PRODUCT MONOGRAPH

Pr MYRBETRIQ®

mirabegron extended-release tablets
25 mg and 50 mg

Selective beta 3-adrenoceptor agonist

Astellas Pharma Canada, Inc.
Markham, ON L3R 0B8

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[Pr]MYRBETRIQ®

mirabegron

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Extended-release tablets: 25 mg, 50 mg	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

MYRBETRIQ (mirabegron) 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 MYRBETRIQ 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 MYRBETRIQ in pediatric patients have not been established.

CONTRAINDICATIONS

MYRBETRIQ is contraindicated in:

- Patients with severe uncontrolled hypertension defined as systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥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 MYRBETRIQ 50 mg, MYRBETRIQ 100 mg, and active control once daily, respectively. Neoplasms reported by 2 patients treated with MYRBETRIQ 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 MYRBETRIQ 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 MYRBETRIQ 50 mg, and these markers subsequently returned to baseline while both patients continued MYRBETRIQ (see ADVERSE REACTIONS).

Cardiovascular

QTc Prolongation: MYRBETRIQ 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 MYRBETRIQ 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: MYRBETRIQ can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with MYRBETRIQ, especially in hypertensive patients. MYRBETRIQ was not studied in patients with severe uncontrolled hypertension (systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg) and, therefore is not recommended in these patients (see CONTRAINDICATIONS). In a healthy volunteer study, MYRBETRIQ 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, MYRBETRIQ was associated with increases in systolic and diastolic blood pressure of approximately 0.5-1 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: MYRBETRIQ 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, MYRBETRIQ 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 MYRBETRIQ 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 MYRBETRIQ 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 (≥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 MYRBETRIQ 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. MYRBETRIQ should be administered with caution to patients with clinically significant BOO. MYRBETRIQ 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

MYRBETRIQ 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 MYRBETRIQ 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 MYRBETRIQ. 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 MYRBETRIQ 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 MYRBETRIQ 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
MYRBETRIQ has not been studied in patients with End Stage Renal Disease (CL_{cr} <15 mL/min or eGFR <15 mL/min/1.73 m^2 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^2), the daily dose of MYRBETRIQ 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^2) (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 MYRBETRIQ 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 MYRBETRIQ 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, MYRBETRIQ should not be administered during nursing.

Pediatrics (< 18 years of age): The safety and efficacy of MYRBETRIQ 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 MYRBETRIQ 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 MYRBETRIQ 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 MYRBETRIQ 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 MYRBETRIQ 50 mg, MYRBETRIQ 100 mg and active control once daily, respectively. Neoplasms reported by 2 patients treated with MYRBETRIQ 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 MYRBETRIQ 50 mg, and these markers subsequently returned to baseline while both patients continued MYRBETRIQ.

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 MYRBETRIQ 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), MYRBETRIQ 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 MYRBETRIQ 25 mg, 1375 received MYRBETRIQ 50 mg, and 929 received MYRBETRIQ 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).

MYRBETRIQ was also evaluated for safety in 1632 patients who received MYRBETRIQ 50 mg once daily (n=812 patients) or MYRBETRIQ 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 MYRBETRIQ in a previous 12-week study. In Study 178-CL-049, 1385 patients received MYRBETRIQ continuously for at least 6 months, 1311 patients received MYRBETRIQ for at least 9 months, and 564 patients received MYRBETRIQ 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 MYRBETRIQ 25 mg or 50 mg once daily for up to 12 weeks. The most commonly reported adverse reactions (greater than 2% of MYRBETRIQ patients and greater than placebo) were hypertension, nasopharyngitis, urinary tract infection and headache.

Table 1 – Adverse Events Exceeding the Placebo Rate and Reported by ≥1% of MYRBETRIQ-treated OAB Patients in the 12-week Phase 3 Studies

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

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

Table 2 lists the rates of the most commonly reported adverse reactions, derived from all adverse events in patients treated with MYRBETRIQ 50 mg for up to 52 weeks [178-CL-049]. The most commonly reported adverse reactions (>3% of MYRBETRIQ 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 MYRBETRIQ 50 mg Once Daily in 52-week long-term safety study [178-CL-049]

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

Less Common Clinical Trial Adverse Drug Reactions

Other adverse reactions reported by less than 1% of patients treated with MYRBETRIQ 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 MYRBETRIQ 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 MYRBETRIQ 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 end points 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 MYRBETRIQ 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.

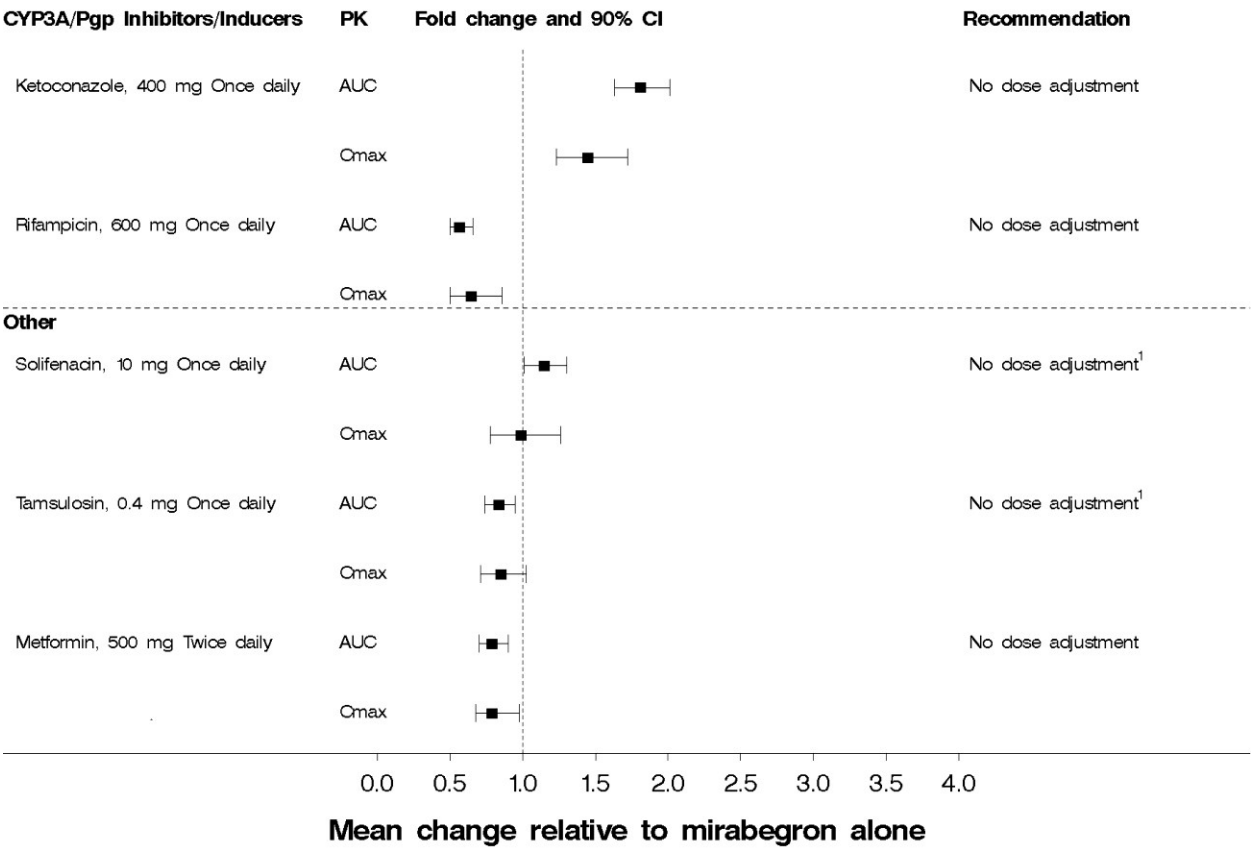
In these studies, the largest increase in mirabegron systemic exposure was seen in the ketoconazole DDI study. As a potent CYP3A4 inhibitor, ketoconazole increased mirabegron C_{max} by 45% and mirabegron AUC by 80% after multiple dose administration of 400 mg of ketoconazole for 9 days prior to the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

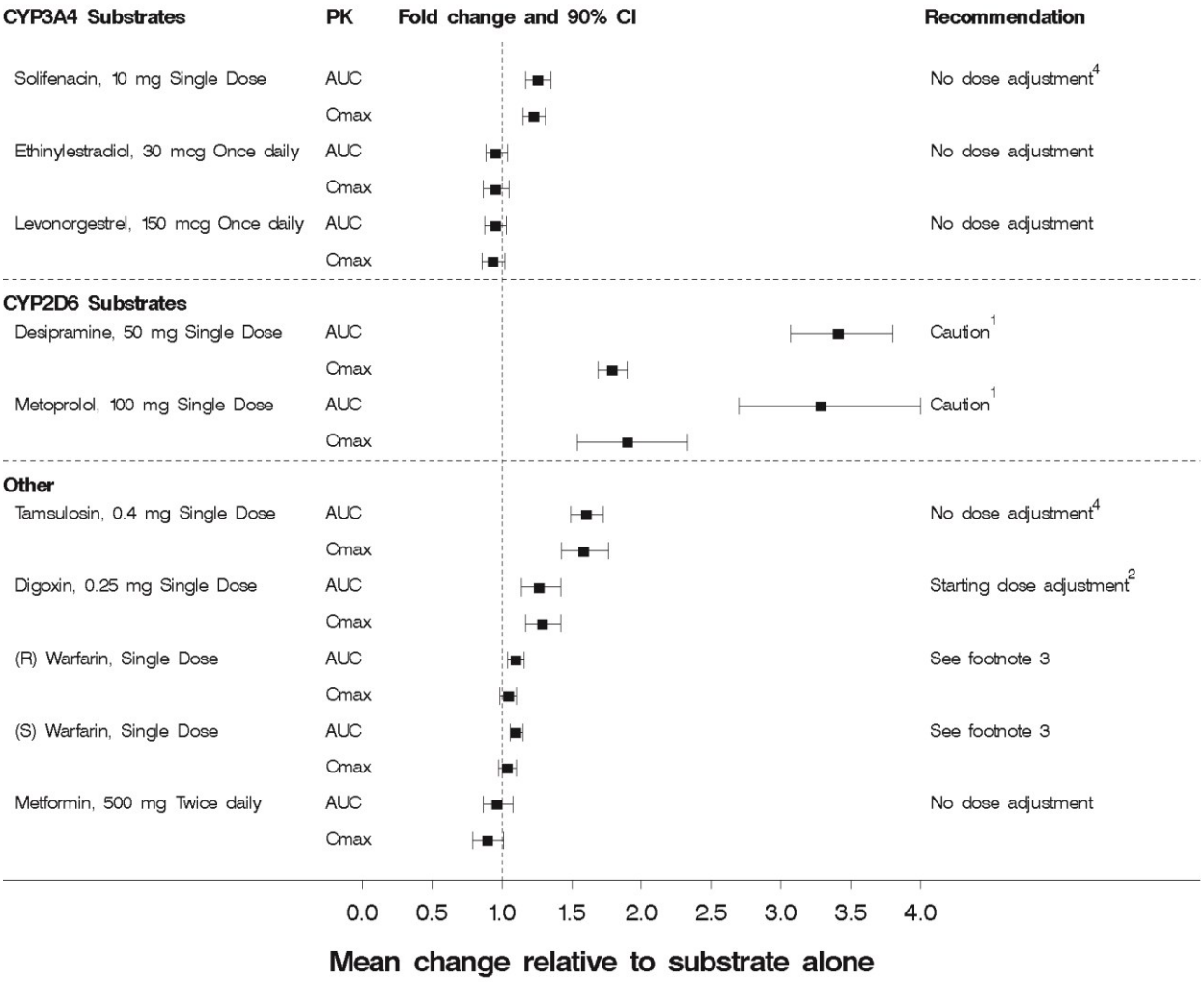
The dose of MYRBETRIQ should not exceed 25 mg when co-administered with narrow therapeutic index drugs metabolized by CYP2D6 such as flecainide and propafenone.

Figure 1 – The Effect of Co-administered Drugs on Exposure of MYRBETRIQ and Dose Recommendation



(1) Although no dose adjustment is recommended with solifenacin or tamsulosin based on the lack of pharmacokinetic interaction, MYRBETRIQ 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 MYRBETRIQ 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 (≥ 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 MYRBETRIQ 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, MYRBETRIQ 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 MYRBETRIQ 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 MYRBETRIQ 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)3 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_{max} and AUC_{inf} by 45% and 17%, respectively. A low-fat meal decreased mirabegron C_{max} and AUC_{inf} by 75% and 51%, respectively. MYRBETRIQ was administered in the phase 3 studies with or without food and safety and efficacy was shown. Therefore, MYRBETRIQ 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, MYRBETRIQ 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).

MYRBETRIQ 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.

MYRBETRIQ is not recommended for use during pregnancy (see CONTRAINDICATIONS).

Recommended Dose and Dosage Adjustment

The recommended initial dose and usual therapeutic dose of MYRBETRIQ 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. MYRBETRIQ 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 MYRBETRIQ 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^2) (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 PHARAMACOLOGY).

MYRBETRIQ 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
MYRBETRIQ 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 overdosage should be symptomatic and supportive. In the event of overdosage, pulse rate, blood pressure and ECG monitoring is recommended.

For management of a suspected drug overdosage, contact your regional Poison Control Centre.

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_2 and M_3 receptors, inducing bladder contraction. The activation of the M_2 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 MYRBETRIQ 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 MYRBETRIQ 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. MYRBETRIQ 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 MYRBETRIQ 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_{max} 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 MYRBETRIQ 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

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.

MYRBETRIQ 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	
	ΔΔHR (bpm)	Time (h)	ΔΔHR (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. MYRBETRIQ 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 (ΔΔSBP) and Diastolic Blood Pressure (ΔΔDBP) with 95% Confidence Intervals on Day 9:

Dose	ΔΔSBP (mm Hg)	Time (h)	ΔΔDBP (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 MYRBETRIQ 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 MYRBETRIQ 50 mg once daily, an increase in mean difference from placebo of approximately 1 bpm for pulse rate and approximately 0.5 - 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 MYRBETRIQ, and again in the afternoon. Approximately 40 - 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)
MYRBETRIQ 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 MYRBETRIQ on IOP using Goldmann applanation tonometry in 310 healthy subjects, a dose of 100 mg MYRBETRIQ 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 MYRBETRIQ 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, MYRBETRIQ 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 (≥ 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^2 as estimated by MDRD), mean mirabegron C_{max} and AUC were increased by 6% and 31% relative to volunteers with normal renal function. In volunteers with moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m^2), C_{max} and AUC were increased by 23% and 66%, respectively. In patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2), mean C_{max} and AUC values were 92% and 118% higher. Mirabegron has not been studied in patients with End Stage Renal Disease (CL_{cr} <15 mL/min or eGFR < 15 mL/min/1.73 m^2 or patients requiring hemodialysis) (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

STORAGE AND STABILITY

Store at 25°C (77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F).

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MYRBETRIQ (mirabegron) extended-release tablets are available as:

- 25 mg oval, brown film-coated tablet, debossed with the Astellas logo " " and "325"
- 50 mg oval, yellow film-coated tablet, debossed with the Astellas logo " " and "355"

MYRBETRIQ (mirabegron) extended-release tablets contain the following excipients: polyethylene oxide, polyethylene glycol, hydroxypropyl cellulose, butylated hydroxytoluene, magnesium stearate, hypromellose, yellow ferric oxide and red ferric oxide (25 mg only).

MYRBETRIQ (mirabegron) extended-release tablets are available in 30- and 90-count HDPE bottles.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

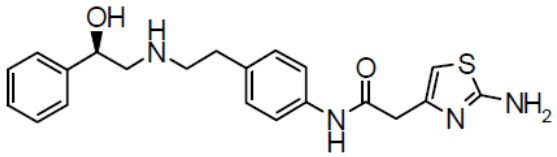
Drug Substance

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: $C_{21}H_{24}N_4O_2S$, 396.51

Structural formula:



Physicochemical properties: A white crystalline powder that is practically insoluble in water. Higher solubility is observed in acidic solution, or buffered solutions with pH ≥ 7.5

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

pKa: Approximately 4.5 and 8

CLINICAL TRIALS

Study Demographics and Trial Design

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

Study #	Trial design and duration	Dosage, route of administration	Number of study subjects randomized/ completed	Mean age (Range)	Gender %
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 MYRBETRIQ 50 mg, oral, qd MYRBETRIQ 100 mg, oral, qd Tolterodine ER 4 mg, oral, qd	497/453 497/440 498/453 495/445	Mean: 59.1 years Range: 18-90 years ≥ 65 years: 37.0% ≥ 75 years: 8.5%	Female: 72.0% Male: 28.0%
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 MYRBETRIQ 50 mg, oral, qd MYRBETRIQ 100 mg, oral, qd	454/385 442/383 433/380	Mean: 60.2 years Range: 20-95 years ≥ 65 years: 39.7% ≥ 75 years: 15.1%	Female: 74.8% Male: 25.2%
178-CL-074	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 MYRBETRIQ 25 mg, oral, qd MYRBETRIQ 50 mg, oral, qd	433/367 433/387 440/386	Mean: 59.1 years Range: 21-91 years ≥ 65 years: 37.2% ≥ 75 years: 9.9%	Female: 68.5% Male: 31.5%
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.	MYRBETRIQ 50 mg, oral, qd MYRBETRIQ 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%

MYRBETRIQ® 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 – 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, MYRBETRIQ 50 mg, MYRBETRIQ 100 mg, or an active control once daily. In Study 178-CL-047, patients were randomized to placebo, MYRBETRIQ 50 mg or MYRBETRIQ 100 mg once daily. In Study 178-CL-074, patients were randomized to placebo, MYRBETRIQ 25 mg or MYRBETRIQ 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

MYRBETRIQ demonstrated statistically significant improvements compared to placebo for both co-primary endpoints (see Table 4).

MYRBETRIQ 25 mg was effective in treating the symptoms of OAB within 8 weeks, and MYRBETRIQ 50 mg was effective in treating the symptoms of OAB within 4 weeks. Efficacy of both 25 mg and 50 mg doses of MYRBETRIQ 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	MYRBETRIQ 50 mg	Tolterodine ER 4 mg	Placebo	MYRBETRIQ 50 mg	Placebo	MYRBETRIQ 25 mg	MYRBETRIQ 50 mg
Mean Number of Incontinence Episodes per 24 Hours (FAS-I) (Co-Primary)								
n	291	293	300	325	312	262	254	257
Mean baseline	2.67	2.83	2.63	3.03	2.77	2.43	2.65	2.51
Mean change from baseline†	-1.17	-1.57	-1.27	-1.13	-1.47	-0.96	-1.36	-1.38
Mean difference from placebo†	--	-0.41	-0.10	--	-0.34	--	-0.40	-0.42
95% Confidence Interval	--	(-0.72, -0.09)	(-0.42, 0.21)	--	(-0.66, -0.03)	--	(-0.74, -0.06)	(-0.76, -0.08)
p-value	--	0.003#	0.11	--	0.026#	--	0.005#	0.001#
Mean Number of Micturitions per 24 Hours (FAS) (Co-Primary)								
n	480	473	475	433	425	415	410	426
Mean baseline	11.71	11.65	11.55	11.51	11.80	11.48	11.68	11.66
Mean change from baseline†	-1.34	-1.93	-1.59	-1.05	-1.66	-1.18	-1.65	-1.60
Mean difference from placebo†	--	-0.60	-0.25	--	-0.61	--	-0.47	-0.42
95% Confidence Interval	--	(-0.90, -0.29)	(-0.55, 0.06)	--	(-0.98, -0.24)	--	(-0.82, -0.13)	(-0.76, -0.08)
p-value	--	<0.001#	0.11	--	0.001#	--	0.007#	0.015#
Mean Volume Voided (ml) per Micturition (FAS) (Secondary)								
n	480	472	475	433	424	415	410	426
Mean baseline	156.7	161.1	158.6	157.5	156.3	164.0	165.2	159.3
Mean change from baseline†	12.3	24.2	25.0	7.0	18.2	8.3	12.8	20.7
Mean difference from placebo†	--	11.9	12.6	--	11.1	--	4.6	12.4
95% Confidence Interval	--	(6.3, 17.4)	(7.1, 18.2)	--	(4.4, 17.9)	--	(-1.6, 10.8)	(6.3, 18.6)
p-value	--	<0.001#	<0.001*	--	0.001#	--	0.15‡	< 0.001#
Mean Level of Urgency (FAS) (Secondary)								
n	480	472	473	432	425	413	410	426
Mean baseline	2.37	2.40	2.41	2.45	2.45	2.36	2.37	2.41
Mean change from baseline†	-0.22	-0.31	-0.29	-0.08	-0.19	-0.15	-0.22	-0.29
Mean difference from placebo†	--	-0.09	-0.07	--	-0.11	--	-0.07	-0.14
95% Confidence Interval	--	(-0.17, -0.02)	(-0.15, 0.01)	--	(-0.18, -0.04)	--	(-0.15, 0.01)	(-0.22, -0.06)
p-value	--	0.018*	0.085	--	0.004*	--	0.083‡	< 0.001‡

† 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

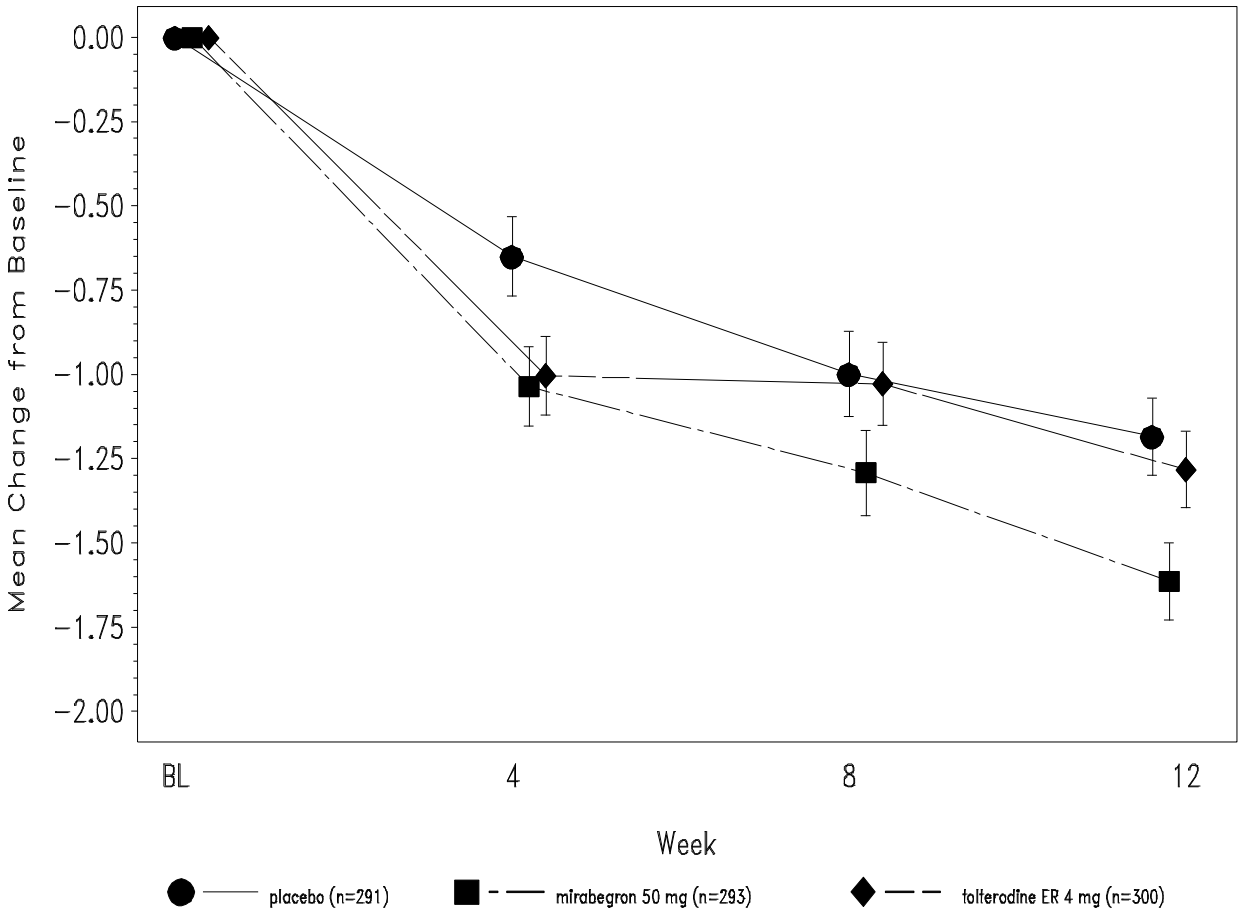


Figure 4. Mean (SE) Change from Baseline in Mean Number of Micturitions per 24 Hours - Study 178-CL-046

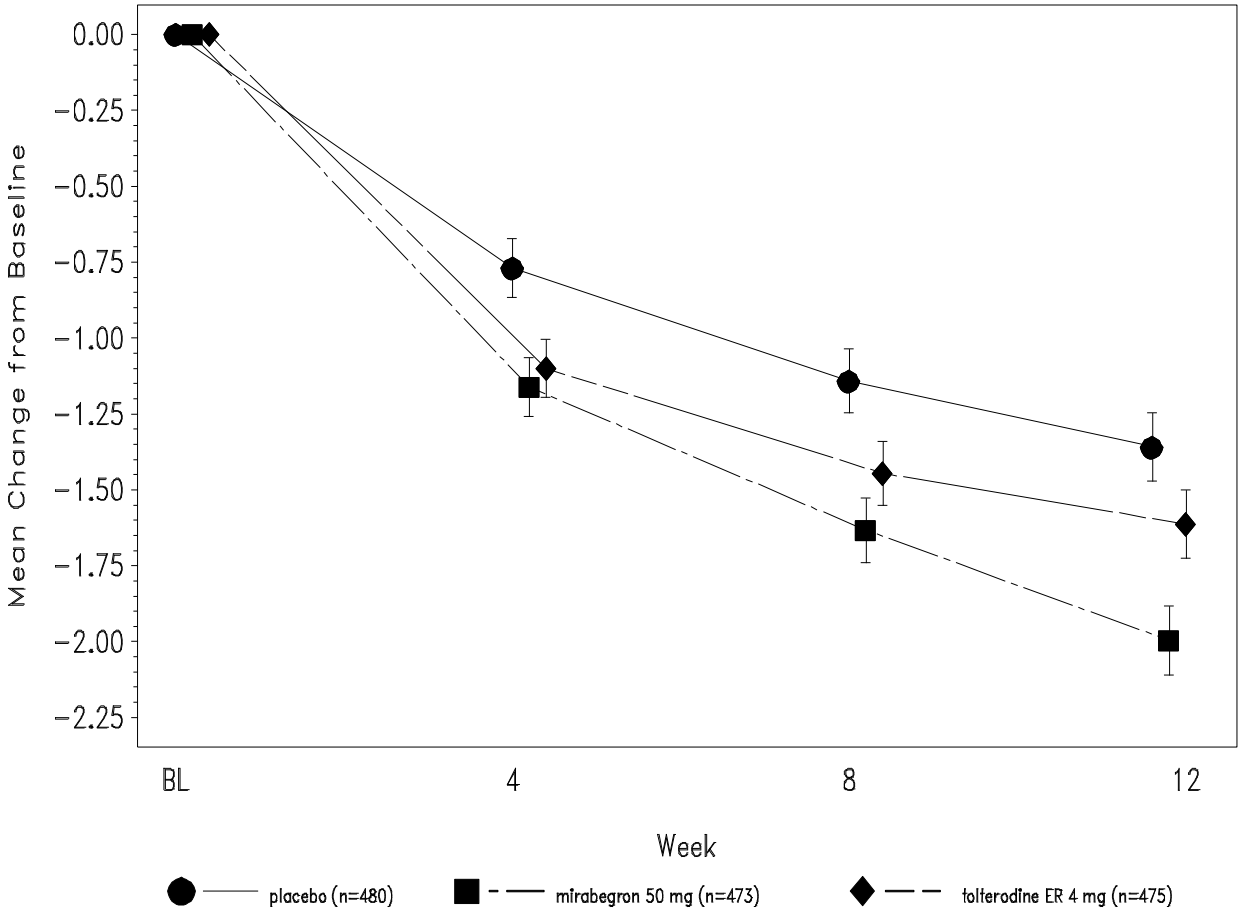


Figure 5. Mean (SE) Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours - Study 178-CL-047

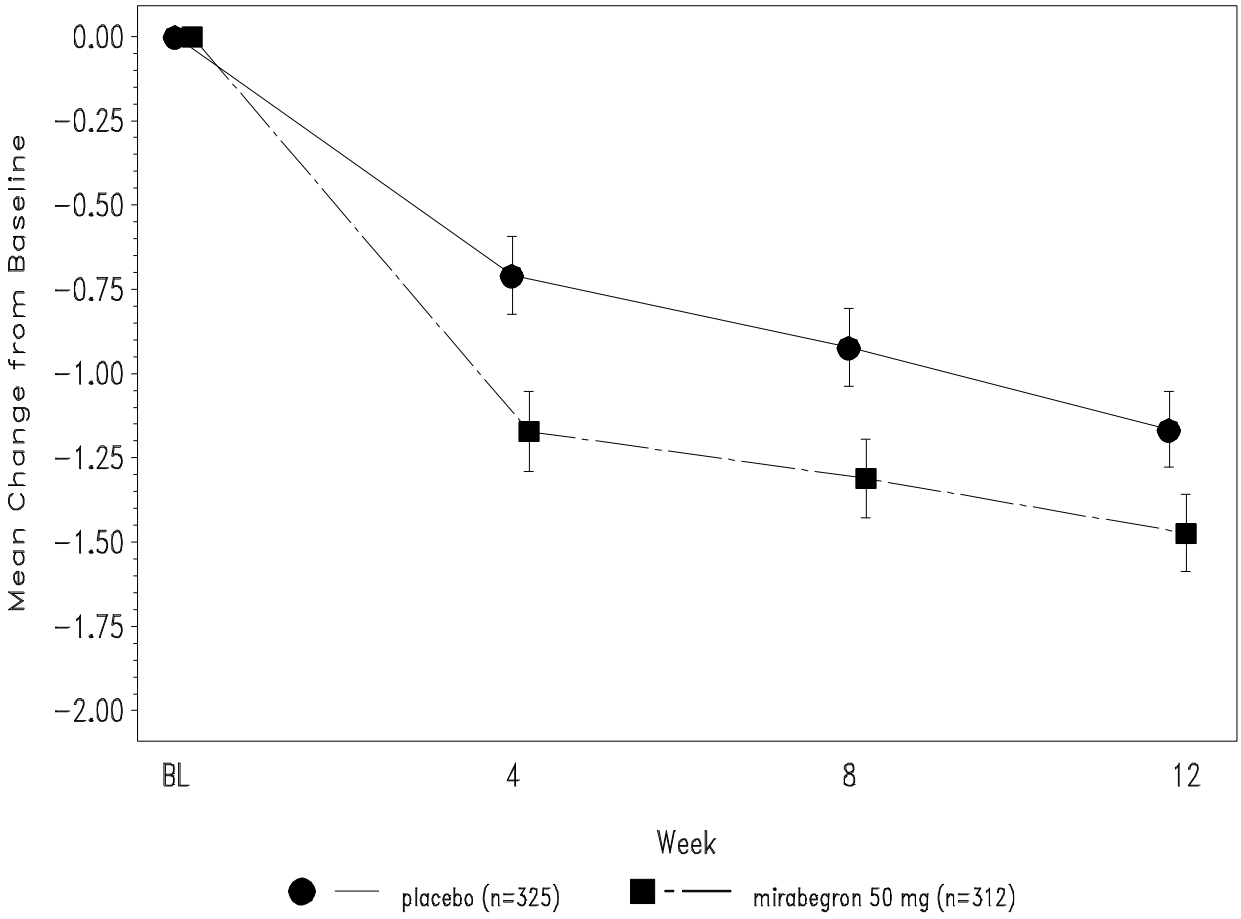


Figure 6. Mean (SE) Change from Baseline in Mean Number of Micturitions per 24 Hours - Study 178-CL-047

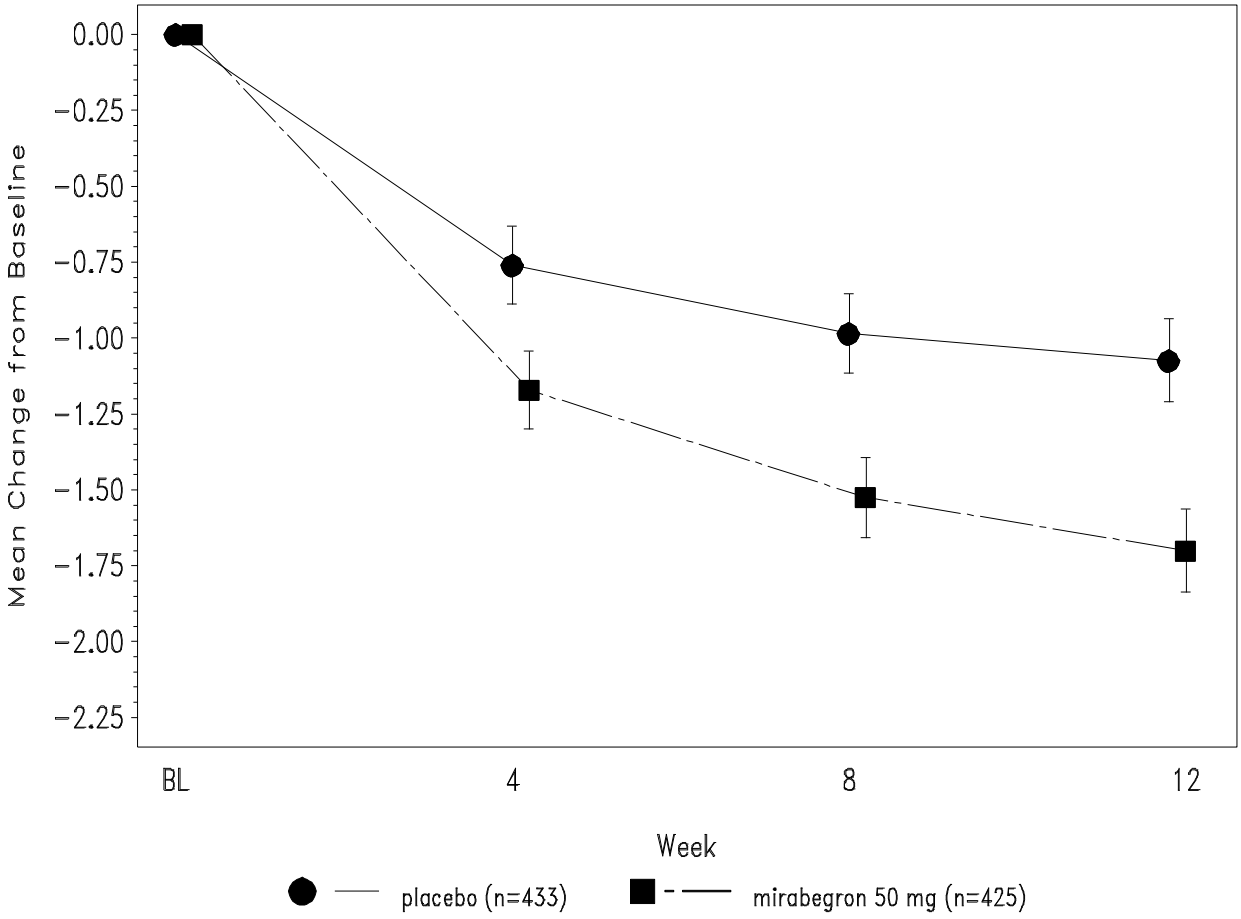


Figure 7. Mean (SE) Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours - Study 178-CL-074

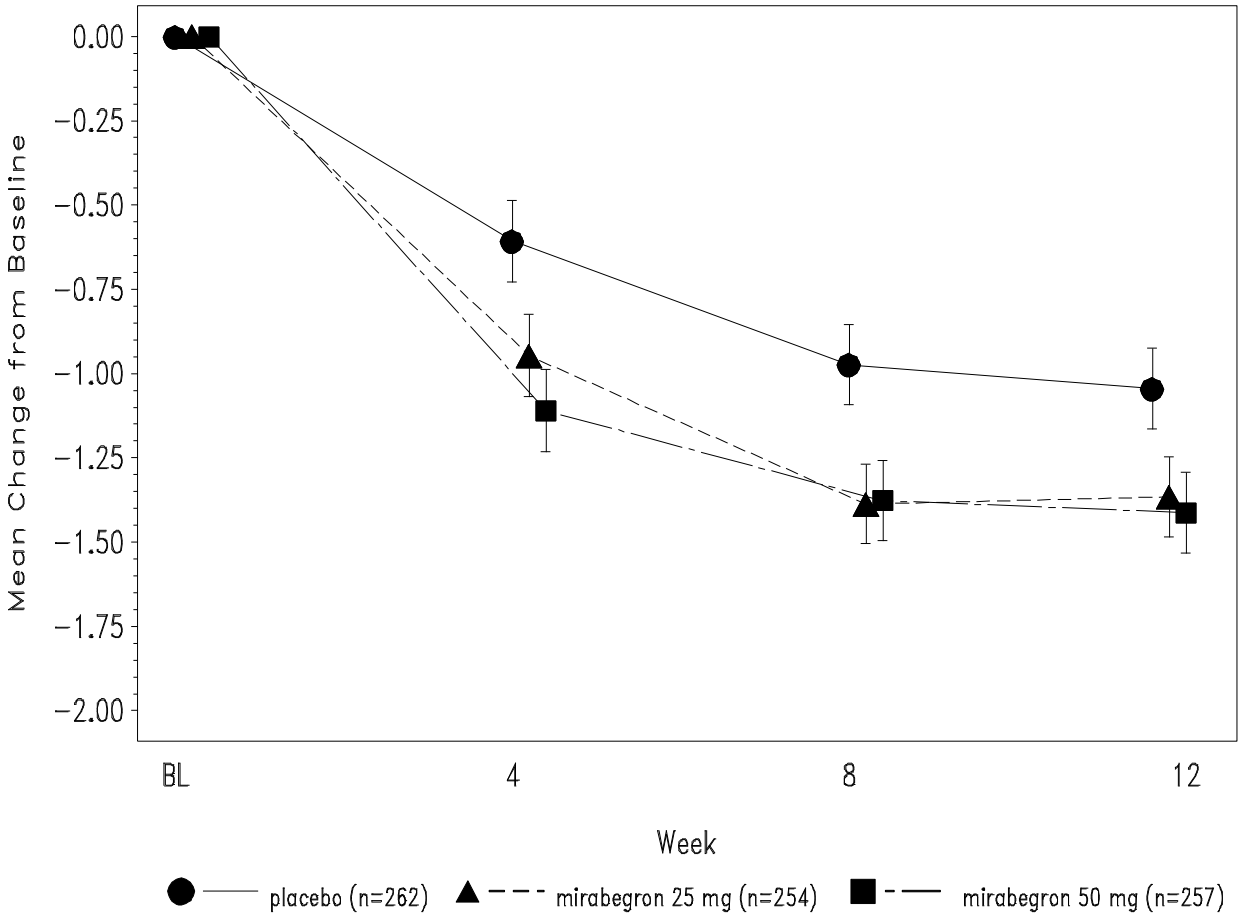
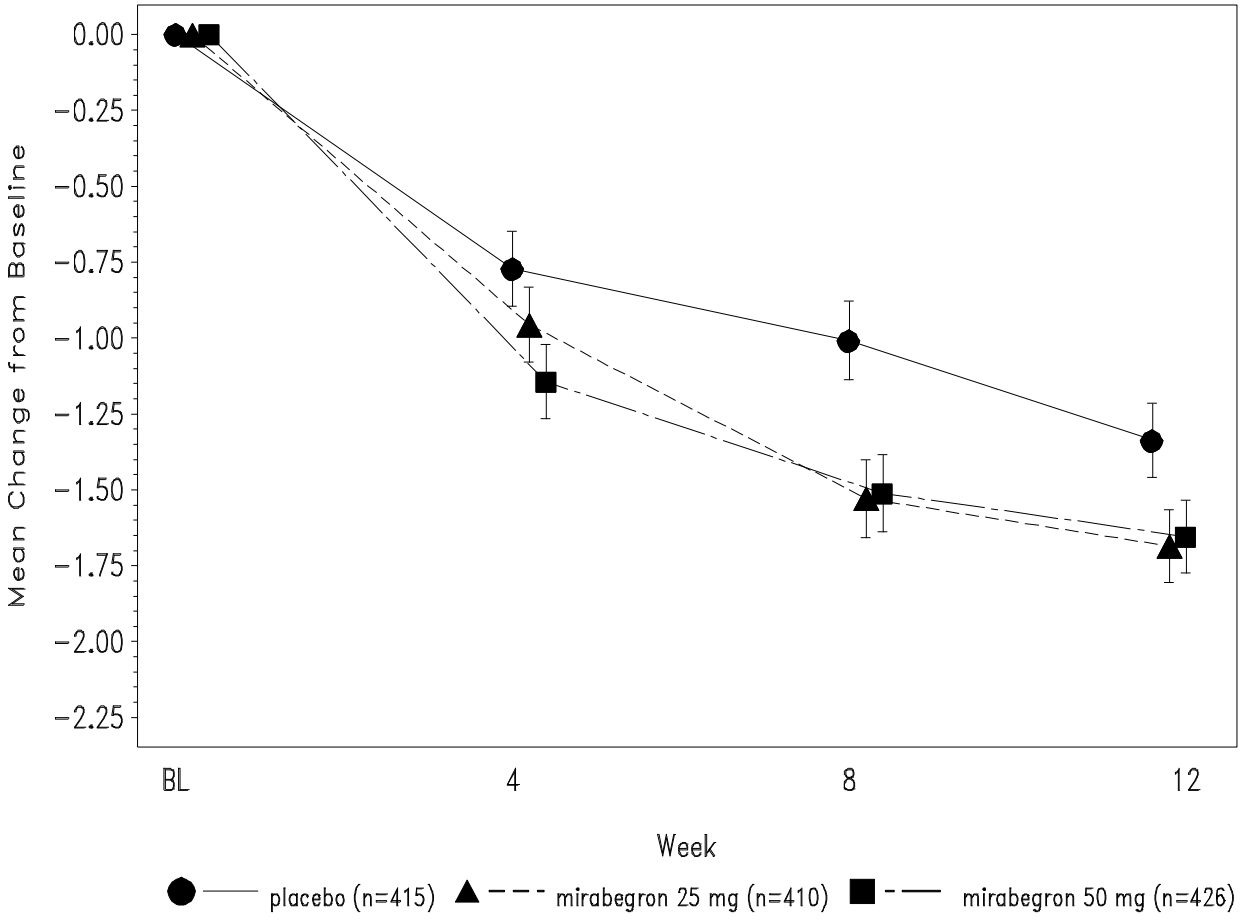


Figure 8. Mean (SE) Change from Baseline in Mean Number of Micturitions per 24 Hours - Study 178-CL-074



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 6.

Table 6 – Affinity of Mirabegron for Human Beta-Adrenoceptor Subtypes

	Ki (nmol/L)		
Test article	**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_{50}) 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_2 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_{50} = 5.1 and 0.78 mcmol/L, respectively). In addition, mirabegron induced relaxation of rat bladder strips precontracted with potassium chloride (KCl) with an EC_{50} value of 11 mcmol/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 ≥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 7. Data presented in the parenthesis represent the safety factors for each finding based on AUC.

Table 7 – 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*)
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)
[a]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. [a]Male animals were administered mirabegron for 14 days prior to mating.
↑: increased; ↓: decreased; NT: not tested

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PART III: CONSUMER INFORMATION

[Pr]MYRBETRIQ®
mirabegron

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

ABOUT THIS MEDICATION

What the medication is used for:
MYRBETRIQ 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:
MYRBETRIQ 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 MYRBETRIQ
- women who are pregnant or breastfeeding

What the medicinal ingredient is:
Mirabegron

What the nonmedicinal ingredients are:
butylated hydroxytoluene, hydroxypropyl cellulose, hypromellose, magnesium stearate, polyethylene glycol, polyethylene oxide, yellow ferric oxide and red ferric oxide (25 mg only).

What dosage forms it comes in:
Extended-release tablets, 25 mg, 50 mg

WARNINGS AND PRECAUTIONS

BEFORE you use MYRBETRIQ 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

MYRBETRIQ 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. MYRBETRIQ may affect the way other medicines work, and other medicines may affect how MYRBETRIQ works. You may need to change the dosage or stop taking one of the medicines.

MYRBETRIQ 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 MYRBETRIQ is 50 mg once daily.

Overdose:

In case of drug overdose, contact your doctor, or a poison control centre, or go to emergency room of the hospital near you immediately, even if there are no 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, MYRBETRIQ 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, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		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 MYRBETRIQ, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children. Store at 25°C (77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F).

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage-paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.astellas.ca
or by contacting the sponsor, Astellas Pharma Canada, Inc., at:
1-888-338-1824

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