetriq (mirabegron) at the 100 mg dose.*
>
> *Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.*
>
> *Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:*

- *A long-term observational study using electronic healthcare databases with appropriate linkages conducted in United States and European databases to evaluate the incidence of serious cardiovascular outcomes (both individual and composite outcomes) in patients administered Myrbetriq (mirabegron).*
- *A long-term observational study in electronic healthcare databases with appropriate linkages to prospectively evaluate the incidence of new malignant events (excluding non-melanoma skin cancer) in patients using Myrbetriq (mirabegron).*

Long-term observational studies to evaluate, respectively, serious cardiovascular outcomes and the incidence of new malignant events, as required by the US FDA as post-marketing commitments, are not included in the pharmacovigilance plan (PP) for mirabegron in Australia.

Risk minimisation activities

The ASA states: *"As outlined in the EU-RMP, no additional risk minimisation activities outside of routine pharmacovigilance will be implemented an in Australia."* Therefore it would appear the sponsor considers that additional risk minimisation is not required, as all safety concerns are adequately addressed by routine risk minimisation.

Routine risk minimisation activities will comprise labelling, including pharmacodynamic effects, contraindications, special warning and precaution statements, instructions for use and/or notification of undesirable effects for all the specified ongoing safety concerns.

Table 13 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 13. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the TGA consolidated request for information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these include a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The sponsor has updated the ASA to correspond with the revised EU-RMP during the process for approval and provides an assurance it will revise the documents if any safety issues occur.	This is acceptable.
2. The sponsor was asked to consider including the important missing information: 'Long-term safety data' as an ongoing safety concern or provide compelling justification as to why such amendment should not be required. This recommendation was based upon the availability of clinical data of only 12 months duration and is consistent with the US FDA concerns about increased reporting of new malignant events in the *"long-term"* (one year) clinical trial of Myrbetriq (mirabegron) at the 100 mg dose.	The sponsor has provided justification to not adopt this approach and instead is planning to conduct a long term observational study in electronic healthcare databases to prospectively evaluate the incidence of new malignant events (excluding non-melanoma skin cancer) in patients using mirabegron in accordance with a United States FDA post-marketing requirement.	The sponsor should provide an assurance that updates on the progress/results/analysis of this study will be included in future periodic safety update reports (PSURs).
3. For completeness the sponsor should consider including the important missing information: 'Use in pregnant and lactating women' as an ongoing safety concern. Consequently the relevant sections of the RMP and/or the ASA will need to be amended accordingly when these documents are next updated.	The sponsor has advised that information about "Use in pregnant and lactating women," is incorporated as the important potential risk: 'Embryo-fetal toxicity' in EU-RMP Ver. 1.5 and has also been added to the ASA version 1.1.	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
4. The sponsor should provide an assurance that the final Targeted Data questionnaires for all the specified important potential risks will be submitted to the TGA when they become available. Consequently these should be included in the RMP and/or the ASA when these documents are next updated.	The sponsor has now provided copies of the Targeted Data questionnaires for the important identified risks: 'Increased heart rate and tachycardia' & 'Hypersensitivity reactions'; the important potential risks: 'QT prolongation', 'Increased blood pressure' & 'Embryo-fetal toxicity'; and the important missing information: 'Decreased lymphocytes' according to the update of the EU-RMP.	This is acceptable.
5. The sponsor should provide compelling justification as to why the long-term observational studies required by the US FDA as post-marketing commitments have not been included in the PP. Alternatively, if the sponsor decides to include these studies within the PP, the relevant sections of the RMP and/or the ASA will need to be updated accordingly and at least draft protocols for these studies should be submitted to the TGA for review.	The sponsor has now added a planned post-authorisation safety study (PASS) to address cardiovascular safety, especially in elderly patients, in the PP of the updated AU-RMP and EU-RMP.	This is acceptable, although it is suggested Sections of the EU-RMP be reworked to provide the required information in relation to the planned PASS, particularly in regard to reporting milestones, when this document is next updated.
6. The ASA refers to routine pharmacovigilance activities rather than routine risk minimisation activities. Nevertheless the sponsor's conclusion that no additional risk minimisation activities are needed is consistent with assessment of the US FDA and it is agreed the specified ongoing safety concerns would not appear to warrant additional risk minimisation activities.	The sponsor has now changed the wording in Section 3 of the ASA.	This is acceptable.
7. The sponsor's proposed application of routine risk minimisation activities would appear to be reasonable	The sponsor notes this comment.	N/A

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
and therefore acceptable.		
8. In regard to the proposed routine risk minimisation activities, the draft PI document is considered satisfactory.	The sponsor notes this comment.	N/A
9. In regard to the proposed routine risk minimisation activities, the draft Consumer Medicine Information (CMI) document is considered satisfactory.	The sponsor notes this comment.	N/A

Second round review

Advisory committee considerations

The submission was considered by the Advisory Committee on the Safety of Medicines (ACSOM) in March 2013.

The ACSOM considered the then current draft protocols of the proposed long term observation neoplasm study (178-CL-113) and cardiovascular study (178-CL-114) and concluded they were unlikely to adequately evaluate the incidence of serious cardiovascular outcomes (both individual and composite outcomes) and the incidence of new malignant events (excluding non-melanoma skin cancer) respectively. The sponsor later provided updated draft protocols for these studies. Nevertheless the sponsor would be requested to address the ACSOM advice regarding deficiencies of the proposed study designs.

The ACSOM expressed concern about mirabegron causing weight loss and that this could potentially encourage off-label use. The committee advised that consideration be given to obtaining clinical data regarding weight loss from the sponsor and if it is found to be of clinical significance, this information should be added to the RMP. This matter was raised with the Delegate for consideration.

The ACSOM was also concerned that the RMP had not included the increased risk of lower urinary tract symptoms (LUTS), including urinary retention, as an ongoing safety concern. The committee noted that relaxation of the smooth muscle in the bladder would not necessarily overcome the narrowing of the urethra and for some people this could lead to a worsening of the symptoms despite the theoretical data given on the specificity of the drug. The committee advised that consideration be given to this in the RMP. It is noted that the sponsor has now included the important potential risk: 'Urinary tract infection' as an ongoing safety concern, although in its current form would not appear to cover the specific concerns of the committee. Consequently it is recommended that the sponsor should include the important potential risk: 'Lower urinary tract symptoms (LUTS), including urinary retention' as an ongoing safety concern or provide compelling justification as to why such amendment should not be required. If the sponsor decides to include this important potential risk within the RMP and/or ASA, consideration must be given as to what routine and additional pharmacovigilance and risk minimisation activities will be proposed for this new ongoing safety concern.

The ACSOM would further review this RMP, including the sponsor's to the committee's advice, at its meeting in July 2013.

Sponsor response to OPR recommendations

It is considered that the sponsor's responses have adequately addressed all of the issues identified in the RMP evaluation report, except as noted in Table 13 against recommendations 2 and 5, which will be drawn to the attention of the sponsor.

In their response the sponsor provided an updated AU-RMP (Version: 1.1, dated 18 March 2013).

OPR evaluator's recommendation

If this application is approved, the registration conditions should include the following:

- The Australian Risk Management Plan Version: 1.1 dated 18 March 2013, to be revised as specified in the sponsor's correspondence dated 27 March 2013, must be implemented.
- Requirements regarding the provisions of PSURs.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Mirabegron is a first-in-class β3-adrenergic agonist proposed for the following indication:

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

The proposed treatment is oral, once daily at 25 mg or 50 mg.

The spproved indications in the US and EU are as follows:

- USA: for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency
- EU: Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence, as may occur in patients with overactive bladder (OAB) syndrome.

Quality

The pharmaceutical chemistry evaluator has no objections to the registration of mirabegron 25 mg and 50 mg prolonged release tablets.

The prolonged-release formulation was developed to overcome the considerable decrease in plasma exposure with food and high peak to trough plasma concentrations with once daily dosing that were observed with a preliminary immediate release formulation used in initial clinical trials.

The proposed commercial formulation is identical to the formulation used in the pivotal Phase III efficacy studies (and the majority of the clinical pharmacology studies).

After oral administration of 25 mg to 100 mg mirabegron, a greater than dose proportional increase in C_{max} and $AUC_{0-\infty}$ was observed. As the PK of mirabegron were essentially linear after IV administration, the lack of dose proportionality with the oral formulation is considered to arise from factors associated with absorption.

Prescribing information in US and Europe (where it is registered) state that it can be taken with or without food, even though administration with food reduced C_{max} and AUC (high-fat meal: 45% and 17% respectively, low-fat meal: 75% and 51%). The reason provided was that in the pivotal Phase III studies, mirabegron was administered with and without food and demonstrated adequate safety and efficacy.

Nevertheless, the PSC recommended that, with regard to the proposed PI the reference to taking the recommended dose with or without food under the *Absorption* and *Dosage and Administration* sections should be amended to reflect the fact that it is preferable to take the recommended dose 1 h before food or 2 h after a meal.

Nonclinical

The nonclinical evaluator had no objections to the registration of mirabegron for the proposed indication at a maximum daily dose of 50 mg.

The sponsor submitted a comprehensive set of toxicity studies, which were conducted in accordance with ICH guidelines and in compliance with GLP.

Mirabegron is not considered to be genotoxic based on the results of a bacterial reverse mutation assay, a human peripheral blood lymphocyte chromosome aberration assay, and a rat bone marrow micronucleus test.

The results of two year carcinogenicity assays in rats and mice did not indicate carcinogenic potential.

Mirabegron did not adversely affect fertility in male and female rats. There was no embryofetal toxicity evident in rats whose dams were exposed to mirabegron levels less than or equal to six times the human therapeutic exposure level.

Adverse fetal toxicity in rabbits, including fetal death, dilated aorta and cardiomegaly, was seen only at systemic exposure levels 36 times higher than the clinical exposure levels.

The sponsor has proposed Pregnancy Category B3, which is acceptable based on the adverse effects seen in the embryofetal toxicity studies.

Mirabegron increased heart rate in rats, rabbits, dogs and monkeys, which at high doses resulted in fatal ventricular tachycardia (exposure levels 29 and 37 times the clinical plasma C_{max}). In all species (including humans) tachycardia appears to result from stimulation of β1-adrenoceptors by mirabegron, which contrasts with the apparent selectivity for β3-adrenoceptors over β1- and β2-adrenoceptors observed with cloned receptors *in vitro*. Mirabegron and its metabolites did not show any potential for QT prolongation.

Clinical

The clinical evaluator reviewed the submitted data, which included:

- 29 clinical pharmacology studies,
- 3 Phase II OAB studies
- 6 Phase III OAB studies, three of which are considered pivotal.
- 2 Phase II studies for other indications (diabetes and bladder outlet obstruction) contributed safety data.

The clinical evaluator recommended that mirabegron should be approved for use in patients with OAB. The clinical evaluator expected that many patients will find the efficacy of mirabegron unacceptably low, but those who fail to show an adequate response could discontinue the drug, and a therapeutic trial of mirabegron is likely to be a worthwhile exercise in patients distressed by OAB symptoms.

Pharmacology

Mirabegron was developed as a selective agonist for human β3-adrenoceptors, which are located mainly in adipose tissue. However, several studies have also confirmed the existence and functional role of β3-adrenoceptors in the bladder relaxation.

The Phase I program consisted of 29 clinical studies that included: 6 biopharmaceutic (bioavailability, food effect and *in vitro-in vivo* correlations studies) studies and 23 human PK studies (18 studies that evaluated the extended release formulation and 5 studies that evaluated an oral solution or immediate release tablet). The five initial clinical studies used the immediate release formulation and the rest used the to-be-marketed formulation (extended/prolonged release; OCAS). The terminal elimination half-life of mirabegron is approximately 50 h, t_{max} was reached in approximately 3.5 h.

Pharmacodynamics

The sponsor did not submit any primary PD studies directly assessing bladder physiology in response to mirabegron.

A study of cardiovascular response to mirabegron in the presence or absence of beta blockers confirmed that mirabegron exerts a minor cardiovascular effect that is partially blocked by β1-selective and non-selective beta antagonists. This result is consistent with a low degree of β1 agonist activity, and shows that selectivity for the β3-adrenoceptors is only relative. The clinical evaluator stated that "the clinical consequences of the minor β1 agonism are minimal".

The sponsor submitted PD population modelling, based on a Phase IIb dose finding study (178-CL-044) and the three pivotal Phase III trials. The clinical evaluator noted that this modelling attempted to create a dose response curve, despite very noisy underlying data. Such modelling does not provide new evidence to inform dosing, beyond that available from direct assessment of the dose ranging and Phase III studies, because it inevitably imports a range of assumptions into the model.

The sponsor submitted two QT studies (178-CL-037 and 178-CL-077). Study 037 enrolled 48 healthy adults (25 men and 23 women). The sponsor summarised the results as follows: "In the overall population of males and females, administration of 100 mg or 200 mg mirabegron did not result in an effect on the QTc interval to a duration equal to or greater than the regulatory threshold of concern (that is, the upper bound of the 95% 1-sided confidence interval (CI) for the largest time-matched mean effect of the drug on the QTc interval excluded 10 msec). A post hoc exploratory subgroup analysis by sex indicated a possible effect of mirabegron at doses of 100 and 200 mg on QTc in females." Study 077 enrolled 352 healthy adults (176 men and 176 women). It confirmed that a single supratherapeutic dose of mirabegron (200 mg) causes mild QT prolongation, which potentially exceeds the 10 msec threshold (upper limit of one-sided 95% CI) in women, who have higher exposure than men. No problems were apparent for the 50 mg dose (proposed for marketing).

Pharmacokinetics

Mirabegron exhibits a decrease in plasma exposure with food. The sponsor proposes that the mechanism behind the food effect is likely to be a combination of adsorption to meal constituents and competition for drug uptake and efflux from meal constituents. The clinical evaluator noted that although the food effect is substantial, the safety and efficacy of the proposed 25 mg and 50 mg doses were assessed in the pivotal, Phase III studies without food restrictions; subjects took mirabegron variably with and without food. The clinical evaluator suggested that problems related to variability in exposure from the food effect have already been accounted for in considering the efficacy and safety of mirabegron in those studies.

There was no significant difference in mirabegron exposure in relation to age (18-55 years versus 65-80 years). Therefore, no dose adjustment for elderly patients (65 and older) is required.

The exposure was approximately 40-50% higher in females compared to males, but when corrected for body weight, the difference between genders is only approximately 20-30%. Phase III studies were conducted in men and in women, with no evidence of different safety between the genders.

The PK of mirabegron in volunteers with hepatic impairment were compared to those in healthy control volunteers matched for sex, age and body mass index (BMI) in Study 178-CL-039. Following mirabegron 100 mg in volunteers with *mild* hepatic impairment (Child-Pugh Class A), mean C_{max} and AUC_{inf} were 9% and 19% higher, respectively, relative to

healthy volunteers. In volunteers with moderate hepatic impairment (Child-Pugh Class B), mean C_{max} and AUC_{inf} values were 175% and 65% higher, respectively. A reduction of the dose to 25 mg once daily in patients with moderate hepatic impairment is therefore recommended.

The magnitude of the increases in exposure with mild hepatic impairment are unlikely to be clinically relevant and are small compared to intersubject variability with healthy volunteers, so no dose adjustment is recommended.

Mirabegron has not been studied at all in patients with severe hepatic impairment (Child-Pugh Class C) and should not be used in this patient population, even at a reduced dose. The proposed PI contains appropriate warnings against use in this population.

In Study 178-CL-038, the PK of mirabegron in volunteers with renal impairment were compared to the PK in healthy volunteers matched for sex, age and weight.

Following mirabegron 100 mg, in volunteers with mild renal impairment (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m^2), mean mirabegron C_{max} and AUC_{inf} were 6% and 31% higher, respectively, 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_{inf} were 23% and 66% higher, respectively. In volunteers with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2), mean C_{max} and AUC_{inf} values were 92% and 118% higher, respectively.

On the basis of these results, the sponsor's proposed PI recommends a halving of the dose to 25 mg once daily in patients with severe renal impairment, but no adjustment in patients with mild to moderate renal impairment. The clinical evaluator stated that this appears reasonable, given that doses up to 100 mg were assessed in pivotal Phase III studies and had an acceptable safety profile.

Mirabegron has not been studied in patients with End Stage Renal Disease (eGFR < 15 mL/min/1.73 m^2 or patients requiring hemodialysis) and should not be used in this patient population. The PI appropriately warns against such use.

The inhibitory effects of mirabegron on CYP2D6 are sufficient to recommend caution when combining mirabegron with other CYP2D6 substrates if these substrates have a narrow therapeutic index. Multiple daily dosing with mirabegron 160 mg (immediate release (IR) formulation) resulted in a 90% increase in C_{max} and a 229% increase in AUC_{inf} of a single 100 mg dose of the CYP2D6 substrate metoprolol. Similarly, multiple daily dosing with mirabegron 100 mg resulted in a 79% increase in C_{max} and a 241% increase in AUC_{inf} of a single 50 mg dose of the CYP2D6 substrate desipramine.

Justification of dose selection for the Phase III studies

Dosage selection for the pivotal studies was largely based on the Phase IIb study (178-CL-044). It was a multinational, multicentre, double-blind, randomised, parallel group, placebo- and tolterodine-controlled study with six treatment groups. Like the three pivotal Phase III studies, it employed a single-blind, 2-week placebo run-in period followed by a randomised, double-blind, placebo-controlled, 12-week treatment period.

There was a dose trend across the range 25 mg to 200 mg, suggesting that 200 mg might be more effective than lower doses, but mild QT prolongation has been observed at this dose. The results in the 25 mg group were not statistically significantly different from placebo, but the sample size was relatively small. The placebo subtracted difference in mean number of micturitions per day was 0.45. The proposed dose of 50 mg showed a statistically significant treatment effect (0.64 micturitions), as did 100 mg, but the difference between 50 mg and 100 mg was minor. The statistical significance of the difference between a reduction of 0.45 micturitions (25 mg) and 0.64 micturitions (50 mg) was not directly assessed.

The sponsor chose 50 mg and 100 mg for further evaluation, and assessed both of these doses in two pivotal studies (Study 046 and Study 047). The FDA suggested another assessment of the 25 mg dose, so the third pivotal Phase III study (Study 074) assessed 25 mg as well as 50 mg (see *Efficacy* subsection below).

Note that study 045 (Phase IIb) was also a dose ranging study. Entry criteria were similar to the three pivotal Phase III studies, except that patients had to have some urgency incontinence. Patients were randomised to placebo (n=211), mirabegron 25 mg (n=209), mirabegron 50 mg (n=208), and mirabegron 100 mg (n=207). Statistically significant effects for the primary outcome (number of micturitions per day) were obtained for all three doses of mirabegron with similar placebo-subtracted treatment effects (25 mg: -0.66, 50 mg: -0.74, 100 mg: -0.78).

Efficacy

The pivotal analysis set comprised efficacy data from three Phase III trials (178-CL-046, 178-CL-047 and 178-CL-074). Across the three trials, three doses of mirabegron (25 mg, 50 mg, 100 mg) were evaluated: only one trial evaluated the 25 mg dose, all three trials evaluated the 50 mg dose, and two trials evaluated the 100 mg dose. One trial included a tolterodine arm (in addition to a placebo arm); but both mirabegron and tolterodine were compared to placebo, and were not directly compared to each other. The dose of tolterodine was 4 mg, which is the recommended dose.

The sponsor requested consideration of only two doses of mirabegron in the application, so the efficacy evaluation focussed on these two doses: 25 mg and 50 mg.

The design of the three trials was the same: a 2-week run-in period, followed by a 12-week, double-blind treatment period.

Inclusion/exclusion criteria

The main criterion for inclusion was OAB (for 3 or more months) with 8 micturitions per day and at least one episode of Grade 3 or 4 urgency per day (on average) during the 3 day screening diary. Incontinence was not necessary for inclusion in the study. This is consistent with the current definition of OAB and meant that patients with fairly mild OAB were eligible. It also meant that the studies were not well designed for demonstrating improvements in continence. In evaluating the safety of mirabegron, it is important to note that patients thought to be at high risk of urinary retention, or hypertension, were excluded.

The mean age of study participants was 60 years; about three-quarters were women, reflecting the higher prevalence among women. The mean duration of OAB symptoms was 6-7 years, about 40% had urgency incontinence, 5% had surgery for OAB and 50% had used an antimuscarinic (70% of these discontinued because of insufficient effect and 25% because of poor tolerability).

Outcomes measured/endpoints

Co-primary efficacy outcomes:

- Change from baseline to end of treatment (12 weeks) in mean number of micturitions per 24 h, based on a 3-day micturition diary
- Change from baseline to end of treatment (12 weeks) in mean number of incontinence episodes per 24 h, based on a 3-day micturition diary

Key Secondary efficacy outcomes:

- Change from baseline in volume voided per micturition (note: this is correlated with the primary outcome of mean number of micturitions)

· Change from baseline at 4 weeks for the two co-primary efficacy outcomes

The EMA Guidance on *Clinical Investigation of Medicinal Products for the Treatment of Urinary Incontinence* recommends the use of a subjective measure (such as satisfaction with treatment) as the primary outcome in Phase III trials. In the three pivotal Phase III trials for mirabegron (summarised in Table 14), subjective outcomes were non-key secondary outcomes.

Table 14. Pivotal Phase III trials

Trial #	Objective	Design and control type	Test products, dose regimen and administration route	Subject numbers and type	Duration of Treatment
178-CL-046 in Europe and Australia	Efficacy and safety of mirabegron compared to placebo and tolterodine SR	Phase 3, randomized, double-blind, placebo-controlled and active controlled	Treatment groups: placebo, mirabegron 50 or 100 mg, or tolterodine SR 4 mg, or matching placebo po; once daily with or without food	1987 Adults with OAB	2-week run-in followed by 12-week double blind treatment period
178-CL-047 in Canada, United States	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo-controlled	Treatment groups: placebo, mirabegron 50 or 100 mg or matching placebo po; once daily with or without food	1329 Adults with OAB	2-week placebo run-in followed by 12-week double blind treatment period
178-CL-074 in Canada, Europe and United States	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo-controlled	Treatment groups: placebo, mirabegron 25 or 50 mg or matching placebo po; once daily with or without food	1306 Adults with OAB	2-week placebo run-in followed by 12-week double blind treatment period

Minimal clinically important difference used for sample size calculation

In each of the three trials, sample size was based on a minimal clinically important difference for a placebo-subtracted reduction in mean micturitions per 24 h of 0.7. Sample size for the other co-primary outcome of number of incontinence episodes, was based on Wilcoxon sum-rank test and no minimal clinically important difference was reported.

Results

The main efficacy results are shown in Tables 15, 16 and 17.

Table 15. Pooled results for co-primary and selected secondary efficacy endpoints at 12 weeks for mirabegron 50 mg and from study 046 for mirabegron 50 mg and tolterodine (extended release (ER)) 4 mg

Parameter	Pooled Studies (046, 047, 074)		Study 046		
	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg
Mean Number of Incontinence Episodes per 24 Hours (FAS-I) (Co-Primary)					
n	878	862	291	293	300
Mean baseline	2.73	2.71	2.67	2.83	2.63
Mean change from baseline†	-1.10	-1.49	-1.17	-1.57	-1.27
Mean difference from placebo†	--	-0.40	--	-0.41	-0.10
95% Confidence Interval	--	(-0.58, -0.21)	--	(-0.72, -0.09)	(-0.42, 0.21)
p-value	--	<0.001#	--	0.003#	0.11
Mean Number of Micturitions per 24 Hours (FAS) (Co-Primary)					
n	1328	1324	480	473	475
Mean baseline	11.58	11.70	11.71	11.65	11.55
Mean change from baseline†	-1.20	-1.75	-1.34	-1.93	-1.59
Mean difference from placebo†	--	-0.55	--	-0.60	-0.25
95% Confidence Interval	--	(-0.75, -0.36)	--	(-0.90, -0.29)	(-0.55, 0.06)
p-value	--	<0.001#	--	0.001#	0.11

Parameter	Pooled Studies (046, 047, 074)		Study 046		
	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg
Mean Volume Voided (mL) per Micturition (FAS) (Secondary)					
n	1328	1322	480	472	475
Mean baseline	159.2	159.0	156.7	161.1	158.6
Mean change from baseline†	9.4	21.4	12.3	24.2	25.0
Mean difference from placebo†	--	11.9	--	11.9	12.6
95% Confidence Interval	--	(8.3, 15.5)	--	(6.3, 17.4)	(7.1, 18.2)
p-value	--	<0.001#	--	<0.001#	<0.001*
Mean Level of Urgency (FAS) (Secondary)					
n	1325	1323	480	472	473
Mean baseline	2.39	2.42	2.37	2.40	2.41
Mean change from baseline†	-0.15	-0.26	-0.22	-0.31	-0.29
Mean difference from placebo†	--	-0.11	--	-0.09	-0.07
95% Confidence Interval	--	(-0.16, -0.07)	--	(-0.17, -0.02)	(-0.15, 0.01)
p-value	--	<0.001#	--	0.018*	0.085

Parameter	Pooled Studies (046, 047, 074)		Study 046		
	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg
Mean Number of Urgency Incontinence Episodes per 24 Hours (FAS-I) (Secondary)					
n	858	834	283	286	289
Mean baseline	2.42	2.42	2.43	2.52	2.37
Mean change from baseline†	-0.98	-1.38	-1.11	-1.46	-1.18
Mean difference from placebo†	--	-0.40	--	-0.35	-0.07
95% Confidence Interval	--	(-0.57, -0.23)	--	(-0.65, -0.05)	(-0.38, 0.23)
p-value	--	<0.001#	--	0.003*	0.26
Mean Number of Episodes with Urgency Grades 3 or 4 per 24 Hours (FAS) (Secondary)					
n	1324	1320	479	470	472
Mean baseline	5.61	5.80	5.78	5.72	5.79
Mean change from baseline†	-1.29	-1.93	-1.65	-2.25	-2.07
Mean difference from placebo†	--	-0.64	--	-0.60	-0.42
95% Confidence Interval	--	(-0.89, -0.39)	--	(-1.02, -0.18)	(-0.84, -0.00)
p-value	--	<0.001#	--	0.005*	0.050*

Parameter	Pooled Studies (046, 047, 074)		Study 046		
	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg
Treatment Satisfaction – Visual Analogue Scale (FAS) (Secondary)					
n	1195	1189	428	414	425
Mean baseline	4.87	4.82	4.11	3.95	3.87
Mean change from baseline†	1.18	1.96	1.89	2.55	2.44
Mean difference from placebo†	--	0.76	--	0.66	0.55
95% Confidence Interval	--	(0.52, 1.01)	--	(0.25, 1.07)	(0.14, 0.95)
p-value	--	<0.001*	--	0.001*	0.008*

Pooled studies consisted of studies 046 (EU / Australia), 047 (North America [NA]) and 074 (EU / NA).
† Least squares mean adjusted for baseline, gender, and geographical region.
* 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.

Table 16. Results for Coprimary and Key Secondary Endpoints, Study 074, which assessed Mirabegron 25 mg

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Coprimary Efficacy Endpoints †		Key Secondary Efficacy Endpoints †					
			Change from BL to FV in Mean Number of Incontinence Episodes per 24 Hours (FAS-I)	Change from BL to FV in Mean Number of Micturitions per 24 Hours (FAS)	Change from BL to FV in Mean Volume Voided (mL) per Micturition (FAS)	Change from BL to Week 4 in Mean Number of Incontinence Episodes per 24 Hours (FAS-I)	Change from BL to Week 4 in Mean Number of Micturitions per 24 Hours (FAS)	Change from BL to FV in Mean Level of Urgency (FAS)	Change from BL to FV in Mean Number of Urgency Incontinence Episodes per 24 Hours (FAS-I)	Change from BL to FV in Mean Number of Urgency Episodes (Grade 3 or 4) per 24 Hours (FAS)
178-CL-074 ‡ (CAPRICORN)	Placebo 433/367	n	262	415	415	262	415	413	256	413
		Baseline	2.43 (0.145)	11.48 (0.142)	164.0 (2.79)	2.43 (0.145)	11.48 (0.142)	2.36 (0.027)	2.24 (0.138)	5.42 (0.163)
		Change from Baseline	-0.96 (0.122) (-1.19, -0.72)	-1.18 (0.124) (-1.42, -0.94)	8.3 (2.23) (3.9, 12.7)	-0.62 (0.120) (-0.85, -0.38)	-0.78 (0.124) (-1.02, -0.53)	-0.15 (0.028) (-0.21, -0.10)	-0.95 (0.110) (-1.16, -0.73)	-1.35 (0.154) (-1.66, -1.05)
	Mirabegron OCAS 25 mg 433/387	n	254	410	410	254	410	410	247	410
		Baseline	2.65 (0.160)	11.68 (0.153)	165.2 (2.84)	2.65 (0.160)	11.68 (0.153)	2.37 (0.028)	2.45 (0.137)	5.57 (0.179)
		Change from Baseline	-1.36 (0.124) (-1.60, -1.11)	-1.65 (0.125) (-1.90, -1.41)	12.8 (2.24) (8.4, 17.2)	-0.96 (0.122) (-1.20, -0.72)	-0.96 (0.124) (-1.20, -0.71)	-0.22 (0.029) (-0.28, -0.17)	-1.31 (0.112) (-1.53, -1.09)	-1.68 (0.155) (-1.99, -1.38)
		Difference from Placebo	-0.40 (0.174)# (-0.74, -0.06)	-0.47 (0.176)# (-0.82, -0.13)	4.6 (3.16) (-1.6, 10.8)	-0.34 (0.172) (-0.68, -0.01)	-0.18 (0.176) (-0.53, 0.16)	-0.07 (0.040) (-0.15, 0.01)	-0.36 (0.157) (-0.67, -0.05)	-0.33 (0.219) (-0.76, 0.10)
	Mirabegron OCAS 50 mg 440/386	n	257	426	426	255	424	426	251	426
		Baseline	2.51 (0.146)	11.66 (0.156)	159.3 (2.53)	2.52(0.147)	11.67 (0.157)	2.41 (0.027)	2.33 (0.140)	5.80 (0.173)
		Change from Baseline	-1.38 (0.123) (-1.62, -1.14)	-1.60 (0.122) (-1.84, -1.36)	20.7 (2.20) (16.4, 25.0)	-1.13 (0.122) (-1.36, -0.89)	-1.14 (0.122) (-1.38, -0.90)	-0.29 (0.028) (-0.35, -0.24)	-1.33 (0.111) (-1.55, -1.12)	-1.94 (0.152) (-2.24, -1.64)
		Difference from Placebo	-0.42 (0.173)# (-0.76, -0.08)	-0.42 (0.174)# (-0.76, -0.08)	12.4 (3.13)# (6.3, 18.6)	-0.51 (0.171)# (-0.85, -0.17)	-0.37 (0.174) (-0.71, -0.03)	-0.14 (0.040) (-0.22, -0.06)	-0.39 (0.156) (-0.69, -0.08)	-0.59 (0.217) (-1.01, -0.16)

Table 17. Treatment satisfaction – Visual Analog Scale, Study 074

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Change from BL to FV in Treatment Satisfaction – Visual Analog Scale (FAS) †
178-CL-074 (CAPRICORN)	Placebo 433/367	n	377
		Baseline	5.13 (0.190)
		Adjusted Change from Baseline	1.05 (0.154) (0.75, 1.35)
	Mirabegron OCAS 25 mg 433/387	n	389
		Baseline	5.15 (0.185)
		Adjusted Change from Baseline	1.54 (0.152) (1.24, 1.84)
		Difference from Placebo	0.49 (0.216)* (0.07, 0.91)
	Mirabegron OCAS 50 mg 440/386	n	388
		Baseline	5.13 (0.188)
		Adjusted Change from Baseline	1.88 (0.152) (1.58, 2.18)
		Difference from Placebo	0.83 (0.216)* (0.41, 1.25)

† Least squares mean adjusted for baseline, gender, and geographical region.
* 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.

In the pooled analysis, the mean number of voluntary micturitions per 24 hours was 11-12 episodes at baseline and this reduced by a mean of 1.20 micturitions in the placebo group and 1.75 micturitions in the mirabegron 50 mg group, giving a placebo-subtracted treatment effect of 0.55 micturitions. This was statistically significant (with multiplicity adjustment), but is (arguably) of questionable clinical importance (the minimal clinically important difference used in sample size calculations was 0.7).

This is the mean or average improvement. Particular individual patients might achieve greater benefits (with other patients receiving no benefit at all). Similar comments apply to the number of incontinence episodes (the other co-primary endpoint; see Table 15).

The baseline Treatment Satisfaction Visual Analogue Scale (TS-VAS) was 4.8 in the placebo group and 4.9 in the mirabegron 50 mg group. It improved, over 12 weeks, by 1.18 in the placebo group and 1.96 in the mirabegron 50 mg group, giving a placebo-subtracted treatment effect of 0.76. This was statistically significant without multiplicity adjustment, but not with. A fully effective drug would potentially produce a rating of 10 (complete satisfaction with treatment), giving an overall improvement of 6 points, and a placebo-subtracted improvement of 4-5 points.

Results in the 50 mg and 100 mg groups were generally similar to each other, as were the results for tolterodine 4 mg. Superiority or non-inferiority of mirabegron 50 mg versus mirabegron 100 mg was not directly assessed; nor for mirabegron 50 mg versus tolterodine 4 mg.

The lower dose of 25 mg was only assessed in one pivotal study (074). It achieved statistical significance (with multiplicity adjustment) for the placebo-subtracted treatment effect for the two co-primary outcomes, with similar size of treatment effect as that for the 50 mg dose (Table 16). However, for the key secondary endpoints of change in number of incontinence episodes at 4 weeks (co-primary was at 12 weeks) and change in volume

voided at 12 weeks, the 25 mg dose did not achieve statistical significance; whereas the 50 mg dose achieved statistical significance with multiplicity adjustment (Table 17). The 25 mg dose also had a smaller effect on treatment satisfaction than the 50 mg dose (placebo-subtracted change: 0.49 versus 0.89; 10-point scale), although both were statistically significant (but only without the multiplicity adjustment). In general, the 50 mg dose achieved statistically significant results on more secondary endpoints than the 25 mg dose. Superiority or non-inferiority of mirabegron 25 mg versus mirabegron 50 mg was not directly assessed.

Methodological limitations of the three pivotal Phase III trials for efficacy

12-week studies might not provide a good indication of long-term efficacy.

Based on the one study (046) that included an active control arm (tolterodine extended release (ER) 4mg), the efficacy of mirabegron appeared to be similar to tolterodine 4 mg, but they were not directly compared (that is, each was compared separately to placebo). More specifically, the study was not designed (and not analysed) to assess the superiority or non-inferiority of mirabegron to tolterodine. This has implications for the PI and whether claims that mirabgeron has similar efficacy to tolterodine should be allowed.

The different doses of mirabegron were not directly compared (that is, each dose was compared separately to placebo).

It was not necessary for all study participants to have incontinence. Therefore, analysis of the co-primary outcome of incontinence episodes per 24 h (based on a 3-day diary) was performed in a subset of the FAS (FAS-I). If this analysis was performed on the full FAS, the overall treatment effect for incontinence would be reduced.

The TGA has adopted the EMA guidance on *Clinical Investigation of Medicinal Products for the Treatment of Urinary Incontinence*. This guidance states: *because OAB is not a life threatening condition, the patient's perception of improvement (or lack thereof) should be the main outcome in trials*. However, in each of the three pivotal Phase III trials, subjective (quality-of-life) measures were non-key secondary outcomes only.

Supportive studies for efficacy

In addition to the three pivotal phase 3 studies (Studies 046, 047 and 074), the sponsor performed a number of supportive studies, as follows:

- 1 supportive Phase III study (178-CL-048),
- 2 supportive Phase IIb studies (178-CL-045 and 178-CL-044),

These are discussed under *Justification of dose selection for the Phase III studies*

- 1 Phase IIa proof-of-concept study (178-CL-008),
- 1 Phase III active-controlled long-term safety study (178-CL-049), and
- 1 Phase III open label, long-term safety study (178-CL-051).

Study 048 was conducted in Japan. Patients were required to have one episode of urgency incontinence per day, so the study population corresponds roughly to the FAS-I population in the pivotal Phase III studies. Patients were randomised to placebo (n=350), mirabegron 50 mg (n=349) or tolterodine 4 mg (355). The primary outcome was micturition frequency. At baseline this was about 11 episodes per 24 h, which is similar to the three pivotal studies. Placebo treatment was associated with a mean reduction of 0.86 micturition episodes from a baseline of 11.29 episodes. Active treatment with mirabegron 50 mg was associated with a further reduction of 0.86 (placebo-subtracted), and this was statistically significant (95% CI for the difference from placebo, -1.16 to -0.57). Tolterodine, the active control, showed a somewhat less beneficial change, with a mean

placebo-subtracted change in micturition frequency of -0.61 episodes per 24 h (95% CI -0.90 to -0.32).

Study 008 was a small randomised, double-blind, parallel group, proof-of-concept study of the efficacy of mirabegron in comparison with placebo and tolterodine in patients with symptomatic OAB. It had only 63-65 subjects per dose group, and therefore lacked the statistical power of most of the other supportive studies. It was also very short. A 2-week single-blind placebo run-in period was followed by a 4-week double-blind treatment period, and then a 2-week single-blind placebo follow-up period. The doses employed (100 mg twice daily and 150 mg twice daily) were also higher than the recommended dose of 25 or 50 mg once daily. For all of these reasons, it is only weakly supportive of the proposed usage of mirabegron.

Study 049 was a long-term safety study with no placebo group, though it did employ tolterodine as an active control. The assessment of efficacy was a secondary focus, and the study was not powered or designed to show non-inferiority or superiority of mirabegron over tolterodine. Entry criteria were similar to the three pivotal Phase III studies. 1385 patients received mirabegron for at least 6 months, 1311 for at least 9 months, and 564 for 1 year. Mean number of micturitions for mirabegron 50 mg was reduced by 1.27 per day (95% CI: 1.11, 1.44) and for tolterodine by 1.36 (95% CI: 1.23, 1.56). This compares with 1.20 for the placebo group in the pooled analysis of the three pivotal Phase III trials (12 weeks duration) and 1.75 for mirabegron 50 mg. Without a placebo group, the efficacy results for the long-term safety study are difficult to interpret.

Study 051 was another long-term safety study in OAB patients. It assessed two doses of mirabegron (50 mg daily and 100 mg daily), but it did not randomise between the dose groups, and it had no control group of non-mirabegron recipients.

Safety

10,552 subjects were exposed to mirabegron in the clinical study program: this includes 1800 healthy volunteers and 8752 patients. Most patients (8433) had OAB; the remainder (319) were men with LUTS/BOO and some men/women with type 2 diabetes mellitus.

Pooled data from Phase II/III studies, with 12-week follow-up and a placebo comparison group, were available for 4414 patients. The incidence of TEAEs in the total mirabegron population (53.4%) was similar to that in the placebo group (55.2%), as was the distribution across mild/moderate/severe categories. Treatment-related AEs (TRAEs), as reported by the study investigators, showed a slight excess in the mirabegron groups (20.5%) compared to the placebo group (18.2%). Discontinuations that were thought to be drug-related, also showed a slight excess: 2.4% of mirabegron recipients, compared to 1.7% of placebo recipients, an excess of 0.7% or 7 in 1000 patients.

Urinary AEs, including urinary retention, occurred with a low incidence in all treatment groups, with no substantial differences between active treatment and placebo. The pivotal Phase III trials (and some of the other studies) specifically excluded patients thought to be at risk of urinary retention; however, safety study in patients with bladder outlet obstruction did not demonstrate increased urinary retention.

Laboratory results (for example for liver and renal function) and haematology parameters were unremarkable.

There was no notable difference between the incidence of SAEs in the placebo group (1.8%) versus the pooled mirabegron group (1.7%).

Mirabegron was also evaluated for safety in 1632 patients (50 mg: 812, 100 mg: 820) in a 12 month, randomised, fixed dose, double-blind, active controlled (tolterodine) safety study in patients with OAB (Study 049). Of these patients, 731 received mirabegron in a previous 12-week efficacy study.

In study 049, 1385 patients received mirabgron for at least 6 months, 1311 for at least 9 months, and 564 for 1 year. Treatment emergent AEs were reported in 60% (485/812) mirabegron 50 mg and 63% (508/812) tolerodine patients and were mostly of mild to moderate severity. Mirabegron had less dry mouth (2.8% versus 8.6%). Discontinuations due to TEAEs were reported for 6.4% and 6.0% of patients, respectively.

Two unconfirmed, but potentially serious risks were identified, which have become the focus of planned post-marketing studies in the US and Europe (using routine healthcare databases):

Potential increased risk of cardiovascular events

During clinical trials, mirabegron 50 mg was associated with a small increase in mean pulse rate (1 beat per min versus placebo) and blood pressure (<1 mm Hg versus placebo). Modelling by the FDA concluded that the small increases in systolic blood pressure seen in the three 12-week, Phase III trials translate into a small increase in the 10-year cardiovascular disease risk of 0.2%.

Potential increased risk of neoplasms

In the 12-month safety study, a higher incidence of neoplasms was reported for the mirabegron 100 mg group (11/820, 1.3%), compared to mirabegron 50 mg (1/812, 0.1%), and tolterodine (5/812, 0.5%). The relative risk for all mirabegron (50 mg + 100 mg) versus tolterodine was 1.5 (95% CI: 0.5, 6.4). The neoplasms reported included a variety of commonly occurring cancer types (breast, lung, prostate), with no type occurring in more than 2 study participants.

Other safety issues

Although mirabegron is β3-selective, its effect on intraocular pressure (β2 effect) was assessed in 305 normotensive people randomised to receive mirabegron 100 mg daily or placebo for 56 days. Intraoccular pressure changed from 15.3 mmHg to 15.0 mmHg in the mirabegron group and from 15.4 to 15.2 in the placebo group. Visual acuity and biomicroscopy data was unremarkable and no episodes of glaucoma were reported.

As discussed under *Pharmacodynamics* above, a mild QT-prolonging effect was observed at the supratherapeutic dose of 200 mg, especially in women.

Although mirabegron does not require dose adjustment when combined with other drugs, it may modify the PK of drugs metabolised CYP2D6, increasing their levels, which could be relevant for drugs with narrow therapeutic indices.

Mirabegron increases exposure to digoxin when the two are co-administered, so digoxin should be introduced at a low dose and titrated according to blood levels.

Exposure to mirabegron is increased (approximately doubled) in the setting of severe renal impairment. The PI therefore recommends halving the dose to 25 mg once daily in patients with severe renal impairment, but no adjustment is recommended in patients with mild to moderate renal impairment. Given that the proposed dose (50 mg) is half the maximum dose tested in the pivotal studies (100 mg), patients with severe renal impairment would experience an exposure that has been shown to have an acceptable safety profile. Similarly, a reduction of the dose to 25 mg once daily in patients with moderate hepatic impairment is recommended in the PI, and would be expected to produce an exposure similar to that experienced by normal subjects receiving a standard dose.

Mirabegron has not been studied at all in patients with severe hepatic impairment (Child-Pugh Class C) or in patients with ESRF. The proposed PI contains appropriate warnings against use in these two populations, under *Warnings and Precautions*.

Falls, syncope and hypotension did not occur with increased incidence in mirabegron recipients.

Over the whole clinical program, two events were suggestive of moderate skin reactions, reported as Stevens-Johnson syndrome and leukocytoclastic vasculitis. These two cases prompted a search for other potential hypersensitivity reactions, and one additional case of urticaria was identified. All cases were reviewed by an Expert Committee of hypersensitivity specialists, which concluded that there appears to be a risk of serious skin reactions and hypersensitivity in some susceptible individuals, but the incidence is low, and patients recovered when study drug was ceased.

Deaths in the major study populations were reviewed. The clinical evaluator concluded that these were infrequent and there were no concerning patterns.

Mirabegron was approved for marketing in Japan (tradename Betanis) in July, 2011 at the 25 mg and 50 mg doses. The FDA reviewed 18 spontaneous reports from Japan of urinary retention, some requiring catheterisation. After review of these reports, the FDA concluded that episodes of urinary retention in some patients, especially those taking anti-muscarinics and in men with benign prostatic hypertrophy, are notable.

Risk management plan

The TGA OPR has advised the sponsor that the Australian RMP Version: 1.1 dated 18 March 2013, must be revised as specified in the sponsor's correspondence dated 27 March 2013.

The sponsor has provided responses to ACSOM's queries about the routine database studies to assess possible increased (long-term) risks for cardiovascular events and cancer. The routine database studies will report in 2019. Provision of detailed study reports will be a condition of registration. ASCOM would be reviewing the sponsor's responses to its recommendations at its July meeting.

Risk-benefit analysis

Delegate considerations

The average, placebo-subtracted treatment effect for the pre-specified co-primary outcomes in the three pivotal Phase III trials was small. For the co-primary outcome of mean number of micturitions per day, the minimal clinically important difference (placebo-subtracted), used in the sample size calculations, was 0.7. For the 50 mg dose, the pooled treatment effect reported from the three pivotal Phase III trials was 0.55 (95% CI: 0.75, 0.36). For the 25 mg dose the treatment effect (reported from study 074) was 0.47 (95% CI: 0.82, 0.13).

Potential safety issues with mirabegron arise from the mild QT-prolonging effect observed at the supratherapeutic dose of 200 mg (especially in women) and the possibility of drug interactions. Although mirabegron does not require dose adjustment when combined with other drugs, it may modify the PK of drugs metabolised by CYP2D6, increasing their levels, which could be relevant for drugs with narrow therapeutic indices. Mirabegron also increases exposure to digoxin when the two are co-administered, so digoxin should be introduced at a low dose and titrated according to blood levels.

Mirabegron can cause systemic off-target β-agonist effects. Specifically, minor increases in pulse rate and blood pressure have been observed and their potential effect on long term cardiovascular outcomes will need further evaluation via the planned post-marketing database study.

The data on bladder outlet obstruction from the safety studies was unremarkable, but post-marketing surveillance in Japan has identified cases where mirabegron could be a contributing factor.

In general, the frequency of AEs seems similar to antimuscarinic agents; however the profile is different (for example, less dry mouth).

Mirabegron might possibly provide a worthwhile clinical benefit in some patients. The introduction of mirabegron could possibly provide an alternative therapeutic option for some patients.

The Delegate considered there were four questions in particular that needed to be addressed:

1. Given the similar placebo-subtracted treatment effect for the 25 mg and 50 mg dose for the pre-specified co-primary outcomes, should the dosing instruction be a starting dose of 25 mg dose for 8 weeks, possibly increasing to 50 mg, depending on efficacy and tolerability?

As discussed, the one pivotal Phase III trial that included the 25 mg dose did not directly compare it to the 50 mg dose. The separate comparisons to placebo suggest that 25 mg dose is as effective as the 50 mg dose, at 12 weeks for the two co-primary outcomes. However, the placebo-subtracted treatment effect for the 25 mg dose was smaller than for the 50 mg dose for the subjective outcome of satisfaction with treatment.

The Delegate was inclined to ask the sponsor to amend the PI to specifically recommend starting with a 25 mg dose for 8 weeks, possibly increasing to 50 mg, depending on efficacy and tolerability (as per the FDA Prescribing Information) because:

The results for the pre-specified co-primary outcomes (number of micturitions and incontinence episodes at 12 weeks), in the pivotal Phase III trial (074), are statistically and methodologically the most robust evidence available. Based on these results, 25 mg is as effective, on average, as 50 mg. Consequently, a trial of 25 mg for 8 weeks would be worthwhile and would mean that patients were exposed to the lowest effective dose of the drug. This is important because mirabegron does not cure OAB; and patients who decide to continue taking it could be exposed to it for several years.

2. Should the dosing instructions be amended to state that it is preferable to take the recommended dose 1 h before food or 2 h after a meal (as per PSC advice), given that PK studies show that absorption is reduced when it is taken with meals? The design of the pivotal Phase III trials did not include any recommendations about taking mirabegron with or without food.

Neither the US or EU PIs state that it is preferable to take the recommended dose 1 h before food or 2 h after a meal. The Delegate was inclined not to insist on this change to the PI because none of the Phase III trials required this, so efficacy as measured in trials reflects current PI.

3. Do the pivotal Phase III trials, which reported a small increase in mean pulse rate (< 1 beat per min) and mean blood pressure (< 1 mm Hg), raise concerns about potential long-term increased risk of cardiovascular events? Is the PI and RMP, including post-marketing studies in the US and Europe using routine databases, adequate in regard to these issues or are further changes suggested?

The post-marketing studies have been approved by the FDA. The concern about cardiovascular events arose out of evidence showing that mirabegron increased BP (and pulse rate) in healthy volunteers and also in patients enrolled in the Phase III trials. However the average increase in the Phase III trials was small (< 1 mmHg) and modelling done by the FDA estimated that this would increase the 10-year risk of cardiovascular events by only 0.2%. Given that the currently-available data suggest only a small increase

in risk, confirmation via a routine database study (reporting in 2019) is adequate; pending advice from the July 2013 ACSOM meeting. The Delegate was inclined not to require the inclusion of information about the potential increased risk of cardiovascular events in the PI; instead, the Delegate proposed to add a sub-section on *Increases in blood pressure and heart rate* to the *Precautions* section of the Australian PI.

4. Does the 12-month safety study, which reported 11 neoplasms among patients randomised to 100 mg mirabegron, raise concerns about potential long-term risk of cancer? Is the PI and RMP, including post-marketing studies in US and Europe using routine databases, adequate in regard to these issues or are further changes suggested?

The concern about the long-term risk of cancer arose out of the 12-month safety study. A possible signal occurred for the 100 mg, but not the 50 mg, dose of mirabegron. The cancers reported were common types; and no particular type of cancer was reported in more than two patients. The relative risk for all mirabegron (50 mg + 100 mg) versus tolterodine was 1.5 (95% CI: 0.5, 6.4) (12/1632 versus 5/812, with adjustment for patient-years of exposure). Pending advice from the July ACSOM meeting, the proposed database study in US and Europe (reporting in 2019) is an appropriate response to the signal. The Delegate was inclined not to require the inclusion of information about the increased risk of cancer in the PI because there was no signal for the 50 mg dose (proposed for registration), the cancers were common types, no type occurred in more than 2 patients, 12-months is a short time for cancer to develop, and the numbers are small (12 versus 5).

Request for further information from the sponsor

In its response to this overview, the Delegate requested the sponsor address the following issues:

1. The current dosing information approved in the US is:

   The recommended starting dose is 25 mg once daily with or without food. Myrbetiq (trade name for mirabegron in the US) 25 mg is effective within 8 weeks. Based on individual patient efficacy and tolerability the dose may be increased to 50 mg once daily.

   The current dosing information approved in the EU is:

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

   The proposed Australian dosing is:

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

   The sponsor should comment on the reasoning behind the different recommended starting doses in the US and EU PIs.

2. Was the subgroup analysis for patients who failed prior OAB antimuscarinic therapy pre-specified?

3. The sponsor should comment on the potential for mirabegron to increase cardiovascular events and the potential signal for neoplasia; and the possible mechanism of action of each.

4. The sponsor should comment on whether the treatment effects for the co-primary endpoints are clinically meaningful and on what basis this has been determined.

5. Does the sponsor have any information on the potential for off-label use for weight loss?

Proposed action

At this stage the Delegate was inclined to approve this submission from Astellas Pharma Australia Pty Ltd to register Betmiga (mirabegron, prolonged-release 25 mg and 50 mg tablets) based on the quality, safety and efficacy of the product being satisfactorily established for the indication below and for the reasons stated above in the Risk-Benefit analysis:

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

The following would be imposed as conditions of registration:

- Implementation of the Australian Risk Management Plan, comprising the European Risk Management Plan Version 1.0, dated 4 August 2011, with an Australian Specific Annex.
- The following studies must be submitted to the TGA as soon as possible after completion for evaluation:
  - The post-marketing database studies of long-term risk of cardiovascular events and cancer
  - Any other studies that identify safety concerns or provide updated safety information

The Delegate also proposed revisions to the PI and CMI. Details are beyond the scope of the AusPAR.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM and to request the committee's advice on the following issues in particular:

1. Given the similar placebo-subtracted treatment effect for the 25 mg and 50 mg dose for the pre-specified co-primary outcomes, should the dosing instruction be a starting dose of 25 mg dose for 8 weeks, possibly increasing to 50 mg, depending on efficacy and tolerability?
2. Should the dosing instructions be amended to state that it is preferable to take the recommended dose 1 h before food or 2 h after a meal (as per PSC advice), given that pharmacokinetic studies show that absorption is reduced when it is taken with meals? The design of the pivotal Phase III trials did not include any recommendations about taking mirabegron with/without food.
3. Do the pivotal Phase III trials, which reported a small increase in mean pulse rate (< 1 beat per min) and mean blood pressure (< 1 mm Hg), raise concerns about potential long-term increased risk of cardiovascular events? Is the PI and RMP, including post-marketing studies in US and Europe using routine databases, adequate in regard to these issues or are further changes suggested?
4. Does the 12-month safety study, which reported 11 neoplasms among 820 patients randomised to 100 mg mirabegron, raise concerns about potential long-term risk of cancer? Is the PI and RMP, including post-marketing studies in US and Europe using routine databases, adequate in regard to these issues or are further changes suggested?

Response from sponsor

The sponsor provided the following response to the Delegate's specific request:

Delegate's question 1. Comment on the reasoning behind the different recommended starting doses in the US and EU PIs?

On April 5, 2012, an FDA Advisory Committee for Reproductive Health Drugs convened for the purpose of evaluating the benefit-risk profile of mirabegron in the treatment of OAB. During the meeting, several committee members proposed to consider mirabegron 25 mg as a starting dose because it appeared to represent the lowest effective dose. Based upon reservations from some members, a 25 mg starting dose for mirabegron was recommended in the US [Center for Drug Evaluation and Research, Office Director Memo for Myrbetriq (mirabegron), 2012].

In Europe, the Committee for Medicinal Products for Human Use (CHMP) noted that the beneficial effects seen with mirabegron were modest but comparable to the benefits of other medicines authorised for this condition. Regarding its safety, most side effects were comparable to those of other medicines used for treating overactive bladder syndrome. The CHMP therefore decided that the benefits of mirabegron are greater than its risks and recommended that it be given marketing authorization at the proposed therapeutic starting dose of 50 mg [Betmiga (mirabegron), 2013].

The FDA recommendation is based on the effect of mirabegron 25 mg on the two co-primary endpoints of micturition frequency and incontinence episodes. The EU PI approach takes into consideration additional aspects of response to therapy such as the more comprehensive alleviation of OAB manifestations, the patient reported outcomes indices, and the rapidity of onset of therapeutic effect all of which differentiated between mirabegron 50 mg and 25 mg. The management of the composite of symptoms comprising OAB is essential for effective outcomes, patient satisfaction and patient adherence. Mirabegron 50 mg remains the preferred recommended starting dose to address the constellation of OAB symptoms as quickly and as comprehensively as possible. The differential effects of mirabegron 50 mg and mirabegron 25 mg are described in greater detail below [refer to the response to the Delegate's question 4 and *Recommended Starting Dose,* below].

Delegate's question 2. Was the subgroup analysis for patients who failed prior OAB antimuscarinic therapy pre-specified?

Integrated analyses were pre-specified prior to database lock of the first primary Phase III study. The pre-specified pooled analyses of the co-primary efficacy endpoints were conducted for multiple subgroup parameters, including patients who were antimuscarinic treatment-naïve and in patients who failed previous OAB antimuscarinic therapy. Efficacy with mirabegron was demonstrated in patients who were antimuscarinic treatment-naive and in patients who failed previous OAB antimuscarinic therapy. The population included approximately 48% antimuscarinic treatment-naïve patients and approximately 52% patients previously treated with antimuscarinic therapy.

Delegate's question 3. Comment on the potential for mirabegron to increase cardiovascular events and the potential signal for neoplasia; and the possible mechanism of action of each.

The sponsor referred to its Response documents (dated 16 May 2013 and 6 June 2013) with regards to the questions raised in the RMP evaluation report. In the Response documents, the concerns for cardiovascular events and neoplasia raised have been addressed with robust risk management strategies including product labelling as well as the planned post-approval safety studies to monitor cardiovascular safety and risks of neoplasia [Studies 178-CL-113 and 178-CL-114].

The following comments are further provided on the potential and the possible mechanism of action for each of the concerns:

Cardiovascular events:

Mirabegron is an agonist of the human β3 adrenergic receptor. Although mirabegron showed very low intrinsic activity for cloned human β1-adrenergic receptor and β2-adrenergic receptor, results in humans indicate that β1-adrenergic receptor stimulation occurred at a mirabegron dose of 200 mg. In view of the *in vitro* and *in vivo* data with mirabegron and its potential for β1-adrenergic receptor stimulation at supratherapeutic dose of 200 mg, cardiovascular safety was an area of focus. As such, a comprehensive program was developed to evaluate potential cardiovascular safety signals, including an independent blinded cardiovascular adjudication committee to categorise the events. Based on the blinded independent adjudication review of the Major Adverse Cardiac Events (MACE), the data revealed that the event rates were similar for placebo, mirabegron and tolterodine. The results of the mirabegron cardiovascular comprehensive program revealed that in the OAB population, mirabegron 50 mg was associated with a mean change of approximately one beat per minute in pulse, and clinically relevant categorical changes in pulse were similar between mirabegron 50 mg and tolterodine. The mean change in systolic and diastolic blood pressure was approximately 0.4 to 0.6 mmHg. Both categorical changes in blood pressure, as well as hypertension AEs, were similar between mirabegron and placebo. Mirabegron entered the market in Japan in September 2011, in the US in October 2012, in Canada in April 2013, and most recently in some European countries such as the United Kingdom. Based on postmarketing experience in Japan and the US, no new major cardiovascular safety concerns have been reported or identified.

However, the potential cardiovascular concerns and the responsibility of introducing an agent with a new mechanism lead the Sponsor to propose a long-term EU and US observational study on cardiovascular events [Study 178-CL-114]. The sponsor's objective in conducting this long-term EU and US observational study on cardiovascular events is to continue to enhance the comprehensive commitment to gather substantial cardiovascular data with mirabegron in the setting of real-world medical practice.

Neoplasia:

There was no potential signal for neoplasia identified in the nonclinical and clinical mirabegron development program.

Reference is made to the sponsor's Research Report: *Mirabegron and Neoplasms* (provided in the submission) for a detailed evaluation of preclinical data and clinical evaluation of neoplasm events, including blinded review by an independent adjudication committee of oncology experts. In summary, the sponsor concluded that the available nonclinical and clinical data do not support an association of mirabegron exposure with the observed imbalance of new malignant events in the Global Phase II/III clinical program. This conclusion was based upon the following: 1) the absence of genotoxicity and carcinogenicity as demonstrated in nonclinical experiments conducted across the lifespan in various (rat and mice) species; 2) review of the individual 12-week study data revealed an imbalance of adjudicated new malignancies in a single study [Study 178-CL-047], which was not replicated in the other 5 studies included in the pooled Global OAB 12-week Population; 3) the lack of evidence of increased risk of new malignant events with longer exposure to mirabegron; 4) the biological implausibility for mirabegron to a) influence the growth of a wide array of malignancies given that the imbalance was not dominated by a specific malignancy or collection of similar malignancies and b) result in the development of tumours (particularly slow growing tumours) in humans during the short-term treatment period observed in the mirabegron clinical program; and 5) the demonstration in an epidemiologic analysis that the observed rates of the most frequent malignancies reported in mirabegron-treated patients are not larger than expected rates in an age-adjusted population.

However, in accordance with a US FDA post-marketing requirement, the sponsor is planning to conduct a long-term observational study in electronic healthcare databases to prospectively evaluate the incidence of new malignant events (excluding non-melanoma skin cancer) in patients using mirabegron [Study 178-CL-113].

Delegate's question 4. Comment on whether the treatment effects for the co-primary endpoints are clinically meaningful and on what basis this has been determined.

Mirabegron consistently provided an improved response over placebo for the objective and subjective patient reported efficacy endpoints evaluated. For the majority of the endpoints evaluated, the nominal P values reported were < 0.05 compared with placebo. This consistency was observed in the individual primary studies as well as the pooled analyses. Mirabegron 50 mg consistently demonstrated a statistically significant reduction in the co-primary endpoints of adjusted mean change from baseline to final visit versus placebo in mean number of incontinence episodes and micturitions per 24 h using a stringent multiplicity analysis. Mirabegron 50 mg also demonstrated a statistically significant increase from baseline to final visit in mean volume voided per micturition compared with placebo.

A statistically significant improvement was observed with mirabegron 50 mg compared with placebo in both the objective measures of OAB syndrome manifestations such as incontinence and micturition frequency and in the translation of these measures into the patient's experience of the syndrome as measured by validated and standard instruments of patient-reported outcome (PRO). Mirabegron 50 mg demonstrated an improvement compared with placebo in the PRO measures evaluated in the primary phase 3 studies. In the responder analyses based on the minimally important difference (MID) definitions for Overactive Bladder Questionnaire (OAB-q) domains and Patient Perception of Bladder Condition (PPBC), more patients treated with mirabegron 50 mg compared with placebo met the MID criteria at the final visit for all of the OAB-q parameters including symptom bother and total health-related quality of life (HRQL) score, and the PPBC. The correlation between PPBC and symptom bother score and PPBC and the total HRQL score supports the consistency of effect of mirabegron 50 mg on the PRO indices. The directional parallelism between the subjective and objective measures substantially supports the clinical significance of the effect of mirabegron 50 mg in patients with OAB.

Furthermore, the effects of mirabegron on incontinence episodes and micturition frequency observed in the 12-week primary studies were compared to the results of an updated systematic review and meta-analysis on the effects of antimuscarinic drugs for the treatment of OAB (Chapple *et al*, 2008[32]). The effects of mirabegron were also compared to efficacy data from studies of OAB patients with a similar duration of treatment (12-weeks), demographic profile and baseline characteristics to those in the mirabegron program for approved OAB products using data from the FDA medical and statistical reviews.

The mean difference from placebo for incontinence episodes and micturition frequency following administration of mirabegron 50 mg is within the range of values following administration of approved OAB agents, which are generally accepted to provide meaningful benefit to patients.

Delegate's question 5. Does the sponsor have any information on the potential for off-label use for weight loss?

In the sponsor's Response to the RMP Evaluation Report (dated 16 May 2013), the potential for off-label use for weight loss was addressed, and relevant data were summarised. A brief summary is provided below.

[32] Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. *Eur Urol*. 2008;54(3):543-62.

Nonclinical studies: Lipolytic effects of mirabegron on rodent fat cells and the effects on energy expenditure, body temperature and glucose tolerance in genetically obese rodents, were not found in dogs and monkeys or in man [Studies 178-PH-002, 178-PH-010, 178-PH-017, 178-PT-004, 178-TX-018, 178-TX-014, 178-TX-021, 178-TX-026, 178-TX-013, 178-TX-017]. These nonclinical data show that mirabegron does not induce lipolysis or body weight loss in non-rodent species.

Clinical studies: In healthy subject studies, mirabegron showed a transient increase in plasma nonesterified fatty acids suggesting lipolysis after a single dose, but not upon repeat dose administration; while no effect was observed on mean blood glucose, C-peptide, triglyceride, insulin levels and oral temperature compared with placebo, under either fasted or fed conditions, upon single or repeat dose administration suggesting that mirabegron does not affect lipid or glucose metabolism in healthy subjects [Studies 178-CL-001, 178-CL-002]. Furthermore, results indicated that changes in mean body weight in patients with type 2 diabetes did not differ between patients treated with placebo plus metformin or mirabegron plus metformin [Study 178-CL-004].

In summary, there is no evidence to suggest that mirabegron may facilitate weight loss/control even at high exposure in patients, and the potential for off-label use for weight loss is not supported by the nonclinical and clinical data of mirabegron.

Other comments on efficacy and safety

The sponsor also provided the following information in response to the Delegate's request for ACPM's advice on several issues:

Recommended starting dose: 25 mg versus 50 mg

The goal of an OAB medication is to improve the symptoms of urge urinary incontinence, urgency and urinary frequency while minimising the side effects. Management of the composite of symptoms comprising OAB is essential for effective outcomes, patient satisfaction and patient adherence. Mirabegron 50 mg demonstrated a statistically significant improvement compared with placebo in both the objective measures of OAB syndrome manifestations (such as incontinence and micturition) and in the translation of these measures into the patient's experience of the syndrome as measured by PRO instruments. Mirabegron at a dose of 50 mg led to significant changes in HRQL measures in parallel with the improvements in objective measures of OAB. Patients treated with mirabegron 50 mg showed significant improvement in the components of the OAB-q, the PPBC instrument and the Treatment Satisfaction-Visual Analog Scale (TS-VAS) score in both the pooled data set for all subjects treated with mirabegron 50 mg in the primary studies and in the individual studies. While mirabegron 25 mg demonstrated superiority compared with placebo in reducing the co-primary endpoints (objective endpoints): mean number of incontinence episodes per 24 h at the final visit and mean number of micturitions per 24 h at the final visit; mirabegron 25 mg dose was not statistically significant for any of the key secondary efficacy endpoints (subjective endpoints). Efficacy was consistently observed after 4 weeks of treatment with mirabegron 50 mg, but not with mirabegron 25 mg; the speed of improvement in symptoms of OAB is known to affect adherence to therapy. In exposure-efficacy response modelling, the dose selection of 50 mg was supported since the median relative increase in efficacy for micturition frequency is 62% higher for mirabegron 50 mg relative to efficacy with mirabegron 25 mg.

The safety of mirabegron has been well characterised in a large safety database including 5648 OAB patients with characteristics representative of the OAB population. There were no clinically meaningful differences in the safety profile of mirabegron 25 mg compared to mirabegron 50 mg.

In summary, substantial data, comprehensively analysed, support the efficacy and safety of mirabegron 50 mg in the treatment of patients suffering from OAB. Based on its

significant changes in HRQL measures in parallel with the improvements in objective measures of OAB with no clinical difference in the safety profile of mirabegron 50 mg compared with mirabegron 25 mg, mirabegron 50 mg remains the preferred recommended starting dose in order to address the constellation of symptoms of OAB as quickly as possible. The selection of mirabegron 50 mg as the therapeutic dose is consistent with the approved EU Summary of Product Characteristics (SmPC).

Dosing instruction with regards to food

The sponsor refers to its Response document (dated 25 June 2013) with regards to the question raised in the PSC Evaluation Report. Specifically, it was emphasised that the safety and efficacy of mirabegron in the Phase III clinical program has been evaluated under conditions identical to those recommended in the proposed PI. In the primary EU/NA 12-week, double-blind, Phase III studies conducted in patients with OAB, patients were instructed to take study medication in the morning with a glass of water, with or without food.

Overall, the data support the current proposed recommendation for mirabegron, which does not specify a requirement for dosing in relation to food. The clinical program reflects and is identical to the conditions that mirabegron will be administered in the setting of real-world medical practice. Thus, the sponsor proposes to maintain the current recommendation with the proposed wording, consistent with the approved EU SmPC and US PI.

Risks of CV events, cancer and monitoring

Refer to the response to Question 3 above.

Other related issues

The sponsor confirms that the latest proposed RMP for Australia is version 1.1 (dated 18 March 2013) as submitted to the TGA on 27 March 2013. To the sponsor's knowledge, all outstanding issues with RMP were addressed in the response to the RMP evaluation report (responses submitted on 16 May 2013 and 6 June 2013). The AU-RMP will be updated as necessary to reflect changes to the PI and CMI following finalisation of these documents post-ACPM.

The database study reports will be submitted to the TGA when available in 2019.

The sponsor has addressed changes to the PI and CMI requested by the Delegate and provided updated documents. Details of these are beyond the scope of the AusPAR.

Conclusion

The sponsor supports the Delegate's recommendation for approval and believes that the outstanding issues raised in the Delegate's request for ACPM advice have hereby been addressed in this response.

Mirabegron offers an additional pharmacologic treatment option for patients with OAB and addresses an unmet medical need in improving the symptoms of OAB with a different safety profile from antimuscarinic therapy. The effect of mirabegron has been consistently shown to be superior to placebo for the co-primary, key secondary and quality of life endpoints and within range of the effects observed with other OAB products. Mirabegron at a proposed therapeutic dose of 50 mg once daily represents a new and well-tolerated treatment option for patients with OAB.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered BETMIGA modified release tablets containing 25 mg and 50 mg of mirabegron to have an overall positive benefit–risk profile for the indication;

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

The ACPM advised that a reasonable starting dose would be 25 mg once daily (as in US) as there is no clear additional benefit seen with starting on 50 mg once daily.

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- A statement in the *Dosage and Administration* section of the PI and relevant sections of the CMI advising it would be prudent to take the medicine 1 h before or 2 h after meals
- Amendments to the CMI to better explain QT prolongation.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Betmiga mirabegron 25 and 50 mg film-coated prolonged-release tablet, indicated for:

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

Specific conditions applying to these therapeutic goods

- The Betmiga (mirabegron) Australian Risk Management Plan (AU-RMP) Version 1.1, dated 18 March 2013, to be revised as specified in the sponsor's correspondence dated 27 March 2013, comprising the European Risk Management Plan (EU-RMP) Version 1.0, dated 4 August 2011 with an Australian Specific Annex, included with submission PM-2012-01928-3-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- The following studies must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission:
  - The post-marketing database studies of long-term risk of cardiovascular events and cancer
  - Any other studies that identify safety concerns or provide updated safety information

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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