

PRODUCT MONOGRAPH

<sup>Pr</sup>**APO-MIRABEGRON**

Mirabegron Extended-Release Tablets

25 mg and 50 mg

Selective beta 3-adrenoceptor agonist

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## PrAPO-MIRABEGRON

Mirabegron Extended-Release Tablets

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	Extended-release tablets: 25 mg, 50 mg	Ascorbic acid, D&C yellow #10 aluminum lake, FD&C red #40 aluminum lake (25 mg), hydroxypropyl cellulose, hydroxypropyl methylcellulose, indigotine aluminum lake, magnesium stearate, polyethylene glycol, polyethylene oxide, sunset yellow aluminum lake, and titanium dioxide.

#### INDICATIONS AND CLINICAL USE

APO-MIRABEGRON (mirabegron extended-release tablets) is indicated for the treatment of overactive bladder (OAB) with symptoms of urgency, urgency incontinence and urinary frequency.

##### Geriatrics (≥ 65 years of age):

Of 5648 patients who received mirabegron extended-release tablets in the phase 2 and 3 studies, 2029 (35.9%) were 65 years of age or older, and 557 (9.9%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients younger than 65 years of age and those 65 years of age or older in these studies.

##### Pediatrics (< 18 years of age):

The safety and efficacy of mirabegron extended-release tablets in pediatric patients have not been established.

#### CONTRAINDICATIONS

APO-MIRABEGRON is contraindicated in:

- Patients with severe uncontrolled hypertension defined as systolic blood pressure  $\geq 180$  mm Hg and/or diastolic blood pressure  $\geq 110$  mm Hg.
- Patients who are pregnant.
- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

## WARNINGS AND PRECAUTIONS

### **General**

In a 52-week long-term safety study, serious adverse events of neoplasm were reported by 0.1%, 1.3% and 0.5% of patients treated with mirabegron extended-release tablets 50 mg, mirabegron extended-release tablets 100 mg, and active control once daily, respectively. Neoplasms reported by 2 patients treated with mirabegron extended-release tablets 100 mg included breast cancer, lung neoplasm malignant and prostate cancer.

In a clinical study in Japan, a single case was reported as Stevens-Johnson syndrome with increased serum ALT, AST and bilirubin in a patient taking mirabegron extended-release tablets 100 mg as well as an herbal medication (Kyufu Gold) (see ADVERSE REACTIONS).

In a 52-week long-term safety study, serum ALT/AST increased from baseline by greater than 10-fold in 2 patients (0.3%) taking mirabegron extended-release tablets 50 mg, and these markers subsequently returned to baseline while both patients continued mirabegron extended-release tablets (see ADVERSE REACTIONS).

### **Cardiovascular**

**QTc Prolongation:** Mirabegron extended-release tablets was associated with dose-dependent QTc prolongation that was more pronounced in females. At the maximal recommended therapeutic dose of 50 mg, the largest mean difference from placebo in the QTc interval was <5 ms in healthy male and female subjects at steady-state (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, Cardiac Electrophysiology and Haemodynamics). Consider these observations in clinical decisions to prescribe APO-MIRABEGRON to patients with a known history of QT prolongation, risk factors for torsade de pointes (e.g., hypokalemia) or patients who are taking medications known to prolong the QT interval (see Drug-Drug Interactions, Drugs that Cause QT/QTc Prolongation).

**Blood Pressure:** Mirabegron extended-release tablets can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with APO-MIRABEGRON, especially in hypertensive patients. Mirabegron was not studied in patients with severe uncontrolled hypertension (systolic blood pressure  $\geq 180$  mm Hg and/or diastolic blood pressure  $\geq 110$  mm Hg) and, therefore is not recommended in these patients (see CONTRAINDICATIONS). In a healthy volunteer study, mirabegron extended-release tablets was associated with dose-dependent increases in supine systolic/diastolic blood pressure. At the maximal recommended dose of 50 mg, the mean maximum increase in systolic/diastolic blood pressure was approximately 4.0/3.7 mm Hg greater than placebo. In patients with OAB in clinical trials, mirabegron extended-release tablets was associated with increases in systolic and diastolic blood pressure of approximately 0.5 to 1 mm Hg compared to placebo. Both systolic blood pressure and diastolic blood pressure increases were reversible upon discontinuation of treatment (see ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology and Haemodynamics, Effects on Pulse Rate and Blood Pressure in Patients with OAB).

**Heart Rate Increase:** Mirabegron extended-release tablets is associated with increased heart

rate that correlates with increasing dose (see ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology and Haemodynamics). In a healthy volunteer study, Mirabegron extended-release tablets was associated with dose-dependent increases in heart rate. At the maximal recommended dose of 50 mg, the mean maximum increase in heart rate was approximately 8.5 bpm in females and 5.5 bpm in males at steady-state. In patients with OAB in clinical trials receiving the maximum recommended dose of mirabegron extended-release tablets 50 mg, a mean heart rate increase of approximately 1 bpm compared to placebo was observed that was reversible upon discontinuation of treatment. Accordingly, caution should be used when administering APO-MIRABEGRON to patients who have a history of ischemic heart disease or tachyarrhythmias.

### **Endocrine and Metabolism**

CYP2D6: Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates such as metoprolol and desipramine is increased when co-administered with mirabegron ( $\geq 100$  mg). Therefore, caution is advised if mirabegron is co-administered with these drugs as appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index drugs metabolized by CYP2D6. The dose of APO-MIRABEGRON should not exceed 25 mg when co-administered with narrow therapeutic index drugs, such as flecainide and propafenone (see DRUG INTERACTIONS and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

### **Genitourinary**

Urinary Retention: Urinary retention has been reported in post-marketing experience in patients taking mirabegron, in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB. APO-MIRABEGRON should be administered with caution to patients with clinically significant BOO. APO-MIRABEGRON should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions; ACTION AND CLINICAL PHARMACOLOGY and DRUG INTERACTIONS).

### **Hepatic/Biliary/Pancreatic**

Mirabegron extended-release tablets has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, is not recommended for use in this patient population (see DOSAGE AND ADMINISTRATION, Dosing Consideration).

In patients with moderate hepatic impairment (Child-Pugh Class B), the daily dose of APO-MIRABEGRON should not exceed 25 mg. No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A) (see DOSAGE AND ADMINISTRATION, Dosing Consideration and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).

### **Immune**

Angioedema of the face, lips, tongue, and/or larynx has been reported with mirabegron extended-release tablets. In some cases angioedema occurred after the first dose. Cases of angioedema have been reported to occur hours after the first dose or after multiple doses. Angioedema associated with upper airway swelling may be life threatening. If involvement of the tongue,

hypopharynx, or larynx occurs, promptly discontinue APO-MIRABEGRON and initiate appropriate therapy and/or measures necessary to ensure a patent airway (see ADVERSE REACTIONS).

### **Ophthalmologic**

Ophthalmological examination should be performed regularly during treatment with APO-MIRABEGRON in patients with glaucoma. In a healthy volunteer study, administration of mirabegron at 100 mg dose per day was not associated with any increase in intraocular pressure (IOP) (see ACTION AND CLINICAL PHARMACOLOGY, Effect on IOP).

### **Renal**

Mirabegron extended-release tablets has not been studied in patients with End Stage Renal Disease ( $CL_{cr} < 15$  mL/min or  $eGFR < 15$  mL/min/1.73 m<sup>2</sup> or patients requiring hemodialysis) and, therefore, is not recommended for use in these patient populations (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

In patients with severe renal impairment ( $CL_{cr}$  15 to 29 mL/min or  $eGFR$  15 to 29 mL/min/1.73 m<sup>2</sup>), the daily dose of APO-MIRABEGRON should not exceed 25 mg. No dose adjustment is necessary in patients with mild or moderate renal impairment ( $CL_{cr}$  30 to 89 mL/min or  $eGFR$  30 to 89 mL/min/1.73 m<sup>2</sup>) (see DOSAGE AND ADMINISTRATION, Dosing Considerations and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency).

### **Sexual Function/Reproduction**

In animal studies, female fertility index was 88% (or 2 of 17 animals were infertile) while in males, there was no effect on fertility at non-lethal doses (see TOXICOLOGY). However, due to short duration of the treatment period, effects on male fertility cannot be ruled out (see TOXICOLOGY).

### **Special Populations**

**Pregnant Women:** There are no adequate and well-controlled studies using mirabegron extended-release tablets in pregnant women.

In animal embryo-fetal toxicity studies there was an increased incidence of wavy rib, dilated aorta, cardiomegaly and reduced fetal body weight. Mirabegron was not found to be teratogenic (see TOXICOLOGY).

Because preclinical reproductive toxicity studies may not accurately predict human reproductive toxicity, the use of APO-MIRABEGRON should be avoided in pregnancy (see CONTRAINDICATIONS).

**Nursing Women:** Mirabegron is excreted in the milk of rodents and therefore is predicted to be present in human milk. No studies have been conducted to assess the impact of mirabegron on milk production in humans, its presence in human breast milk, or its effects on the breast-fed child. Because of the potential for serious adverse reactions in nursing infants, APO-MIRABEGRON should not be administered during nursing.

**Pediatrics (< 18 years of age):** The safety and efficacy of mirabegron extended-release tablets in pediatric patients have not been established.

**Geriatrics (≥ 65 years of age):** No overall differences in safety or effectiveness were observed between patients younger than 65 years of age and those 65 years of age or older in these studies. Of 5648 patients who received mirabegron extended-release tablets in the phase 2 and 3 studies, 2029 (35.9%) were 65 years of age or older, and 557 (9.9%) were 75 years of age or older.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The most frequent adverse events (0.2%) leading to discontinuation in Studies 178-CL-046, -047, and -074 for mirabegron extended-release tablets 25 mg or 50 mg dose were nausea, headache, hypertension, diarrhea, constipation, dizziness and tachycardia. Atrial fibrillation (0.2%) and prostate cancer (0.1%) were reported as serious adverse events by more than 1 patient and at a rate greater than placebo.

In Study 178-CL-049, in patients treated with mirabegron extended-release tablets 50 mg once daily, adverse reactions leading to discontinuation reported by more than 2 patients and at a rate greater than active control included: constipation (0.9%), headache (0.6%), dizziness (0.5%), hypertension (0.5%), dry eyes (0.4%), nausea (0.4%), vision blurred (0.4%), and urinary tract infection (0.4%). Serious adverse events reported by at least 2 patients and exceeding active control included cerebrovascular accident (0.4%) and osteoarthritis (0.2%).

In Study 178-CL-049, serious adverse events of neoplasm were reported by 0.1%, 1.3%, and 0.5% of patients treated with mirabegron extended-release tablets 50 mg, mirabegron extended-release tablets 100 mg and active control once daily, respectively. Neoplasms reported by 2 patients treated with mirabegron extended-release tablets 100 mg included breast cancer, lung neoplasm malignant and prostate cancer.

In Study 178-CL-049, serum ALT/AST increased from baseline by greater than 10-fold in 2 patients (0.3%) taking mirabegron extended-release tablets 50 mg, and these markers subsequently returned to baseline while both patients continued mirabegron extended-release tablets.

In a clinical study in Japan, a single case was reported as Stevens-Johnson syndrome with increased serum ALT, AST and bilirubin in a patient taking mirabegron extended-release tablets 100 mg as well as an herbal medication (Kyufu Gold).

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction*

information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In three, 12-week, double-blind, placebo-controlled safety and efficacy studies in patients with overactive bladder (Studies 178-CL-046, -047, and -074), mirabegron extended-release tablets was evaluated for safety in 2736 patients [see PART II: SCIENTIFIC INFORMATION, CLINICAL TRIALS]. Study 178-CL-046 also included an active control. For the combined Studies 178-CL-046, -047, and -074, 432 patients received mirabegron extended-release tablets 25 mg, 1375 received mirabegron extended-release tablets 50 mg, and 929 received mirabegron extended-release tablets 100 mg once daily. In these studies, the majority of the patients were Caucasian (94%) and female (72%) with a mean age of 59 years (range 18 to 95 years).

Mirabegron extended-release tablets was also evaluated for safety in 1632 patients who received mirabegron extended-release tablets 50 mg once daily (n=812 patients) or mirabegron extended-release tablets 100 mg (n=820 patients) in a 1-year, randomized, fixed-dose, double-blind, active-controlled safety study in patients with overactive bladder (Study 178-CL-049). Of these patients, 731 received mirabegron extended-release tablets in a previous 12-week study. In Study 178-CL-049, 1385 patients received mirabegron extended-release tablets continuously for at least 6 months, 1311 patients received mirabegron extended-release tablets for at least 9 months, and 564 patients received mirabegron extended-release tablets for at least 1 year.

Table 1 lists adverse reactions, derived from all adverse events, that were reported in phase 3 studies [178-CL-046, -047, -074] at an incidence greater than placebo and in 1% or more of patients treated with mirabegron extended-release tablets 25 mg or 50 mg once daily for up to 12 weeks. The most commonly reported adverse reactions (greater than 2% of mirabegron extended-release tablets patients and greater than placebo) were hypertension, nasopharyngitis, urinary tract infection and headache.

**Table 1 – Adverse Events Exceeding the Placebo Rate and Reported by  $\geq 1\%$  of Mirabegron Extended-Release Tablets-treated OAB Patients in the 12-week Phase 3 Studies**

	Placebo (%)	Mirabegron Extended-Release Tablets 25 mg (%)	Mirabegron Extended-Release Tablets 50 mg (%)
<b>Number of Patients</b>	<b>1380</b>	<b>432</b>	<b>1375</b>
Hypertension*	7.6	11.3	7.5
Nasopharyngitis	2.5	3.5	3.9
Urinary Tract Infection	1.8	4.2	2.9
Headache	3.0	2.1	3.2
Constipation	1.4	1.6	1.6
Upper Respiratory Tract Infection	1.7	2.1	1.5
Arthralgia	1.1	1.6	1.3
Diarrhea	1.3	1.2	1.5

	Placebo (%)	Mirabegron Extended-Release Tablets 25 mg (%)	Mirabegron Extended-Release Tablets 50 mg (%)
<b>Number of Patients</b>	<b>1380</b>	<b>432</b>	<b>1375</b>
Tachycardia	0.6	1.6	1.2
Abdominal Pain	0.7	1.4	0.6
Fatigue	1.0	1.4	1.2

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

Table 2 lists the rates of the most commonly reported adverse reactions, derived from all adverse events in patients treated with mirabegron extended-release tablets 50 mg for up to 52 weeks [178-CL-049]. The most commonly reported adverse reactions (>3% of mirabegron extended-release tablets patients) were hypertension, urinary tract infection, headache, and nasopharyngitis.

**Table 2: Percentages of Patients with Adverse Reactions, Derived from all Adverse Events, Reported by Greater Than 2% of Patients Treated With Mirabegron Extended-Release Tablets 50 mg Once Daily in 52-week long-term safety study [178-CL-049]**

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

### **Less Common Clinical Trial Adverse Drug Reactions**

Other adverse reactions reported by less than 1% of patients treated with mirabegron extended-release tablets in the three 12-week phase 3 double-blind, placebo-controlled studies in OAB patients are:

**Cardiac disorders:** palpitations, atrial fibrillation, blood pressure increased (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, Cardiac Electrophysiology and Haemodynamics)

**Eye disorders:** eyelid edema, glaucoma (see ACTION AND CLINICAL PHARMACOLOGY,

Pharmacodynamics)

**Gastrointestinal disorders:** dyspepsia, gastritis, abdominal distension

**Infections and Infestations:** sinusitis, rhinitis

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

**Musculoskeletal and connective tissue disorders:** joint swelling

**Renal and urinary disorders:** nephrolithiasis, bladder pain

**Reproductive system and breast disorders:** vulvovaginal pruritus, vaginal infection

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

### **Post-Market Adverse Drug Reactions**

Because these spontaneously reported events are from the worldwide post-marketing experience, from a population of uncertain size, the frequency of events and the role of mirabegron in their causation cannot be reliably determined.

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

**Gastrointestinal disorders:** constipation, diarrhea, nausea

**Nervous system disorders:** dizziness, headache

**Renal and urinary disorders:** urinary retention (see WARNINGS AND PRECAUTIONS)

**Skin and subcutaneous tissue disorders:** angioedema of the face, lips, tongue, and larynx, with or without respiratory symptoms (see WARNINGS AND PRECAUTIONS); pruritus

## **DRUG INTERACTIONS**

### **Overview**

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

In healthy subjects who are genotypically poor metabolizers of CYP2D6 substrates (used as a surrogate for CYP2D6 inhibition), mean  $C_{max}$  and  $AUC_{inf}$  of a single 160 mg dose of a mirabegron immediate-release oral formulation were 14% and 19% higher than in extensive metabolizers, indicating that CYP2D6 genetic polymorphism has minimal impact on the mean plasma exposure to mirabegron. Interaction of mirabegron with a known CYP2D6 inhibitor is not expected and was not studied. No dose adjustment is needed for mirabegron when administered with CYP2D6 inhibitors or in patients who are CYP2D6 poor metabolizers. Administration of mirabegron (100 mg single dose) with the potent CYP3A4 and P-gp inhibitor ketoconazole (400 mg daily) in healthy volunteers resulted in higher mirabegron exposure (45% higher  $C_{max}$  and 81% higher  $AUC_{tau}$ ). Co-administration of rifampin (600 mg qd), a

potent CYP3A and P-gp inducer, resulted in a 35% decrease in  $C_{max}$  and a 44% decrease in  $AUC_{inf}$  of mirabegron (100 mg sd). No dose adjustment is needed for mirabegron when co-administered with ketoconazole, rifampin or other modulators of CYP3A or P-gp.

### **Drugs metabolized by CYP2D6**

Mirabegron is a moderate inhibitor of CYP2D6. Multiple qd dosing of 160 mg mirabegron (administered as the 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. Multiple qd dosing of 100 mg mirabegron 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. Caution is advised if mirabegron is co-administered with this class of drugs as appropriate monitoring and dose adjustment may be necessary. The dose of APO-MIRABEGRON should not exceed 25 mg when co-administered with narrow therapeutic index CYP2D6 substrates, such as flecainide and propafenone (see WARNINGS AND PRECAUTIONS).

### **Digoxin**

Mirabegron is a weak inhibitor of P-gp. With multiple dosing of 100 mg mirabegron once daily, the  $C_{max}$  of a single 0.25 mg dose of digoxin increased 29%, while  $AUC_{last}$  increased 27%. For patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should be prescribed initially. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect. The potential for inhibition of P-gp by mirabegron should be considered when APO-MIRABEGRON is combined with sensitive P-gp substrates, e.g., dabigatran.

### **Warfarin**

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

## **Drug-Drug Interactions**

### ***In Vitro* Studies**

**Effect of Other Drugs on Mirabegron:** Mirabegron is transported and metabolized through multiple pathways. Mirabegron is a substrate for CYP3A4, CYP2D6, butyrylcholinesterase, UGT, the efflux transporter P-glycoprotein (P-gp), the transporters organic anion transporting polypeptide 1A2 (OATP1A2), and the influx organic cation transporters (OCT) OCT1, OCT2, and OCT3. Sulfonylurea hypoglycemic agents glibenclamide (a CYP3A4 substrate), gliclazide (a CYP2C9 and CYP3A4 substrate) and tolbutamide (a CYP2C9 substrate) did not affect the *in vitro* metabolism of mirabegron.

**Effect of Mirabegron on Other Drugs:** Studies of mirabegron using human liver microsomes and recombinant human CYP enzymes showed that mirabegron is a moderate and time-

dependent inhibitor of CYP2D6 and a weak inhibitor of CYP3A. Mirabegron is unlikely to inhibit the metabolism of co-administered drugs metabolized by the following cytochrome P450 enzymes: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2E1 because mirabegron did not inhibit the activity of these enzymes at clinically relevant concentrations. Mirabegron did not induce CYP1A2 or CYP3A. Mirabegron inhibited P-gp-mediated drug transport at high concentrations. Mirabegron is predicted not to cause clinically relevant inhibition of OCT-mediated drug transport. Mirabegron did not affect the metabolism of glibenclamide or tolbutamide.

### ***In Vivo Studies***

The effect of co-administered drugs on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of co-medications was studied in single and multiple dose studies. Most drug-drug interactions were studied using a dose of 100 mg mirabegron extended-release tablets given as an extended-release tablet. Interaction studies of mirabegron with metoprolol and with metformin used a 160 mg immediate-release oral formulation.

The effect of ketoconazole, rifampicin, solifenacin, tamsulosin, and metformin on systemic mirabegron exposure is shown in Figure 1.

The effect of mirabegron on metoprolol, desipramine, combined oral contraceptive-COC (ethinyl estradiol-EE, levonorgestrel-LNG), solifenacin, digoxin, warfarin, tamsulosin, and metformin is shown in Figure 2.

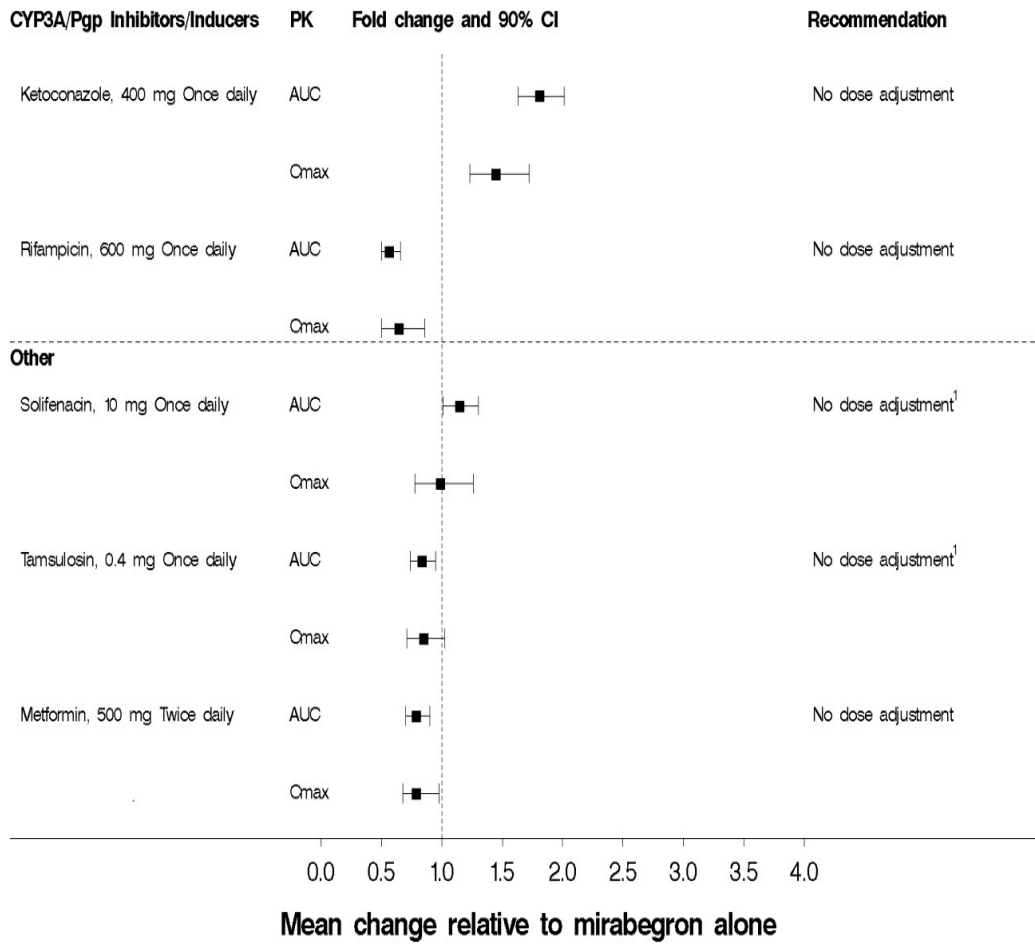
In these studies, the largest increase in mirabegron systemic exposure was seen in the ketoconazole DDI study. As a potent CYP3A4 inhibitor, ketoconazole increased mirabegron  $C_{max}$  by 45% and mirabegron AUC by 80% after multiple dose administration of 400 mg of ketoconazole for 9 days prior to the administration of a single dose of 100 mg mirabegron in 23 male and female healthy subjects.

As a moderate CYP2D6 inhibitor, mirabegron increased the systemic exposure to metoprolol and desipramine:

- Mirabegron increased the  $C_{max}$  of metoprolol by 90% and metoprolol AUC by 229% after multiple doses of 160 mg mirabegron IR tablets once daily for 5 days and a single dose of 100 mg metoprolol tablet in 12 healthy male subjects administered before and concomitantly with mirabegron.
- Mirabegron increased the  $C_{max}$  of desipramine by 79% and desipramine AUC by 241% after multiple dose administration of 100 mg mirabegron once daily for 18 days and a single dose of 50 mg desipramine before and concomitantly with mirabegron in 28 male and female healthy subjects.

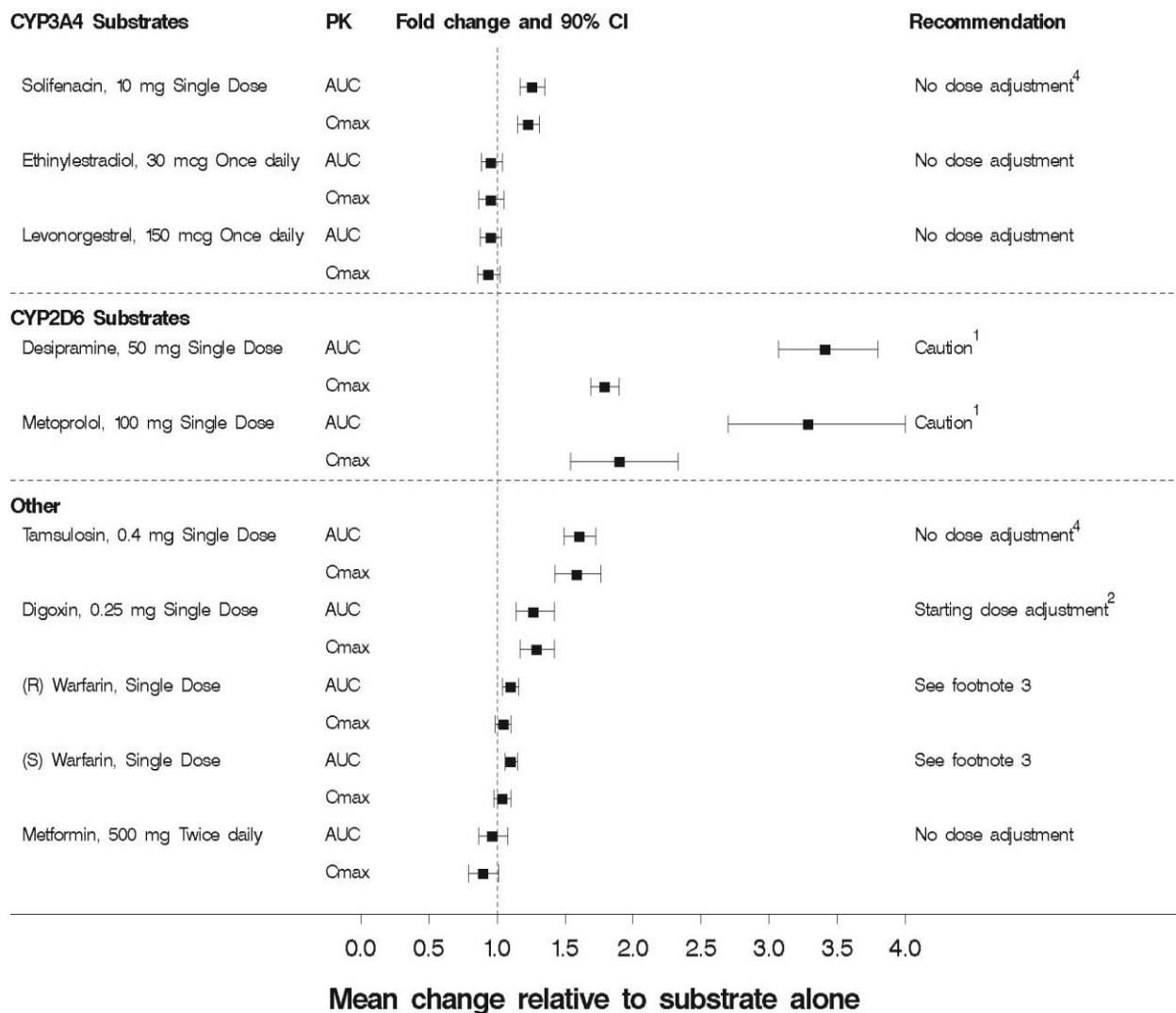
The dose of APO-MIRABEGRON should not exceed 25 mg when co-administered with narrow therapeutic index drugs metabolized by CYP2D6 such as flecainide and propafenone.

**Figure 1 – The Effect of Co-administered Drugs on Exposure of Mirabegron Extended-Release Tablets and Dose Recommendation**



(1) Although no dose adjustment is recommended with solifenacin or tamsulosin based on the lack of pharmacokinetic interaction, APO-MIRABEGRON should be administered with caution to patients taking antimuscarinic medications for the treatment of OAB and in patients with clinically significant BOO because of the risk of urinary retention (see WARNINGS AND PRECAUTIONS).

**Figure 2 – The Effect of Mirabegron Extended-Release Tablets on Exposure of Co-administered Medication**



1) Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates such as metoprolol and desipramine is increased when co-administered with mirabegron ( $\geq 100$  mg). Therefore, caution is advised if mirabegron is co-administered with these drugs as appropriate monitoring and dose adjustment may be necessary. The dose of APO-MIRABEGRON should not exceed 25 mg when co-administered with narrow therapeutic index drugs, such as flecainide and propafenone (see WARNINGS AND PRECAUTIONS; DRUG INTERACTIONS, Overview; and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

2) For patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should initially be prescribed. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect (see DRUG INTERACTIONS, Overview).

3) Warfarin was administered as a single 25 mg dose of the racemate (a mixture of R-warfarin and S-warfarin). Based on this single dose study, mirabegron had no effect on the warfarin pharmacodynamic endpoints such as INR and prothrombin time. However, the effect of mirabegron on multiple doses of warfarin and on warfarin pharmacodynamic end points such as INR and prothrombin time has not been

fully investigated (see DRUG INTERACTIONS, Overview).

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

### **Drugs that Increase Heart Rate or Elevate Blood Pressure**

Caution should be observed if APO-MIRABEGRON is administered with other drugs that also increase heart rate and/or blood pressure (e.g., sympathomimetic or anticholinergic drugs). See WARNINGS AND PRECAUTIONS, Cardiovascular; ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology and Haemodynamics.

### **Drugs that Cause QT/QTc Prolongation**

Caution should be observed if APO-MIRABEGRON is administered with other drugs that also cause QTc prolongation, including, but not limited to, the following: Class IA, IC, and III antiarrhythmics; antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone); antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants (e.g., amitriptyline, imipramine, maprotiline)); opioids (e.g., methadone); macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin, tacrolimus); quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin); antimalarials (e.g., quinine, chloroquine); azole antifungals (e.g., ketoconazole, fluconazole, voriconazole); domperidone; 5-hydroxytryptamine (5-HT)<sub>3</sub> receptor antagonists (e.g., dolasetron, ondansetron); tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, lapatinib); histone deacetylase inhibitors (e.g., vorinostat); beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol). See WARNINGS AND PRECAUTIONS, Cardiovascular; ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology and Haemodynamics.

### **Drug-Food Interactions**

Mirabegron exhibited a decrease in plasma exposure with food that was dependent on meal composition (low-fat versus high-fat). Co-administration of a 50 mg tablet with a high-fat meal reduced mirabegron C<sub>max</sub> and AUC<sub>inf</sub> by 45% and 17%, respectively. A low-fat meal decreased mirabegron C<sub>max</sub> and AUC<sub>inf</sub> by 75% and 51%, respectively. Mirabegron extended-release tablets was administered in the phase 3 studies with or without food and safety and efficacy was shown. Therefore, APO-MIRABEGRON can be taken with or without food at the recommended dose (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **Drug-Laboratory Test Interactions**

At the proposed therapeutic dose of 50 mg, APO-MIRABEGRON is unlikely to affect protein determinations in human urine. A study evaluated the effect of mirabegron and 2 major metabolites on qualitative (protein dipstick) and quantitative protein analysis in human urine. Mirabegron, at urine concentrations of 0.1 mg/mL or higher, interfered with protein dipstick evaluation, depending on reagent used and read-out system. Addition of the 2 major metabolites in urine demonstrated comparable results as mirabegron alone in 4 of 5 tested dipsticks. Mirabegron and the 2 major metabolites in urine can enhance the dipstick signal of a urine

sample containing 50 mg/dL albumin. Mirabegron and the 2 major metabolites did not interfere with quantitative protein analysis in urine. If an unexpected result is obtained with a dipstick test, it is recommended to repeat the analysis with a quantitative protein assay.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

No dose adjustment is necessary for the elderly. The pharmacokinetics of mirabegron are not significantly influenced by age (see ACTION AND CLINICAL PHARMACOLOGY).

APO-MIRABEGRON is not recommended for use in patients with end stage renal disease (ESRD), or in patients with severe hepatic impairment (Child-Pugh Class C) (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). For patients with severe renal impairment or moderate hepatic impairment, see Recommended Dose and Dosage Adjustment.

APO-MIRABEGRON is not recommended for use during pregnancy (see CONTRAINDICATIONS).

### **Recommended Dose and Dosage Adjustment**

The recommended initial dose and usual therapeutic dose of APO-MIRABEGRON is 25 mg administered once daily with or without food. Based on individual patient efficacy and tolerability, the dosage may be increased to a maximum recommended dose of 50 mg once daily with or without food. APO-MIRABEGRON 25 mg is effective within 8 weeks (see CLINICAL TRIALS).

The maximum recommended dose of 50 mg once daily should not be exceeded because of greater than dose-proportional increases in bioavailability (see ACTION AND CLINICAL PHARMACOLOGY, Absorption) and a possible increase in the risk of serious adverse events and adverse events (see ADVERSE REACTIONS).

The dose of APO-MIRABEGRON should not exceed 25 mg once daily with or without food in the following populations:

- Patients with severe renal impairment ( $CL_{cr}$  15 to 29 mL/min or eGFR 15 to 29 mL/min/1.73 m<sup>2</sup>) (see WARNINGS AND PRECAUTIONS, Renal and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency).
- Patients with moderate hepatic impairment (Child-Pugh Class B) (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).
- Patients taking drugs metabolized by CYP2D6 with a narrow therapeutic index, such as flecainide and propafenone (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism; ACTION AND CLINICAL PHARMACOLOGY).

APO-MIRABEGRON is not recommended for use in patients with end stage renal disease (ESRD), or in patients with severe hepatic impairment (Child-Pugh Class C) (see WARNINGS

AND PRECAUTIONS, Renal and Hepatic/Biliary/Pancreatic and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency and Hepatic Insufficiency).

### **Missed Dose**

If a dose is missed, the next scheduled dose should be taken as usual. The patient should not take a double dose to make up for a missed dose.

### **Administration**

APO-MIRABEGRON should be taken once daily with or without food, swallowed whole with water and should not be chewed, divided or crushed.

### **OVERDOSAGE**

Mirabegron has been administered to healthy volunteers at single doses up to 400 mg. At this dose, adverse events reported included palpitations (1 of 6 subjects) and increased pulse rate exceeding 100 bpm (3 of 6 subjects). Multiple doses of mirabegron up to 300 mg daily for 10 days showed increases in pulse rate and systolic blood pressure when administered to healthy volunteers. Treatment for overdose should be symptomatic and supportive. In the event of overdose, pulse rate, blood pressure and ECG monitoring is recommended.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

### **ACTION AND CLINICAL PHARMACOLOGY**

#### **Mechanism of Action**

Mirabegron is a potent and selective beta 3-adrenoceptor (AR) agonist. Mirabegron showed relaxation of bladder smooth muscle in rat and human isolated tissue, increased cAMP concentrations in rat bladder tissue and showed a bladder relaxant effect in rat urinary bladder function models. Mirabegron showed very low intrinsic activity for cloned human beta 1-AR and beta 2-AR *in vitro*. However, oral administration of mirabegron to animals at high doses suggests a potential for cross-activation with beta 1-AR.

Mirabegron increased mean voided volume per micturition and decreased the frequency of non-voiding contractions, without affecting voiding pressure, or residual urine in rat models of bladder overactivity. In a monkey model, mirabegron showed decreased voiding frequency. These results indicate that mirabegron enhances urine storage function by stimulating beta 3-ARs in the bladder. Studies in animal models have shown that mirabegron increases bladder capacity.

During the urine storage phase, when urine accumulates in the bladder, sympathetic nerve stimulation predominates. Noradrenaline is released from nerve terminals, leading predominantly to beta adrenoceptor activation in the bladder musculature, and hence bladder smooth muscle

relaxation.

During the urine voiding phase, the bladder is predominantly under parasympathetic nervous system control. Acetylcholine, released from pelvic nerve terminals, stimulates cholinergic M<sub>2</sub> and M<sub>3</sub> receptors, inducing bladder contraction. The activation of the M<sub>2</sub> pathway also inhibits beta 3-AR induced increases in cAMP. Therefore, beta 3-AR stimulation should not interfere with the voiding process. This was confirmed in rats with partial urethral obstruction, where mirabegron decreased the frequency of non-voiding contractions without affecting the voided volume per micturition, voiding pressure, or residual urine volume.

## **Pharmacodynamics**

### **Urodynamics**

The effects of mirabegron extended-release tablets on maximum flow rate and detrusor pressure at maximum flow rate were assessed in an urodynamic study consisting of 200 male patients with lower urinary tract symptoms (LUTS) and bladder outlet obstruction (BOO).

Administration of mirabegron extended-release tablets at doses of 50 mg and a supra-therapeutic dose of 100 mg once daily for 12 weeks did not adversely affect the maximum flow rate or detrusor pressure at maximum flow rate (see WARNINGS AND PRECAUTIONS).

However, urinary retention has been reported in post-marketing experience in patients taking mirabegron, in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB. APO-MIRABEGRON should be administered with caution to patients with clinically significant BOO.

### **Cardiac Electrophysiology and Haemodynamics**

A randomized, double-blind, placebo- and active-controlled, parallel crossover ECG assessment study was performed in healthy subjects (n = 164 males and 153 females) to evaluate the effect of repeat oral dosing of mirabegron extended-release tablets at the maximum recommended dose (50 mg once daily) and two supra-therapeutic doses (100 and 200 mg once daily) on ECG interval parameters. The supra-therapeutic 100 mg and 200 mg doses represent approximately 2.9-fold and 8.4-fold the C<sub>max</sub> exposure of the maximum recommended 50 mg dose, respectively. ECGs were collected at 18 time points at baseline and on day 10. Each dose level of mirabegron extended-release tablets was evaluated in separate treatment arms each including placebo-control (parallel cross-over design).

The maximum mean differences from placebo in the QTcI interval (individualized heart rate correction) for the male and female sub-groups were as follows:

Placebo-Adjusted Mean Change from Baseline in QTcI with 90% Confidence Intervals on Day 10.

Dose	Female Sub-Group		Male Sub-Group	
	ΔΔQTc (ms)	Time (h)	ΔΔQTc (ms)	Time (h)
50 mg	4.5 (2.2, 6.8)	3.5	3.0 (0.9, 5.0)	4
100 mg	7.7 (5.7, 9.7)	4	4.6 (2.8, 6.5)	4

200 mg	10.4 (7.4, 13.4)	5	7.3 (5.2, 9.4)	4
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A dose-dependent prolongation of the QRS duration was also observed. The maximum mean difference from placebo was 0.6 ms (90% CI 0.3, 0.9) for the 50 mg dose, 1.7 ms (90% CI 1.3, 2.1) at the 100 mg dose, and 4.2 ms (90% CI 3.6, 4.8) for the 200 mg dose in the overall subject population.

Mirabegron extended-release tablets increased heart rate on the ECG in a dose dependent manner across the 50 mg to 200 mg dose range examined (see WARNINGS AND PRECAUTIONS, Cardiovascular; DRUG INTERACTIONS). The maximum mean differences from placebo in heart rate for the male and female sub-groups were as follows:

Placebo-Adjusted Mean Change from Baseline in Heart Rate (bpm) with 90% Confidence Intervals on Day 10.

Dose	Female Sub-Group		Male Sub-Group	
	$\Delta\Delta$ HR (bpm)	Time (h)	$\Delta\Delta$ HR (bpm)	Time (h)
50 mg	8.5 (6.3, 10.8)	5	5.5 (4.3, 6.7)	4.5
100 mg	13.6 (11.0, 16.2)	4	10.9 (8.7, 13.1)	8
200 mg	20.2 (18.3, 22.2)	5	14.4 (12.3, 16.5)	5

Blood pressure was assessed at predose and at 3, 6, 9, and 24 h post-dose on day 9. Mirabegron extended-release tablets was associated with dose-dependent increases in systolic blood pressure and diastolic blood pressure (see WARNINGS AND PRECAUTIONS, Cardiovascular).

Placebo-Adjusted Mean Change from Baseline in Systolic Blood Pressure ( $\Delta\Delta$ SBP) and Diastolic Blood Pressure ( $\Delta\Delta$ DBP) with 95% Confidence Intervals on Day 9:

Dose	$\Delta\Delta$ SBP (mm Hg)	Time (h)	$\Delta\Delta$ DBP (mm Hg)	Time (h)
50 mg	4.0 (1.6, 6.4)	6	3.7 (1.9, 5.4)	6
100 mg	7.7 (5.6, 9.7)	3	4.8 (3.2, 6.3)	24
200 mg	11.6 (8.9, 14.3)	3	7.1 (5.3, 8.9)	24

Daily doses of APO-MIRABEGRON greater than 50 mg/day are not recommended (see DOSAGE AND ADMINISTRATION and OVERDOSAGE).

### Effects on Pulse Rate and Blood Pressure in Patients with OAB

In OAB patients (mean age of 59 years) across three 12-week phase 3 double-blind placebo-controlled studies receiving mirabegron extended-release tablets 50 mg once daily, an increase in mean difference from placebo of approximately 1 bpm for pulse rate and approximately 0.5 to 1 mm Hg in SBP/DBP was observed. Blood pressure and pulse were self-measured by the patients in the morning, prior to taking their once daily dose of mirabegron extended-release tablets, and again in the afternoon. Approximately 40 to 45% of patients in these studies were taking antihypertensive therapies. Changes in pulse rate and blood pressure are reversible upon discontinuation of treatment.

### **Effect on Intraocular Pressure (IOP)**

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

### **Pharmacokinetics**

**Absorption:** After oral administration of mirabegron in healthy volunteers, mirabegron is absorbed to reach peak plasma concentrations ( $C_{max}$ ) at approximately 3.5 hours. The absolute bioavailability increases from 29% at a dose of 25 mg to 35% at a dose of 50 mg. Mean  $C_{max}$  and AUC increase more than dose proportionally over the dose range. This relationship is more apparent at doses above 50 mg. In the overall population of males and females, a 2-fold increase in dose from 50 mg to 100 mg mirabegron increased  $C_{max}$  and  $AUC_{tau}$  by approximately 2.9- and 2.6-fold, respectively, whereas a 4-fold increase in dose from 50 to 200 mg mirabegron increased  $C_{max}$  and  $AUC_{tau}$  by approximately 8.4- and 6.5-fold. Steady state concentrations are achieved within 7 days of once daily dosing with mirabegron. After once daily administration, plasma exposure of mirabegron at steady state is approximately double that seen after a single dose.

#### **Effect of Food**

Co-administration of a 50 mg tablet with a high-fat meal reduced mirabegron  $C_{max}$  and AUC by 45% and 17%, respectively. A low-fat meal decreased mirabegron  $C_{max}$  and AUC by 75% and 51%, respectively. In the phase 3 studies, mirabegron was administered with or without food and demonstrated both safety and efficacy. Therefore, APO-MIRABEGRON can be taken with or without food at the recommended dose (see DOSAGE AND ADMINISTRATION).

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

**Metabolism:** Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Mirabegron is the major circulating component following a single dose of  $^{14}C$ -mirabegron. Two major metabolites were observed in human plasma and are phase 2 glucuronides representing 16% and 11% of total exposure, respectively. These metabolites are not pharmacologically active. Although *in vitro* studies suggest a role for CYP2D6 and CYP3A4 in the oxidative metabolism of mirabegron, *in vivo* results indicate that these isozymes play a limited role in the overall elimination. In healthy subjects who are genotypically poor metabolizers of CYP2D6 substrates (used as a surrogate for CYP2D6 inhibition), mean  $C_{max}$  and  $AUC_{inf}$  of a single 160 mg dose of a mirabegron immediate-release oral formulation were 14% and 19% higher than in extensive metabolizers, respectively. *In vitro* and *ex vivo* studies have shown the involvement of butylcholinesterase, uridine

diphospho-glucuronosyltransferases (UGT) and possibly alcohol dehydrogenase in the metabolism of mirabegron, in addition to CYP3A4 and CYP2D6.

**Excretion:** Total body clearance ( $CL_{tot}$ ) from plasma is approximately 57 L/h following intravenous administration. The terminal elimination half-life ( $t_{1/2}$ ) is approximately 50 hours. Renal clearance ( $CL_R$ ) is approximately 13 L/h, which corresponds to nearly 25% of  $CL_{tot}$ . Renal elimination of mirabegron is primarily through active tubular secretion along with glomerular filtration. The urinary elimination of unchanged mirabegron is dose-dependent and ranges from approximately 6.0% after a daily dose of 25 mg to 12.2% after a daily dose of 100 mg. Following the administration of 160 mg  $^{14}C$ -mirabegron to healthy volunteers, approximately 55% of the dose was recovered in the urine and 34% in the feces. Unchanged mirabegron accounted for 45% of the urinary radioactivity, indicating the presence of metabolites. Unchanged mirabegron accounted for the majority of the fecal radioactivity.

### **Special Populations and Conditions**

**Pediatrics:** The pharmacokinetics of mirabegron in pediatric patients have not been evaluated.

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

**Gender:** The  $C_{max}$  and AUC of mirabegron were approximately 40% to 50% higher in females than in males. When corrected for differences in body weight, the mirabegron systemic exposure is 20% to 30% higher in females compared to males.

**Race:** The pharmacokinetics of mirabegron were comparable between Caucasians and African American Blacks. Cross studies comparison shows that the exposure in Japanese subjects is higher than that in North American subjects. However, when the  $C_{max}$  and AUC were normalized for dose and body weight, the difference is smaller.

**Hepatic Insufficiency:** Following single dose administration of 100 mg mirabegron in volunteers with mild hepatic impairment (Child-Pugh Class A), mean mirabegron  $C_{max}$  and AUC were increased by 9% and 19% relative to volunteers with normal hepatic function. In volunteers with moderate hepatic impairment (Child-Pugh Class B), mean  $C_{max}$  and AUC values were 175% and 65% higher. Mirabegron has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

**Renal Insufficiency:** Following single dose administration of 100 mg mirabegron in volunteers with mild renal impairment (eGFR 60 to 89 mL/min/1.73 m<sup>2</sup> as estimated by MDRD), mean mirabegron  $C_{max}$  and AUC were increased by 6% and 31% relative to volunteers with normal renal function. In volunteers with moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m<sup>2</sup>),  $C_{max}$  and AUC were increased by 23% and 66%, respectively. In patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m<sup>2</sup>), mean  $C_{max}$  and AUC values were 92% and 118% higher. Mirabegron has not been studied in patients with End Stage Renal Disease ( $CL_{cr} < 15$  mL/min or eGFR  $< 15$  mL/min/1.73 m<sup>2</sup> or patients requiring hemodialysis) (see DOSAGE

AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

### **STORAGE AND STABILITY**

Store at room temperature 15°C to 30°C. Protect from moisture.

### **SPECIAL HANDLING INSTRUCTIONS**

None.

### **DOSAGE FORMS, COMPOSITION AND PACKAGING**

APO-MIRABEGRON (mirabegron) extended-release tablets are available as:

- 25 mg brown, capsule shape, biconvex coated tablet. Engraved “APO” on one side, “MB25” on the other side.
- 50 mg yellow, capsule shape, biconvex coated tablet. Engraved “APO” on one side, “MB50” on the other side.

APO-MIRABEGRON (mirabegron) extended-release tablets contain the following excipients: ascorbic acid, D&C yellow #10 aluminum lake, FD&C red #40 aluminum lake (25 mg), hydroxypropyl cellulose, hydroxypropyl methylcellulose, indigotine aluminum lake, magnesium stearate, polyethylene glycol, polyethylene oxide, sunset yellow aluminum lake, and titanium dioxide.

APO-MIRABEGRON (mirabegron) extended-release tablets are available in bottles of 30 and 100 tablets.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

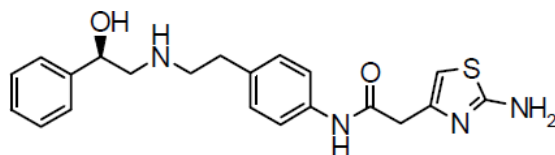
#### Drug Substance

Proper name: mirabegron

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

Molecular formula and molecular mass: C<sub>21</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>S, 396.51 g / mol

Structural formula:



Physicochemical properties: A white crystalline powder that is practically insoluble in water. It is sparingly soluble to slightly soluble in anhydrous ethanol, very slightly soluble to practically insoluble in heptane.

pH of aqueous solution: 7.5 (0.08 mg/mL in water)

pKa: pKa<sub>1</sub> 4.51 and pKa<sub>2</sub> 8.43.

## CLINICAL TRIALS

### Comparative Bioavailability Studies

A randomized, four-period, single-dose (1 x 25 mg), fully-replicate crossover comparative bioavailability study of APO-MIRABEGRON 25 mg extended-release tablets (Apotex Inc.) and PrMYRBETRIQ® 25 mg extended-release tablets (Astellas Pharma Canada, Inc.) was conducted in healthy, adult, Asian male subjects under fasting conditions. Comparative bioavailability data from the 46 subjects that were included in the statistical analysis are presented in the following table:

**SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA**

<b>Mirabegron (1 x 25 mg) Geometric Mean Arithmetic Mean (CV %)</b>				
<b>Parameter</b>	<b>Test<sup>1</sup></b>	<b>Reference<sup>2</sup></b>	<b>% Ratio of Geometric Means</b>	<b>90% Confidence Interval</b>
AUC <sub>0-72h</sub> (ng.h/mL)	89.24 95.36 (37.94)	98.58 105.95 (37.54)	90.5	83.8 - 97.7
AUC <sub>t</sub> (ng.h/mL)	108.91 115.70 (36.12)	119.80 127.94 (35.71)	90.9	84.2 - 98.1
C <sub>max</sub> (ng/mL)	7.93 9.45 (60.56)	8.70 10.38 (62.29)	91.2	79.7 - 104.4
T <sub>max</sub> <sup>3</sup> (h)	4.50 (2.00 - 7.00)	4.38 (1.50 - 8.00)		
T <sub>1/2</sub> <sup>4</sup> (h)	32.88 (24.79)	32.43 (23.21)		
<sup>1</sup> APO-MIRABEGRON (mirabegron) extended-release tablets, 25 mg (Apotex Inc.) <sup>2</sup> PrMYRBETRIQ® (mirabegron) extended-release tablets, 25 mg (Astellas Pharma Canada, Inc.) <sup>3</sup> Expressed as the median (range) only <sup>4</sup> Expressed as the arithmetic mean (CV%) only				

A randomized, four-period, single-dose (1 x 25 mg), fully-replicate crossover comparative bioavailability study of APO-MIRABEGRON 25 mg extended-release tablets (Apotex Inc.) and PrMYRBETRIQ® 25 mg extended-release tablets (Astellas Pharma Canada, Inc.) was conducted in healthy, adult, Asian male subjects under high-fat/high-calorie fed conditions. Comparative bioavailability data from the 46 subjects that were included in the statistical analysis are presented in the following table:

**SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA**

<b>Mirabegron (1 x 25 mg) Geometric Mean Arithmetic Mean (CV %)</b>				
<b>Parameter</b>	<b>Test<sup>1</sup></b>	<b>Reference<sup>2</sup></b>	<b>% Ratio of Geometric Means</b>	<b>90% Confidence Interval</b>
AUC <sub>0-72h</sub> (ng.h/mL)	51.88 54.65 (30.8)	55.59 58.74 (31.1)	93.3	88.6 - 98.3
AUC <sub>i</sub> (ng.h/mL)	63.66 66.69 (29.7)	68.38 71.87 (29.6)	93.1	88.4 - 98.1
C <sub>max</sub> (ng/mL)	3.40 3.83 (51.3)	3.78 4.29 (52.6)	89.9	81.0 - 99.8
T <sub>max</sub> <sup>3</sup> (h)	4.88 (2.00 - 16.00)	5.00 (3.00 - 8.00)		
T <sub>1/2</sub> <sup>4</sup> (h)	30.48 (26.60)	31.03 (25.07)		
<sup>1</sup> APO-MIRABEGRON (mirabegron) extended-release tablets, 25 mg (Apotex Inc.) <sup>2</sup> PrMYRBETRIQ® ( mirabegron) extended-release tablets, 25 mg (Astellas Pharma Canada, Inc.) <sup>3</sup> Expressed as the median (range) only <sup>4</sup> Expressed as the arithmetic mean (CV%) only				

A randomized, four-period, single-dose (1 x 50 mg), fully-replicate crossover comparative bioavailability study of APO-MIRABEGRON 50 mg extended-release tablets (Apotex Inc.) and PrMYRBETRIQ® 50 mg extended-release tablets (Astellas Pharma Canada, Inc.) was conducted in healthy, adult, Asian male subjects under fasting conditions. Comparative bioavailability data from the 42 subjects that were included in the statistical analysis are presented in the following table:

#### SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

<b>Mirabegron (1 x 50 mg) Geometric Mean Arithmetic Mean (CV %)</b>				
<b>Parameter</b>	<b>Test<sup>1</sup></b>	<b>Reference<sup>2</sup></b>	<b>% Ratio of Geometric Means</b>	<b>90% Confidence Interval</b>
AUC <sub>0-72h</sub> (ng.h/mL)	243.40 269.40 (47.47)	271.98 290.91 (39.91)	89.5	83.0 - 96.5
AUC <sub>i</sub> (ng.h/mL)	288.46 316.84 (46.00)	319.05 340.35 (68.32)	90.4	84.1 - 97.2
C <sub>max</sub> (ng/mL)	24.53 32.52 (77.84)	28.52 35.25 (68.32)	86.0	74.7 - 99.0
T <sub>max</sub> <sup>3</sup> (h)	4.63 (2.00 - 8.00)	4.00 (1.50 - 6.00)		
T <sub>1/2</sub> <sup>4</sup> (h)	30.08 (19.31)	29.57 (17.25)		

<b>Mirabegron (1 x 50 mg) Geometric Mean Arithmetic Mean (CV %)</b>				
<b>Parameter</b>	<b>Test<sup>1</sup></b>	<b>Reference<sup>2</sup></b>	<b>% Ratio of Geometric Means</b>	<b>90% Confidence Interval</b>
<sup>1</sup> APO-MIRABEGRON (mirabegron) extended-release tablets, 50 mg (Apotex Inc.) <sup>2</sup> PrMYRBETRIQ <sup>®</sup> (mirabegron) extended-release tablets, 50 mg (Astellas Pharma Canada, Inc.) <sup>3</sup> Expressed as the median (range) only <sup>4</sup> Expressed as the arithmetic mean (CV%) only				

A randomized, four-period, single-dose (1 x 50 mg), fully-replicate crossover comparative bioavailability study of APO-MIRABEGRON 50 mg extended-release tablets (Apotex Inc.) and PrMYRBETRIQ<sup>®</sup> 50 mg extended-release tablets (Astellas Pharma Canada, Inc.) was conducted in healthy, adult, Asian male subjects under high-fat/high-calorie fed conditions. Comparative bioavailability data from the 47 subjects that were included in the statistical analysis are presented in the following table:

**SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA**

<b>Mirabegron (1 x 50 mg) Geometric Mean Arithmetic Mean (CV %)</b>				
<b>Parameter</b>	<b>Test<sup>1</sup></b>	<b>Reference<sup>2</sup></b>	<b>% Ratio of Geometric Means</b>	<b>90% Confidence Interval</b>
AUC <sub>0-72h</sub> (ng.h/mL)	142.60 152.72 (37.76)	151.73 167.97 (42.31)	94.0	87.8 - 100.6
AUC <sub>I</sub> (ng.h/mL)	170.58 180.91 (35.94)	180.63 198.62 (41.07)	94.4	88.4 - 100.9
C <sub>max</sub> (ng/mL)	11.14 13.60 (65.20)	12.58 17.30 (85.92)	88.5	77.3 - 101.4
T <sub>max</sub> <sup>3</sup> (h)	5.50 (2.00 - 10.00)	5.00 (3.00 - 8.00)		
T <sub>1/2</sub> <sup>4</sup> (h)	29.17 (18.74)	28.66 (16.41)		
<sup>1</sup> APO-MIRABEGRON (mirabegron) extended-release tablets, 50 mg (Apotex Inc.) <sup>2</sup> PrMYRBETRIQ <sup>®</sup> (mirabegron) extended-release tablets, 50 mg (Astellas Pharma Canada, Inc.) <sup>3</sup> Expressed as the median (range) only <sup>4</sup> Expressed as the arithmetic mean (CV%) only				

## **Study Demographics and Trial Design**

**Table 3 – Summary of Patient Demographics For Clinical Trials In Specific Indication**

<b>Study #</b>	<b>Trial design and duration</b>	<b>Dosage, route of administration</b>	<b>Number of study subjects randomized/ completed</b>	<b>Mean age (Range)</b>	<b>Gender %</b>
178-CL-046	Parallel-group, multinational, multicenter study with a single-blind placebo run-in period of 2 weeks followed by a randomized, double- blind, active and placebo-controlled 12- week treatment period.	Placebo oral, qd	497/453	Mean: 59.1 years Range: 18-90 years ≥ 65 years: 37.0% ≥ 75 years: 8.5%	Female: 72.0% Male: 28.0%
		Mirabegron extended-release tablets 50 mg, oral, qd	497/440		
		Mirabegron extended-release tablets 100 mg, oral, qd	498/453		
		Tolterodine ER 4 mg, oral, qd	495/445		
178-CL-047	Parallel-group, multinational, multicenter study with a single-blind placebo run-in period of 2 weeks followed by a randomized, double- blind, placebo-controlled 12- week treatment period.	Placebo oral, qd	454/385	Mean: 60.2 years Range: 20-95 years ≥ 65 years: 39.7% ≥ 75 years: 15.1%	Female: 74.8% Male: 25.2%
		Mirabegron extended-release tablets 50 mg, oral, qd	442/383		
		Mirabegron extended-release tablets 100 mg, oral, qd	433/380		
178-CL-074	Parallel-group, multinational, multicenter study with a single-blind placebo run-in period of 2 weeks followed by a randomized,	Placebo oral, qd	433/367	Mean: 59.1 years Range: 21-91 years ≥ 65 years: 37.2% ≥ 75 years: 9.9%	Female: 68.5% Male: 31.5%
		Mirabegron extended-release tablets 25 mg, oral, qd	433/387		

Study #	Trial design and duration	Dosage, route of administration	Number of study subjects randomized/ completed	Mean age (Range)	Gender %
	double- blind, placebo-controlled 12-week treatment period.	Mirabegron extended-release tablets 50 mg, oral, qd	440/386		
178-CL-049	Parallel-group, multinational, multicenter long-term study with a single- blind placebo run-in period of 2 weeks followed by a randomized, double- blind, active-controlled 12-month treatment period.	Mirabegron extended-release tablets 50 mg, oral, qd  Mirabegron extended-release tablets 100 mg, oral, qd  Tolterodine ER 4 mg, oral, qd	815/629  824/645  813/621	Mean: 59.7 years Range: 21-87 years ≥ 65 years: 37.3% ≥ 75 years: 9.7%	Female: 74.2% Male: 25.8%

Mirabegron extended-release tablets was evaluated in three, 12-week, double-blind, randomized, placebo-controlled, parallel group, multicenter clinical trials in patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency (Studies 178-CL-046, -047, and -074). Entry criteria required that patients had symptoms of overactive bladder for at least 3 months duration, at least 8 micturitions per day, and at least 3 episodes of urgency with or without incontinence over a 3-day period. The majority of patients were Caucasian (94%) and female (72%) with a mean age of 59 years (range 18 to 95 years). The population included both naïve patients who had not received prior antimuscarinic pharmacotherapy for overactive bladder (48%) and those who had received prior antimuscarinic pharmacotherapy for OAB (52%).

In Study 178-CL-046, patients were randomized to placebo, mirabegron extended-release tablets 50 mg, mirabegron extended-release tablets 100 mg, or an active control once daily. In Study 178-CL-047, patients were randomized to placebo, mirabegron extended-release tablets 50 mg or mirabegron extended-release tablets 100 mg once daily. In Study 178-CL-074, patients were randomized to placebo, mirabegron extended-release tablets 25 mg or mirabegron extended-release tablets 50 mg once daily.

The co-primary efficacy endpoints in all 3 trials were (1) change from baseline to end of treatment (Week 12) in mean number of incontinence episodes per 24 hours and (2) change from baseline to end of treatment (Week 12) in mean number of micturitions per 24 hours, based on a 3-day micturition diary. Secondary endpoints included change from baseline to end of treatment (Week 12) in mean volume voided per micturition, change from baseline to week 4 in mean

number of incontinence episodes per 24 hours, change from baseline to week 4 in mean number of micturitions per 24 hours, mean level of urgency, mean number of urgency incontinence episodes per 24 hours, mean number of urgency episodes and quality of life measures.

## Study Results

Mirabegron extended-release tablets demonstrated statistically significant improvements compared to placebo for both co-primary endpoints (see Table 4).

Mirabegron extended-release tablets 25 mg was effective in treating the symptoms of OAB within 8 weeks, and mirabegron extended-release tablets 50 mg was effective in treating the symptoms of OAB within 4 weeks. Efficacy of both 25 mg and 50 mg doses of mirabegron extended-release tablets was maintained through the 12-week treatment period.

Figures 3 through 8 show the co-primary endpoints, mean change from baseline (BL) over time in number of incontinence episodes per 24 hours and mean change from baseline over time in number of micturitions per 24 hours, in Studies 178-CL-046, -047 and -074.

**Table 4 – Co-primary and Selected Secondary Efficacy Endpoints at End of Treatment, Primary Phase 3 Studies**

Parameter	Study 178-CL-046			Study 178-CL-047		Study 178-CL-074		
	Placebo	Mirabegron Extended- Release Tablets 50 mg	Tolterodine ER 4 mg	Placebo	Mirabegron Extended- Release Tablets 50 mg	Placebo	Mirabegron Extended- Release Tablets 25 mg	Mirabegron Extended- Release Tablets 50 mg
<b>Mean Number of Incontinence Episodes per 24 Hours (FAS-I) (Co-Primary)</b>								
n	291	293	300	325	312	262	254	257
Mean baseline	2.67	2.83	2.63	3.03	2.77	2.43	2.65	2.51
Mean change from baseline†	-1.17	-1.57	-1.27	-1.13	-1.47	-0.96	-1.36	-1.38
Mean difference from placebo†	--	-0.41	-0.10	--	-0.34	--	-0.40	-0.42
95% Confidence	--	(-0.72, -0.09)	(-0.42, 0.21)	--	(-0.66, -0.03)	--	(-0.74, -0.06)	(-0.76, -0.08)

Parameter	Study 178-CL-046			Study 178-CL-047		Study 178-CL-074		
	Placebo	Mirabegron Extended- Release Tablets 50 mg	Tolterodine ER 4 mg	Placebo	Mirabegron Extended- Release Tablets 50 mg	Placebo	Mirabegron Extended- Release Tablets 25 mg	Mirabegron Extended- Release Tablets 50 mg
Interval								
p-value	--	0.003#	0.11	--	0.026#	--	0.005#	0.001#
<b>Mean Number of Micturitions per 24 Hours (FAS) (Co-Primary)</b>								
n	480	473	475	433	425	415	410	426
Mean baseline	11.71	11.65	11.55	11.51	11.80	11.48	11.68	11.66
Mean change from baseline†	-1.34	-1.93	-1.59	-1.05	-1.66	-1.18	-1.65	-1.60
Mean difference from placebo†	--	-0.60	-0.25	--	-0.61	--	-0.47	-0.42
95% Confidence Interval	--	(-0.90, -0.29)	(-0.55, 0.06)	--	(-0.98, -0.24)	--	(-0.82, -0.13)	(-0.76, -0.08)
p-value	--	<0.001#	0.11	--	0.001#	--	0.007#	0.015#
<b>Mean Volume Voided (mL) per Micturition (FAS) (Secondary)</b>								
n	480	472	475	433	424	415	410	426
Mean baseline	156.7	161.1	158.6	157.5	156.3	164.0	165.2	159.3
Mean change from baseline†	12.3	24.2	25.0	7.0	18.2	8.3	12.8	20.7
Mean difference from placebo†	--	11.9	12.6	--	11.1	--	4.6	12.4
95% Confidence Interval	--	(6.3, 17.4)	(7.1, 18.2)	--	(4.4, 17.9)	--	(-1.6, 10.8)	(6.3, 18.6)

Parameter	Study 178-CL-046			Study 178-CL-047		Study 178-CL-074		
	Placebo	Mirabegron Extended- Release Tablets 50 mg	Tolterodine ER 4 mg	Placebo	Mirabegron Extended- Release Tablets 50 mg	Placebo	Mirabegron Extended- Release Tablets 25 mg	Mirabegron Extended- Release Tablets 50 mg
n								
p-value	--	<0.001#	<0.001*	--	0.001#	--	0.15‡	< 0.001#
<b>Mean Level of Urgency (FAS) (Secondary)</b>								
n	480	472	473	432	425	413	410	426
Mean baseline	2.37	2.40	2.41	2.45	2.45	2.36	2.37	2.41
Mean change from baseline†	-0.22	-0.31	-0.29	-0.08	-0.19	-0.15	-0.22	-0.29
Mean difference from placebo†	--	-0.09	-0.07	--	-0.11	--	-0.07	-0.14
95% Confide nce Interval	--	(-0.17, - 0.02)	(-0.15, 0.01)	--	(-0.18, - 0.04)	--	(-0.15, 0.01)	(-0.22, - 0.06)
p-value	--	0.018*	0.085	--	0.004*	--	0.083‡	< 0.001‡

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

\* Statistically significantly superior compared to placebo at the 0.05 level without multiplicity adjustment.

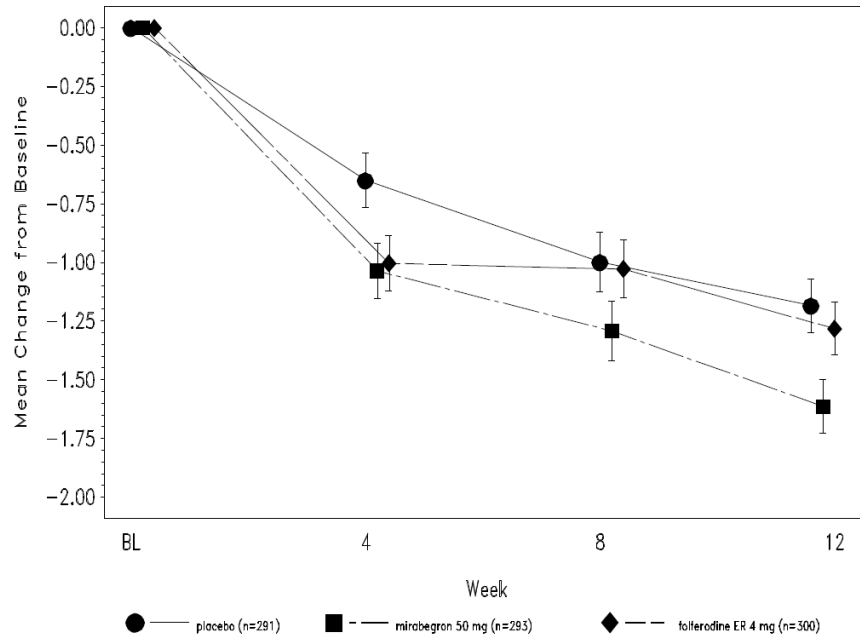
# Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment.

‡ Not statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment.

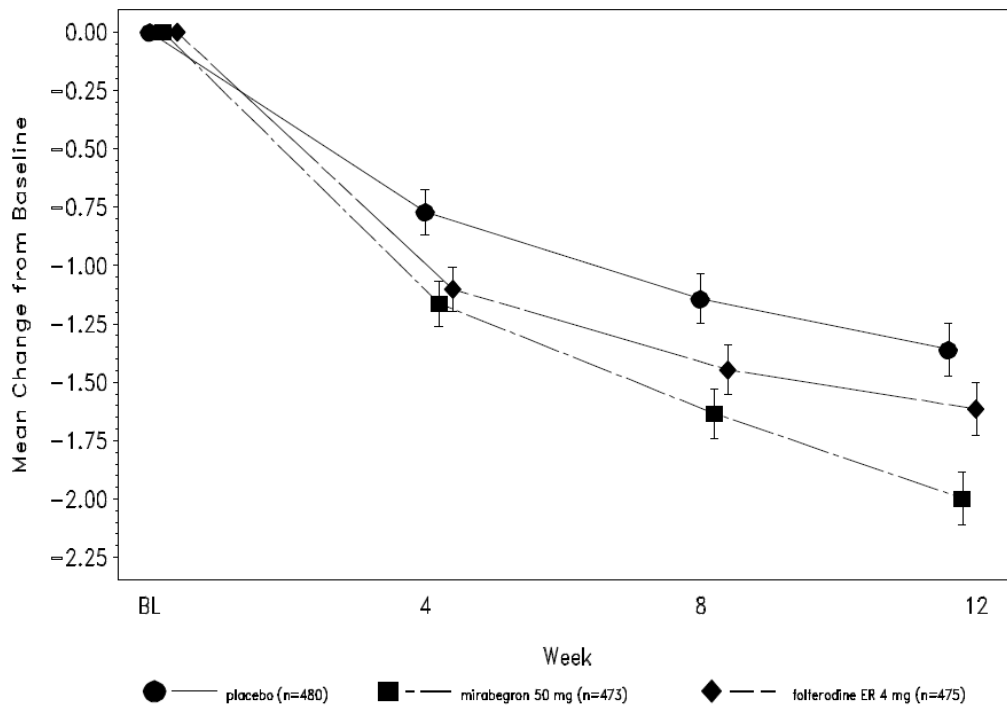
FAS: Full analysis set, all randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 post-baseline visit diary with a micturition measurement.

FAS-I: Subset of FAS who also had at least 1 incontinence episode in the baseline diary. Khullar et al, 2013; Nitti et al, 2012

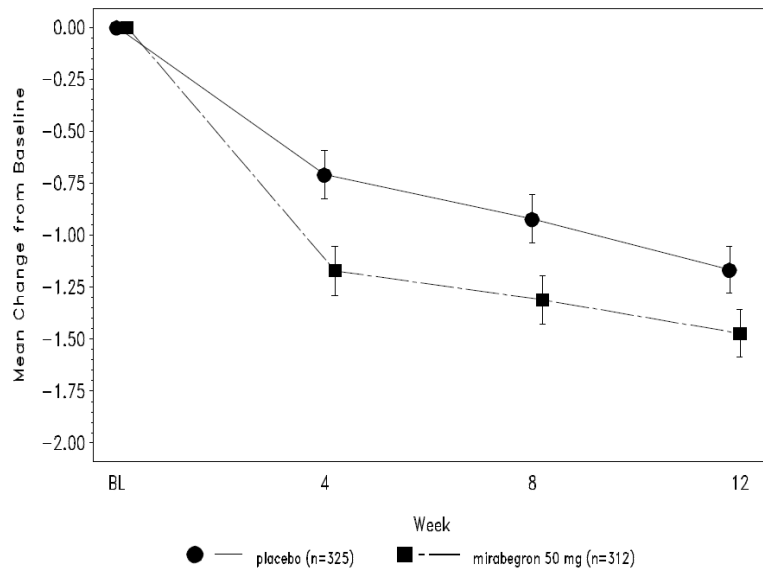
**Figure 3. Mean (SE) Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours –Study 178-CL-046**



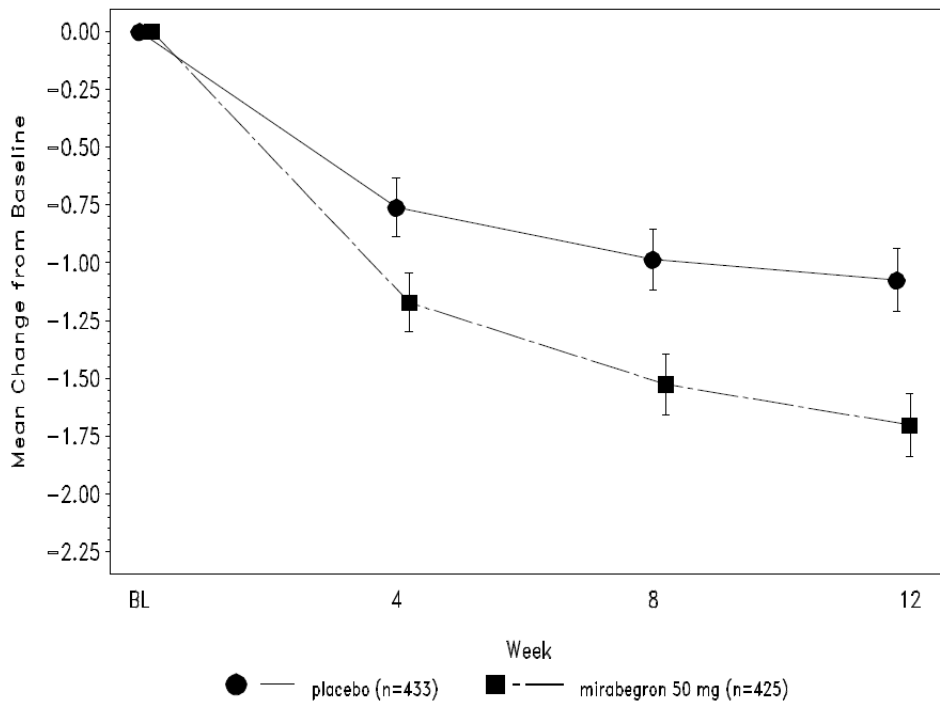
**Figure 4. Mean (SE) Change from Baseline in Mean Number of Micturitions per 24 Hours - Study 178-CL-046**



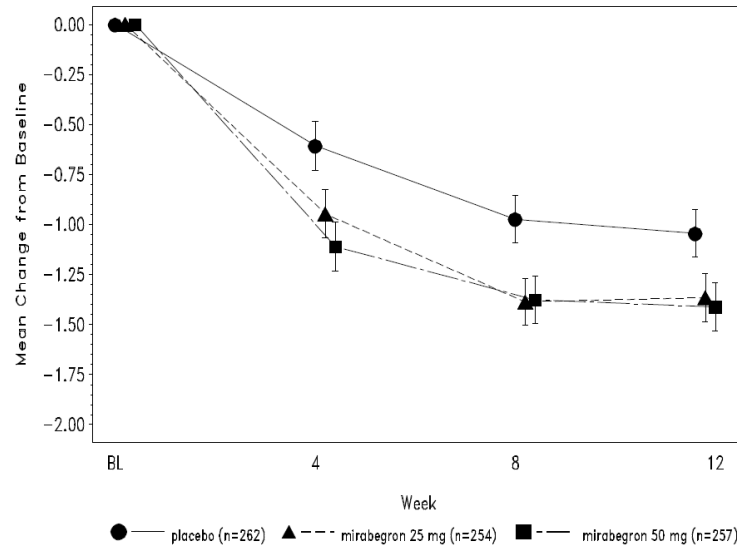
**Figure 5. Mean (SE) Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours - Study 178-CL-047**



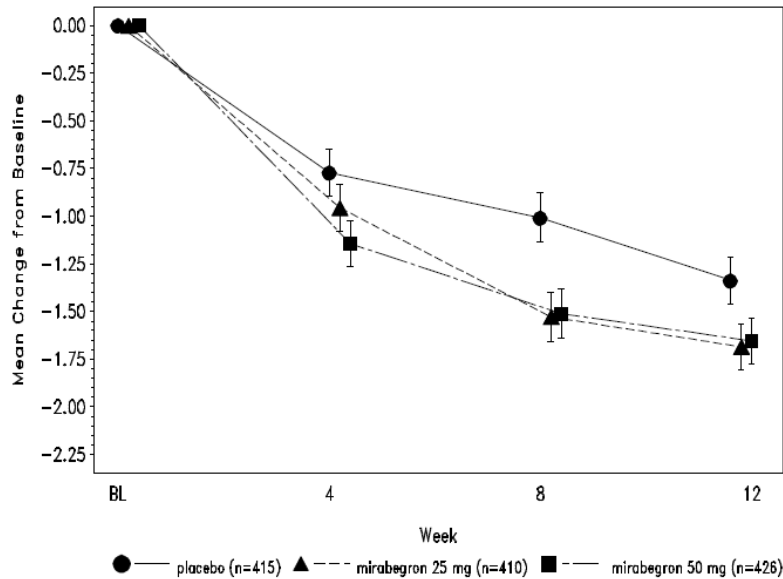
**Figure 6. Mean (SE) Change from Baseline in Mean Number of Micturitions per 24 Hours - Study 178-CL-047**



**Figure 7. Mean (SE) Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours - Study 178-CL-074**



**Figure 8. Mean (SE) Change from Baseline in Mean Number of Micturitions per 24 Hours - Study 178-CL-074**



## DETAILED PHARMACOLOGY

### Agonistic Activity and Selectivity to Human Beta Adrenoceptor

In a receptor binding study using membrane fractions from Chinese hamster ovary (CHO) cells expressing human beta adrenoceptor (AR) subtypes, mirabegron showed high affinity for the human beta 3-AR (105-fold higher affinity for beta 3-AR versus beta 1-AR and 33-fold higher

affinity for beta 3-AR versus beta 2-AR) as shown in Table 5.

**Table 5 – Affinity of Mirabegron for Human Beta-Adrenoceptor Subtypes**

Test article	Ki (nmol/L)		
	Beta 1	Beta 2	Beta 3
Mirabegron	4,200 ± 900	1,300 ± 300	40 ± 20.2

Ki values are expressed as the mean ± SE of 3 runs.

Agonistic activity of mirabegron to beta AR subtypes (beta 1-, 2-, and 3-AR) from human was examined with CHO cells expressing each of these beta AR subtypes. Intracellular cyclic adenosine monophosphate (cAMP) concentrations were used as an indicator of beta-AR agonistic activity. Mirabegron showed an agonistic activity to the human beta 3-AR with a 50% effective concentration (EC<sub>50</sub>) value of 1.5 nmol/L. The intrinsic activity at the human beta 3-AR, defined as the cAMP concentration relative to the maximum response induced by isoproterenol, for mirabegron was 0.8, indicating that mirabegron is a full agonist at this receptor subtype. On the other hand, mirabegron showed intrinsic activities for human beta 1- and beta 2-AR of 0.1, and 0.2, respectively, and the potency *in vitro* was low as compared to that at the human beta 3-AR. However, oral administration of mirabegron to animals at high doses suggests a potential for cross-activation with beta 1-AR.

#### **Affinity for Receptors Other than Beta Adrenoceptor**

Mirabegron showed low affinity for alpha 1A-AR, muscarinic M<sub>2</sub> receptors, sodium channel site 2, dopamine transporters, and norepinephrine transporters.

#### **Bladder Relaxant Effect**

Mirabegron showed a relaxant effect in isolated rat and human bladder strips precontracted with carbachol (EC<sub>50</sub> = 5.1 and 0.78 mcmmol/L, respectively). In addition, mirabegron induced relaxation of rat bladder strips precontracted with potassium chloride (KCl) with an EC<sub>50</sub> value of 11 mcmmol/L. The relaxant effect of mirabegron in bladder tissues from the rat was not affected by selective beta 1- or beta 2-AR antagonists. Further, mirabegron increased cAMP concentrations in rat bladder tissue. These findings indicate that the relaxant effect of mirabegron was mediated by a beta 3-AR-induced increase in bladder cAMP levels in rats; a similar mechanism is extrapolated to be present in humans [Takeda et al, 1999; Igawa et al, 2001].

#### **Effect on Bladder Function**

Effects on bladder function *in vivo* were studied in anesthetized and in conscious animals. In anesthetized animals, bladder function parameters were assessed at different levels of bladder filling. In conscious animals, the effects of mirabegron on micturition frequency and bladder capacity were studied in monkeys after water-loading and in rats with a hyperactive bladder due to cerebral infarction. In addition, the effects of mirabegron in conscious rats with bladder outlet obstruction were assessed using cystometry.

Studies were also performed to assess the effect of mirabegron on the frequency of bladder contractions *in vivo*. In anesthetized rats with a bladder pressure set at about 40 mm Hg, voiding reflexes were initiated at a frequency of about 6 times per 10 min. Under these conditions, mirabegron decreased the frequency but not the force of rhythmic bladder contractions at a dose of 3 mg/kg iv. In contrast, oxybutynin increased the bladder contractile frequency but decreased the contractile force. In rats with partial urethral obstruction, mirabegron decreased the frequency of non-voiding contractions without affecting voided volume per micturition, voiding pressure, or residual urine volume at doses  $\geq 1$  mg/kg iv. Antimuscarinics decreased voided volume per micturition and increased residual urine volume, without affecting non-voiding contractions. These data showed that mirabegron alters the frequency of non-voiding contractions but does not affect the force of contraction.

To investigate whether the pharmacological effects of mirabegron were present following oral or gastrointestinal administration, further studies were performed. In rats intraduodenal (id) administration of mirabegron (3 and 10 mg/kg, id) decreased the frequency of rhythmic bladder contractions. Rats orally administered mirabegron for 14 days followed by intraduodenal instillation of mirabegron showed no attenuation in the decreased frequency of rhythmic bladder contractions. In water-loaded conscious cynomolgus monkeys, mirabegron, at a dose of 3 mg/kg, po increased the functional bladder capacity and decreased the voiding frequency (1 and 3 mg/kg po). Although the water-loaded conscious cynomolgus monkey model is not established as a model of bladder overactivity, mirabegron did show an increase in bladder capacity at a dose that was within the therapeutic range (1.2-fold higher than the human equivalent dose at maximum recommended human dose). In the rat cerebral infarction model for bladder hyperactivity, mirabegron increased bladder capacity at a dose of 3 mg/kg po.

These data show that mirabegron can relax urinary bladder during filling in the rat, dog and monkey. These data are consistent with beta 3-AR agonists in bladder function models [Woods et al, 2001] and indicate that mirabegron relaxes the bladder and increases the storage function during filling.

In the bladder outlet obstruction model, mirabegron reduced urination frequency and non-voiding bladder activity without affecting voiding pressure.

## **TOXICOLOGY**

Nonclinical studies have identified target organs of toxicity that are consistent with clinical observations. Transient increases in liver enzymes and hepatocyte changes (necrosis and decrease in glycogen particles) were seen in rats. An increase in heart rate was observed in rats, rabbits, dogs and monkeys.

Genotoxicity and carcinogenicity studies have shown no genotoxic or carcinogenic potential *in vivo*.

In the female rat fertility study, at a lethal dose of 300 mg/kg/day, the number of pregnant females was reduced by 12%. No effects on female fertility or early embryogenesis were observed at a human equivalent dose of 19.2-fold the Maximum Recommended Human Dose

(MRHD) (estimated systemic exposure 21.5-fold the human exposure at MRHD). In the male rat fertility study, animals dosed for a total period of 14 days prior to mating showed no effect on copulation index or fertility index at doses up to 100 mg/kg/day (93.3-fold the human systemic exposure at MRHD). However, due to the short duration of the treatment period, effects on male fertility cannot be ruled out.

A reversible increased incidence of a skeletal finding of wavy rib was observed at doses that were greater than or equal to 100 mg/kg/day. No embryo-fetal toxicity was observed in rats at systemic exposures that were 6.2-fold higher than the human systemic exposure at the MRHD.

In the rabbit embryo-fetal development study, reduced fetal weight was observed at doses equal to or greater than 10 mg/kg/day. At the lethal dose of 30 mg/kg/day, fetal findings of dilated aorta and cardiomegaly mediated by beta 1-AR cross activation were reported. No embryo-fetal toxicity was observed in rabbits at systemic exposures that were 0.7-fold the human systemic exposure at the MRHD.

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

Moderate dermal sensitization was observed.

Systems comparison of findings between test species and the corresponding safety factor for each finding can be found in Table 6. Data presented in the parenthesis represent the safety factors for each finding based on AUC.

**Table 6 – Systemic Toxicology Findings and Safety Factors: Species**

Body System	Findings in Toxicology Studies (Safety Factors)			
	Rat	Rabbit	Dog	Monkey
CNS	Lacrimation, prone position (0.2)	NT	NT	↓ activity, ptosis (2.1)
Ocular	Mydriasis (44.2)	Mild local Irritant	Ocular Discharge (0.5)	No Effect (7.9)
Respiratory	NT	NT	↑ Respiratory Rate (0.2*)	No Effect (7.9)
Heart Rate	NT	↑ Heart Rate (1.2)*	↑ Heart Rate (0.5)	No Effect (7.9)
QTc Interval	NT	NT	↑ QTcB Interval (2.7)	No Effect (7.9)
Blood Pressure	NT	NT	↓ BP (0.02*)	No Effect (7.9)
Vascular	NT	Slight local irritation iv.	Facial flushing (<0.5)	NT
Gastrointestinal	Loose Stools (1.7)	NT	Emesis (2.7)	Emesis (11.5*)

Body System	Findings in Toxicology Studies (Safety Factors)			
	Rat	Rabbit	Dog	Monkey
Liver	↑ Liver weight (1.7)	NT	No Effect (13.8)	No Effect (7.9)
Kidney	No Effect (58.7)	NT	No Effect (13.8)	No Effect (7.9)
Skin/Dermal	NT	No local effect	No Effect (13.8)	No Effect (7.9)
Immune	No Effect (58.7)	NT	No Effect (13.8)	No Effect (7.9)
Musculoskeletal	No Effect (58.7)	NT	No Effect (13.8)	No Effect (7.9)
<sup>a</sup> Reproductive (Paternal)	No Effect (93.2)	NT	NT	NT
Reproductive (Maternal)	↓ Fertility (19.2*)	NT	NT	NT
Embryo-fetal	↓ food consumption and body weight gain (6.2)	↓ body weight gain (0.7)	NT	NT
Embryo-fetal	↓ ossification (6.2)	↓ fetal body wt (0.7)	NT	NT
Post-natal	↓ pup body wt, viability (5.8)	NT	NT	NT
Hematology	↓ platelets (0.2)	NT	No Effect (13.8)	No Effect (7.9)
Clinical Chemistry	↑ ALT (1.7)	NT	No Effect (13.8)	No Effect (7.9)
Urinalysis	No Effect (58.7)	NT	No Effect (13.8)	No Effect (7.9)

Data in parentheses are the safety factors for each organ system listed. Safety factors were calculated by dividing the animal systemic exposure (animal AUC) at NOAEL, by the human mean AUC at the MRHD. \*Where AUC data was not available, the safety factor was calculated by dividing the human equivalent dose for the NOAEL by the MHRD. <sup>a</sup>Male animals were administered mirabegron for 14 days prior to mating.

↑: increased; ↓: decreased; NT: not tested

## REFERENCES

1. Aizawa N, Homma Y, Igawa Y. Effects of Mirabegron, a Novel  $\beta$ 3-Adrenoceptor Agonist, on Primary Bladder Afferent Activity and Bladder Microcontractions in Rats Compared With the Effects of Oxybutynin. *Eur Urol*. 2012; 62:1165-73.
2. Bhide AA, et al. Use of mirabegron in treating overactive bladder. *Int Urogynecol J*. 2012 Oct;23(10):1345-8. Epub 2012 Mar 13.
3. Chapple CR, Kaplan SA, Mitcheson D, et al. Randomized Double-blind, Active-controlled Phase 3 Study to Assess 12-Month Safety and Efficacy of Mirabegron, a  $\beta$ (3)-Adrenoceptor Agonist, in Overactive Bladder. *Eur Urol*. 2013 Feb;63(2):296-305.
4. Dickinson J, Lewand M, Sawamoto T, et al. Effect of Renal or Hepatic Impairment on the Pharmacokinetics of Mirabegron. *Clin Drug Investig*. 2013 Jan;33(1):11-23.
5. Eltink C, Lee J, Schaddelee M, et al. Single dose pharmacokinetics and absolute bioavailability of Mirabegron, a  $\beta$ 3-adrenoceptor agonist for treatment of overactive bladder. *J Clin Pharm and Thera*; 2012; epub DOI 10.5414/CP201782
6. Igawa Y, Yamazaki Y, Takeda H, Kaidoh K, Akahane M, Ajisawa Y, et al. Relaxant effects of isoproterenol and selective beta 3-adrenoceptor agonists on normal, low compliant and hyperreflexic human bladders. *J Urol*. 2001;165:240-4.
7. Khullar V, Amarenco G, Angulo JC, et al. Efficacy and Tolerability of Mirabegron, a  $\beta$ (3)-Adrenoceptor Agonist, in Patients with Overactive Bladder: Results from a Randomised European-Australian Phase 3 Trial. *Eur Urol*. 2013 Feb;63(2):283-95.
8. Malik M, Gelderen EM, Lee JH, et al. Proarrhythmic Safety of Repeat Doses of Mirabegron in Healthy Subjects: A Randomized, Double-Blind, Placebo-, and Active-Controlled Thorough QT Study. *Nature*; 2012; 92/6:696-706.
9. Nitti V, Auerbach S, Martin N, et al. Results of a randomized Phase III trial of Mirabegron in patients with overactive bladder. *J Urol*. 2012 Oct 15
10. Takasu T, Ukai M, Sato S, et al. Effect of (R)-2-(2-(2-Aminothiazol-4-yl)-4'-{2-[(2-hydroxy-2-phenylethyl)amino]ethyl} Acetanilide (YM178), a Novel Selective  $\beta$ 3-Adrenoceptor Agonist, on Bladder Function. *J Pharm and Exper Ther*; 2007; 321: 642-647.
11. Takeda M, Obara K, Mizusawa T, Tomita Y, Arai K, Tsutsui T, et al. Evidence for beta 3-adrenoceptor subtypes in relaxation of the human urinary bladder detrusor: analysis by molecular biological and pharmacological methods. *J Pharmacol Exp Ther*. 1999; 288:1367-73
12. Woods M, Carson N, Norton NW, Sheldon JH, Argentieri TM. Efficacy of the beta 3-adrenergic receptor agonist CL-316243 on experimental bladder hyperreflexia and detrusor

instability in the rat. J Urol. 2001;166:1142-7.

13. PrMYRBETRIQ® (mirabegron extended-release tablets, 25 mg and 50 mg), submission control 192447, Product Monograph, Astellas Pharma Canada, Inc. (JUN 02, 2016)

**PART III: CONSUMER INFORMATION**

**Pr APO-MIRABEGRON**

**Mirabegron Extended-Release Tablets**

**This leaflet is part III of a three-part "Product Monograph" published when APO-MIRABEGRON was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-MIRABEGRON. Contact your doctor or pharmacist if you have any questions about the drug.**

**ABOUT THIS MEDICATION**

**What the medication is used for:**

APO-MIRABEGRON treats the symptoms of an overactive bladder such as:

- suddenly needing to empty your bladder (called urgency)
- having to empty your bladder more than usual (called urinary frequency)
- not being able to control when you empty your bladder (called urgency incontinence)

**What it does:**

APO-MIRABEGRON contains mirabegron. It works by relaxing the bladder smooth muscle, thereby reducing the symptoms of an overactive bladder.

**When it should not be used:**

- you have very high uncontrolled blood pressure
- if you are allergic to mirabegron or any of the ingredients in APO-MIRABEGRON
- women who are pregnant or breastfeeding

**What the medicinal ingredient is:**

Mirabegron

**What the nonmedicinal ingredients are:**

Ascorbic acid, D&C yellow #10 aluminum lake, FD&C red #40 aluminum lake (25 mg), hydroxypropyl cellulose, hydroxypropyl methylcellulose, indigotine aluminum lake, magnesium stearate, polyethylene glycol, polyethylene oxide, sunset yellow aluminum lake, and titanium dioxide.

**What dosage forms it comes in:**

Extended-release tablets, 25 mg, 50 mg

**WARNING AND PRECAUTION**

**BEFORE you use APO-MIRABEGRON talk to your doctor or pharmacist if:**

- you have problems emptying your bladder or if you have weak urine stream
- you are pregnant or trying to become pregnant
- you are breastfeeding or planning to breastfeed
- you have severe liver problems
- you have severe kidney problems
- you have an eye problem called Glaucoma
- you have high blood pressure or a history of high blood pressure
- you have any heart disorder, including an irregular heartbeat, an abnormal electrical signal called "prolongation of the QT interval" or a known history of QT interval prolongation
- you have a history of ischemic heart disease or a heart rate that is higher than normal

APO-MIRABEGRON should not be given to patients under 18 years of age.

**INTERACTIONS WITH THIS MEDICATION**

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. APO-MIRABEGRON may affect the way other medicines work, and other medicines may affect how APO-MIRABEGRON works. You may need to change the dosage or stop taking one of the medicines.

APO-MIRABEGRON may interact with the following medications:

- Propafenone, or Flecainide, drugs used to treat irregular heartbeats
- Digoxin
- Drugs known to increase the heartbeat or elevate blood pressure
- Drugs known to prolong the QT/QTc interval and/or cause torsade de pointes

**PROPER USE OF THIS MEDICATION**

**Usual starting dose:**

25 mg once daily with or without food. The tablet should be swallowed whole with a glass of water. Do not crush or chew the tablet. Based upon your response and tolerability, your doctor may increase your dose to 50 mg once daily. The maximum dose for APO-MIRABEGRON is 50 mg once daily.

**Overdose:**

If you think you, or a person you are caring for, have taken too much APO-MIRABEGRON, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada’s toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

**Missed Dose:**

If you forget to take your medicine, then take your next dose at the normal time. Do not take a double dose to make up for a forgotten dose. If you miss several doses, tell your doctor and follow the advice given to you.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

As with all medications, APO-MIRABEGRON can cause side effects. The possible common side effects are as follows:

- Increased blood pressure
- Cold symptoms (Nasopharyngitis)
- Urinary tract infection
- Constipation
- Diarrhea
- Dizziness
- Headache
- Nausea
- Itching

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Uncommon	Rash / Urticaria (hives)			✓
	Urinary Retention (the inability to empty your bladder)			✓
	Atrial fibrillation (rapid and irregular heart beat)			✓
	Cerebrovascular accident (stroke)			✓
Rare	Angioedema (swelling of the face or tongue, difficulty breathing)			✓

*This is not a complete list of side effects. For any unexpected effects while taking APO-MIRABEGRON, contact your doctor or pharmacist.*

**HOW TO STORE IT**

Keep out of the reach and sight of children.

Store at room temperature 15°C to 30°C. Protect from moisture.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

**If you want more information about APO-MIRABEGRON:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website (<http://www.apotex.ca/products>), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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