HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MYRBETRIQ® safely and effectively. See full prescribing information for MYRBETRIQ®.

MYRBETRIQ® (mirabegron) extended-release tablets, for oral use
Initial U.S. Approval: 2012

----------RECENT MAJOR CHANGES----------

- Contraindications (4) 07/2015
- Warnings and Precautions (5.3) 07/2015

----------INDICATIONS AND USAGE----------

MYRBETRIQ® is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency (1).

----------DOSAGE AND ADMINISTRATION----------

- Recommended starting dose is 25 mg once daily, with or without food (2.1).
- 25 mg is effective within 8 weeks. Based on individual efficacy and tolerability, may increase dose to 50 mg once daily (2.1, 14).
- Swallow whole with water, do not chew, divide or crush (2.1).
- *Patients with Severe Renal Impairment or Patients with Moderate Hepatic Impairment:* Maximum dose is 25 mg once daily (2.2, 8.6, 8.7, 12.3).
- *Patients with End Stage Renal Disease (ESRD) or Patients with Severe Hepatic Impairment:* Not recommended (2.2, 8.6, 8.7, 12.3).

----------DOSAGE FORMS AND STRENGTHS----------

Extended-release tablets: 25 mg and 50 mg (3)

----------CONTRAINDICATIONS----------

Hypersensitivity reactions (4)

----------WARNINGS AND PRECAUTIONS----------

- *Increases in Blood Pressure:* MYRBETRIQ® can increase blood pressure. Periodic blood pressure determinations are recommended, especially in hypertensive patients. MYRBETRIQ® is not recommended for use in severe uncontrolled hypertensive patients (5.1).
- *Urinary Retention in Patients With Bladder Outlet Obstruction and in Patients Taking Antimuscarinic Drugs for Overactive Bladder:* Administer with caution in these patients because of risk of urinary retention (5.2).
- *Angioedema:* Angioedema of the face, lips, tongue and/or larynx has been reported with MYRBETRIQ® (5.3, 6.2).
- *Patients Taking Drugs Metabolized by CYP2D6:* MYRBETRIQ® is a moderate inhibitor of CYP2D6. Appropriate monitoring is recommended and dose adjustment may be necessary for narrow therapeutic index CYP2D6 substrates (5.4, 7.1, 12.3).

----------ADVERSE REACTIONS----------

Most commonly reported adverse reactions (> 2% and > placebo) were hypertension, nasopharyngitis, urinary tract infection and headache (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- *Drugs Metabolized by CYP2D6 (e.g., Metoprolol and Desipramine):* Mirabegron is CYP2D6 inhibitor and when used concomitantly with drugs metabolized by CYP2D6, especially narrow therapeutic index drugs, appropriate monitoring and possible dose adjustment of those drugs may be necessary (5.4, 7.1, 12.3).
- *Digoxin:* When initiating a combination of MYRBETRIQ® and digoxin, prescribe the lowest dose of digoxin; monitor serum digoxin concentrations to titrate digoxin dose to desired clinical effect (7.2, 12.3).

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy:* Use only if the benefit to the mother outweighs the potential risk to the fetus (8.1).
- *Nursing mothers:* MYRBETRIQ® is predicted to be excreted in human milk and is not recommended for use by nursing mothers (8.3).
- *Pediatric use:* The safety and effectiveness of MYRBETRIQ® in pediatric patients have not been established (8.4).
- *Geriatric use:* No dose adjustment is recommended for elderly patients (8.5).

See 17 **for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

Revised: [07/2015]

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

MYRBETRIQ® is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended starting dose of MYRBETRIQ® is 25 mg once daily with or without food. MYRBETRIQ® 25 mg is effective within 8 weeks. Based on individual patient efficacy and tolerability the dose may be increased to 50 mg once daily *[see Clinical Studies (14)]*.

MYRBETRIQ® should be taken with water, swallowed whole and should not be chewed, divided, or crushed.

2.2 Dose Adjustments in Specific Populations

The daily dose of MYRBETRIQ® should not exceed 25 mg once daily 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 Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.
- Patients with moderate hepatic impairment (Child-Pugh Class B) *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

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 Use in Specific Populations (8.6, 8.7) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

MYRBETRIQ® extended-release tablets are supplied in two different strengths as described below:

- 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”

4 CONTRAINDICATIONS

MYRBETRIQ® is contraindicated in patients who have known hypersensitivity reactions to mirabegron or any component of the tablet *[see Adverse Reactions (6.1, 6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increases in Blood Pressure

MYRBETRIQ® can increase blood pressure. Periodic blood pressure determinations are recommended, especially in hypertensive patients. MYRBETRIQ® is not recommended for use in patients with severe uncontrolled hypertension (defined as systolic blood pressure greater than or equal to 180 mm Hg and/or diastolic blood pressure greater than or equal to 110 mm Hg) *[see Clinical Pharmacology (12.2)]*.

In two, randomized, placebo-controlled, healthy volunteer studies, MYRBETRIQ® was associated with dose-related increases in supine blood pressure. In these studies, at the maximum recommended dose of 50 mg, the mean maximum increase in systolic/diastolic blood pressure was approximately 3.5/1.5 mm Hg greater than placebo.

In contrast, in OAB patients in clinical trials, the mean increase in systolic and diastolic blood pressure at the maximum recommended dose of 50 mg was approximately 0.5 - 1 mm Hg greater than placebo. Worsening of pre-existing hypertension was reported infrequently in MYRBETRIQ® patients.

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

Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in MYRBETRIQ® patients; however, 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 Clinical Pharmacology (12.2)]*.

5.3 Angioedema

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 (6.2)]*.

5.4 Patients Taking Drugs Metabolized by 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. Therefore, appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index drugs metabolized by CYP2D6, such as thioridazine, flecainide, and propafenone *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In three, 12 week, double-blind, placebo-controlled, safety and efficacy studies in patients with overactive bladder (Studies 1, 2, and 3), MYRBETRIQ® was evaluated for safety in 2736 patients *[see Clinical Studies (14)]*. Study 1 also included an active control. For the combined Studies 1, 2, and 3, 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 4). Of these patients, 731 received MYRBETRIQ® in a previous 12 week study. In Study 4, 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.

The most frequent adverse events (0.2%) leading to discontinuation in Studies 1, 2 and 3 for the 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.

Table 1 lists adverse reactions, derived from all adverse events, that were reported in Studies 1, 2 and 3 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: Percentages of Patients with Adverse Reactions, Derived from All Adverse Events, Exceeding Placebo Rate and Reported by 1% or More Patients Treated With MYRBETRIQ® 25 mg or 50 mg Once Daily in Studies 1, 2, and 3

	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.

Other adverse reactions reported by less than 1% of patients treated with MYRBETRIQ® in Studies 1, 2, or 3 included:

Cardiac disorders: palpitations, blood pressure increased *[see Clinical Pharmacology (12.2)]*
Eye disorders: glaucoma *[see Clinical Pharmacology (12.2)]*
Gastrointestinal disorders: dyspepsia, gastritis, abdominal distension
Infections and Infestations: sinusitis, rhinitis
Investigations: GGT increased, AST increased, ALT increased, LDH increased
Renal and urinary disorders: nephrolithiasis, bladder pain
Reproductive system and breast disorders: vulvovaginal pruritus, vaginal infection
Skin and subcutaneous tissue disorders: urticaria, leukocytoclastic vasculitis, rash, pruritus, purpura, lip edema

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 in Study 4. 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 Study 4

	MYRBETRIQ® 50 mg (%)	Active Control (%)
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

In Study 4, 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%). 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 Study 4, 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 separate 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).

6.2 Postmarketing Experience

Because these spontaneously reported events are from the worldwide postmarketing 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 postmarketing experience:

Skin and subcutaneous tissue: angioedema of the face, lips, tongue, and larynx, with or without respiratory symptoms *[see Warnings and Precautions (5.3)]*

Urologic: urinary retention *[see Warnings and Precautions (5.2)]*

7 DRUG INTERACTIONS

Drug interaction studies were conducted to investigate the effect of co-administered drugs on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of co-administered drugs (e.g., ketoconazole, rifampin, solifenacin, tamsulosin, and oral contraceptives) *[see Clinical Pharmacology (12.3)]*. No dose adjustment is recommended when these drugs are co-administered with mirabegron.

The following are drug interactions for which monitoring is recommended:

7.1 Drugs Metabolized by CYP2D6

Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure of drugs metabolized by CYP2D6 enzyme such as metoprolol and desipramine is increased when co-administered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary when MYRBETRIQ® is co-administered with these drugs, especially with narrow therapeutic index CYP2D6 substrates, such as thioridazine, flecainide, and propafenone *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*.

7.2 Digoxin

When given in combination, mirabegron increased mean digoxin C_{max} from 1.01 to 1.3 ng/mL (29%) and AUC from 16.7 to 19.3 ng.h/mL (27%). Therefore, for patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should initially be considered. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect *[see Clinical Pharmacology (12.3)]*.

7.3 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 *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C
There are no adequate and well-controlled studies using MYRBETRIQ® in pregnant women. MYRBETRIQ® should be used during pregnancy only if the potential benefit to the patient outweighs the risk to the patient and fetus. Women who become pregnant during MYRBETRIQ® treatment are encouraged to contact their physician.

Risk Summary
Based on animal data, mirabegron is predicted to have a low probability of increasing the risk of adverse developmental outcomes above background risk. Reversible adverse developmental findings consisting of delayed ossification and wavy ribs in rats and decreased fetal body weights in rabbits occurred at exposures greater than or equal to 22 and 14 times, respectively, the maximal recommended human dose (MRHD). At maternally toxic exposures decreased fetal weights were observed in rats and rabbits, and fetal death, dilated aorta, and cardiomegaly were reported in rabbits.

Animal Data
In the rat embryo/fetal developmental toxicity study, pregnant rats received daily oral doses of mirabegron at 0, 10, 30, 100, or 300 mg/kg from implantation to closure of the fetal hard palate (7th to 17th day of gestation). Maternal systemic exposures were approximately 0, 1, 6, 22, or 96 times greater than exposures in women treated at the MRHD of 50 mg based on AUC. No embryo/fetal toxicities were observed in rats exposed up to 6 times the human systemic exposure at the MRHD of 50 mg. At systemic exposures equal to or greater than 22 times the human systemic exposure at the MRHD, delayed ossification and wavy ribs were observed in fetuses at an increased incidence. These findings were reversible.

In the rabbit embryo/fetal developmental toxicity study, pregnant rabbits received daily oral doses of mirabegron at 0, 3, 10, or 30 mg/kg from implantation to closure of the fetal hard palate (6th to 20th day of gestation). Maternal systemic exposures were 0, 1, 14, or 36 times that in women treated at the MRHD of 50 mg based on AUC. The embryo/fetal No Adverse Effect Level (NOAEL) was similar to the exposure in women at the MRHD and was established in this species based on reduced fetal body weight observed at systemic exposures that were 14-fold higher than the human systemic exposure at MRHD. At higher doses, where systemic exposures were 36-fold higher than the human exposure at MRHD, maternal body weight gain and food consumption were reduced, one of 17 pregnant rabbits died, the incidence of fetal death increased, and fetal findings of dilated aorta and cardiomegaly were reported.

The effects of mirabegron on prenatal and postnatal development was assessed in pregnant rats dosed at 0, 10, 30, or 100 mg/kg/day from the seventh day of gestation until 20 days after birth. Maternal systemic exposures were 0, 1, 6, and 22 times the exposure in women at the MRHD based on AUC. Rat pups exposed to mirabegron in utero and through 21 days of lactation had no discernable adverse effects at maternal systemic exposures 6 times the MRHD. A slight but statistically significant decrease in the survival of pups was observed 4 days after birth at exposures 22 times the MRHD (92.7% survival) compared to the control group (98.8%), however, there was no effect on survival of pups 21 days after birth. Absolute body weight of pups was not affected on the day of birth. However, at the 30 mg/kg dose (22-fold higher systemic exposure than humans at MHRD) body weight gain of pups was reduced 5% to 13% from postnatal day 4 to 7 but not throughout the remainder of the lactation period. In utero and lactational exposure did not affect behavior or fertility of offspring at exposures up to 22 times the MRHD.

8.3 Nursing Mothers

It is not known whether MYRBETRIQ® is excreted in human milk. Mirabegron was found in the milk of rats at concentrations twice the maternal plasma level. Mirabegron was found in the lungs, liver, and kidneys of nursing pups. No studies have been conducted to assess the impact of MYRBETRIQ® on milk production in humans, its presence in human breast milk, or its effects on the breast-fed child. Because MYRBETRIQ® is predicted to be excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of MYRBETRIQ® in pediatric patients have not been established.

8.5 Geriatric Use

No dose adjustment is necessary for the elderly. The pharmacokinetics of MYRBETRIQ® is not significantly influenced by age *[see Clinical Pharmacology (12.3)]*. 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.

8.6 Renal Impairment

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.

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 Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

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.

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 Clinical Pharmacology (12.3)]*.

8.8 Gender

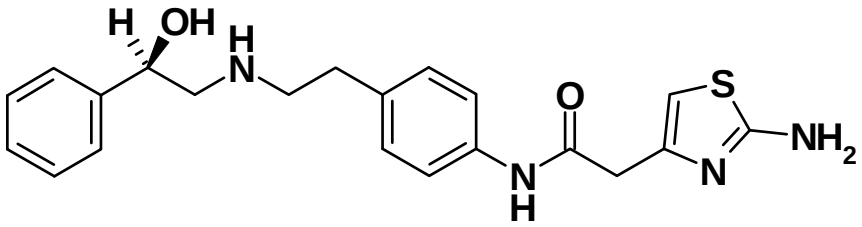
No dose adjustment is necessary based on gender. When corrected for differences in body weight, the MYRBETRIQ® systemic exposure is 20% to 30% higher in females compared to males.

10 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.

11 DESCRIPTION

Mirabegron is a beta-3 adrenergic agonist. The chemical name is 2-(2-aminothiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide having an empirical formula of $C_{21}H_{24}N_4O_2S$ and a molecular weight of 396.51. The structural formula of mirabegron is:



Mirabegron is a white powder. It is practically insoluble in water (0.082 mg/mL). It is soluble in methanol and dimethyl sulfoxide.

Each MYRBETRIQ® extended-release tablet, for oral administration contains either 25 mg or 50 mg of mirabegron and the following inactive ingredients: polyethylene oxide, polyethylene glycol, hydroxypropyl cellulose, butylated hydroxytoluene, magnesium stearate, hypromellose, yellow ferric oxide, and red ferric oxide (25 mg tablet only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mirabegron is an agonist of the human beta-3 adrenergic receptor (AR) as demonstrated by *in vitro* laboratory experiments using the cloned human beta-3 AR. Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of beta-3 AR which increases bladder capacity. Although mirabegron showed very low intrinsic activity for cloned human beta-1 AR and beta-2 AR, results in humans indicate that beta-1 AR stimulation occurred at a mirabegron dose of 200 mg.

12.2 Pharmacodynamics

Urodynamics

The effects of MYRBETRIQ® on maximum urinary flow rate and detrusor pressure at maximum flow rate were assessed in a urodynamic study consisting of 200 male patients with lower urinary tract symptoms (LUTS) and BOO. Administration of MYRBETRIQ® once daily for 12 weeks did not adversely affect the mean maximum flow rate or mean detrusor pressure at maximum flow rate in this study. Nonetheless, MYRBETRIQ® should be administered with caution to patients with clinically significant BOO *[see Warnings and Precautions (5.2)]*.

Cardiac Electrophysiology

The effect of multiple doses of MYRBETRIQ® 50 mg, 100 mg and 200 mg once daily on QTc interval was evaluated in a randomized, placebo- and active- controlled (moxifloxacin 400 mg) four-treatment-arm parallel crossover study in 352 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTcI) was below 10 msec. For the 50 mg MYRBETRIQ® dose group (the maximum approved dosage), the mean difference from placebo on QTcI interval at 4-5 hours post-dose was 3.7 msec (upper bound of the 95% CI 5.1 msec).

For the MYRBETRIQ® 100 mg and 200 mg doses groups (dosages greater than the maximum approved dose and resulting in substantial multiples of the anticipated maximum blood levels at 50 mg), the mean differences from placebo in QTcI interval at 4-5 hours post-dose were 6.1 msec (upper bound of the 95% CI 7.6 msec) and 8.1 msec (upper bound of the 95% CI 9.8 msec), respectively. At the MYRBETRIQ® 200 mg dose, in females, the mean effect was 10.4 msec (upper bound of the 95% CI 13.4 msec).

In this thorough QT study, MYRBETRIQ® increased heart rate on ECG in a dose dependent manner. Maximum mean increases from baseline in heart rate for the 50 mg, 100 mg, and 200 mg dose groups compared to placebo were 6.7 beats per minutes (bpm), 11 bpm, and 17 bpm, respectively. In the clinical efficacy and safety studies, the change from baseline in mean pulse rate for MYRBETRIQ® 50 mg was approximately 1 bpm. In this thorough QT study, MYRBETRIQ® also increased blood pressure in a dose dependent manner *(see Effects on Blood Pressure)*.

Effects on Blood Pressure

In a study of 352 healthy subjects assessing the effect of multiple daily doses of 50 mg, 100 mg, and 200 mg of MYRBETRIQ® for 10 days on the QTc interval, the maximum mean increase in supine SBP/DBP at the maximum recommended dose of 50 mg was approximately 4.0/1.6 mm Hg greater than placebo. The 24-hour average increases in SBP compared to placebo were 3.0, 5.5, and 9.7 mm Hg at MYRBETRIQ® doses of 50 mg, 100 mg and 200 mg, respectively. Increases in DBP were also dose-dependent, but were smaller than SBP.

In another study in 96 healthy subjects to assess the impact of age on pharmacokinetics of multiple daily doses of 50 mg, 100 mg, 200 mg, and 300 mg of MYRBETRIQ® for 10 days, SBP also increased in a dose-dependent manner. The mean maximum increases in SBP were approximately 2.5, 4.5, 5.5 and 6.5 mm Hg for MYRBETRIQ® exposures associated with doses of 50 mg, 100 mg, 200 mg and 300 mg, respectively.

In three, 12-week, double-blind, placebo-controlled, safety and efficacy studies (Studies 1, 2 and 3) in OAB patients receiving MYRBETRIQ® 25 mg, 50 mg, or 100 mg once daily, mean increases in SBP/DBP compared to placebo of approximately 0.5 - 1 mm Hg were observed. Morning SBP increased by at least 15 mm Hg from baseline in 5.3%, 5.1%, and 6.7% of placebo, MYRBETRIQ® 25 mg and MYRBETRIQ® 50 mg patients, respectively. Morning DBP increased by at least 10 mm Hg in 4.6%, 4.1% and 6.6% of placebo, MYRBETRIQ® 25 mg, and MYRBETRIQ® 50 mg patients, respectively. Both SBP and DBP increases were 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 MYRBETRIQ® 100 mg was non-inferior to placebo for the primary endpoint of the treatment difference in mean change from baseline to day 56 in subject-average IOP; upper bound of the two-sided 95% CI of the treatment difference between MYRBETRIQ® 100 mg and placebo was 0.3 mm Hg.

12.3 Pharmacokinetics

Absorption

After oral administration of mirabegron in healthy volunteers, mirabegron is absorbed to reach maximum 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. 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 irrespective of food contents and intake (i.e., with or without food) and demonstrated both safety and efficacy. Therefore, mirabegron can be taken with or without food at the recommended dose *[see Dosage and Administration (2.1)]*.

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 *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 toward beta-3 adrenergic receptor. 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, mean C_{max} and AUC_{tau} were approximately 16% and 17% higher than in extensive metabolizers of CYP2D6, 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 solution to healthy volunteers, approximately 55% of the radioactivity dose was recovered in the urine and 34% in the feces. Approximately 25% of unchanged mirabegron was recovered in urine and 0% in feces.

Specific Populations

Geriatric Patients

The C_{max} and AUC of mirabegron following multiple oral doses in elderly volunteers (≥ 65 years) were similar to those in younger volunteers (18 to 45 years) *[see Use in Specific Populations (8.5)]*.

Pediatric Patients

The pharmacokinetics of mirabegron in pediatric patients have not been evaluated *[see Use in Specific Populations (8.4)]*.

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% - 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.

Renal Impairment

Following single dose administration of 100 mg mirabegron in volunteers with mild renal impairment (eGFR 60 to 89 mL/min/1.73 m^2 as estimated by MDRD), mean mirabegron C_{max} and AUC were increased by 6% and 31% relative to volunteers with normal renal function. In volunteers with moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m^2), C_{max} and AUC were increased by 23% and 66%, respectively. In 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 compared to healthy subjects with normal renal function. Mirabegron has not been studied in patients with End Stage Renal Disease-ESRD (CL_{cr} less than 15 mL/min or eGFR less than 15 mL/min/1.73 m^2 or patients requiring hemodialysis).

Hepatic Impairment

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

Drug Interaction Studies

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) 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-administered drugs was studied after single and multiple doses of mirabegron. Most drug-drug interactions (DDI) were studied using mirabegron 100 mg extended-release tablets. However, interaction studies of mirabegron with metoprolol and with metformin were studied using mirabegron 160 mg immediate release (IR) tablets.

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:

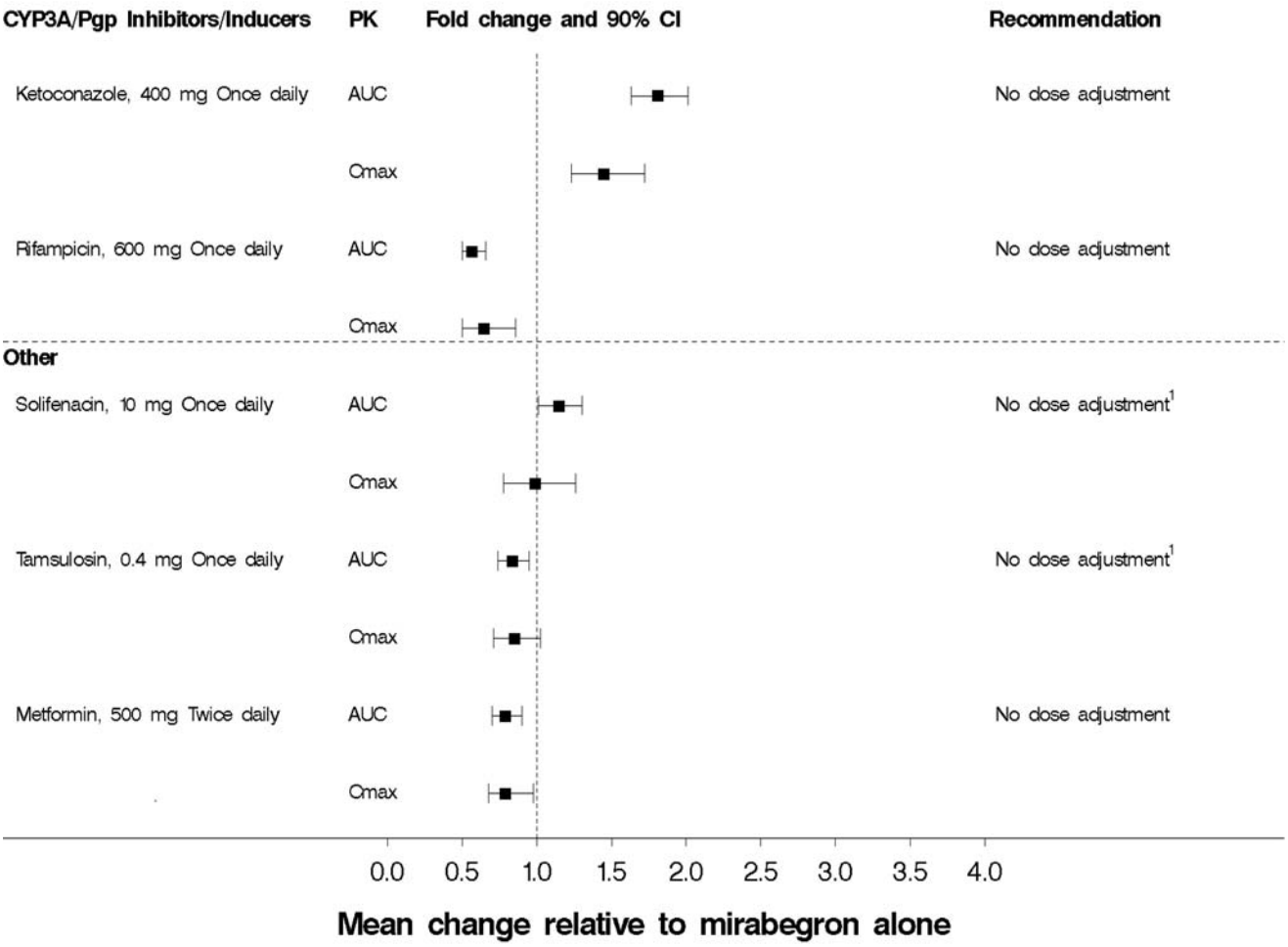
- Mirabegron increased the C_{max} of metoprolol by 90% and metoprolol AUC by 229% after multiple doses of 160 mg mirabegron IR tablets once daily for 5 days and a single dose of 100 mg metoprolol tablet in 12 healthy male subjects administered before and concomitantly with mirabegron.

- 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.

Caution is advised if MYRBETRIQ® is co-administered with CYP2D6 substrates such as metoprolol and desipramine, and especially narrow therapeutic index drugs, such as thioridazine, flecainide, and propafenone *[see Warnings and Precautions (5.4) and Drug Interactions (7.1)]*.

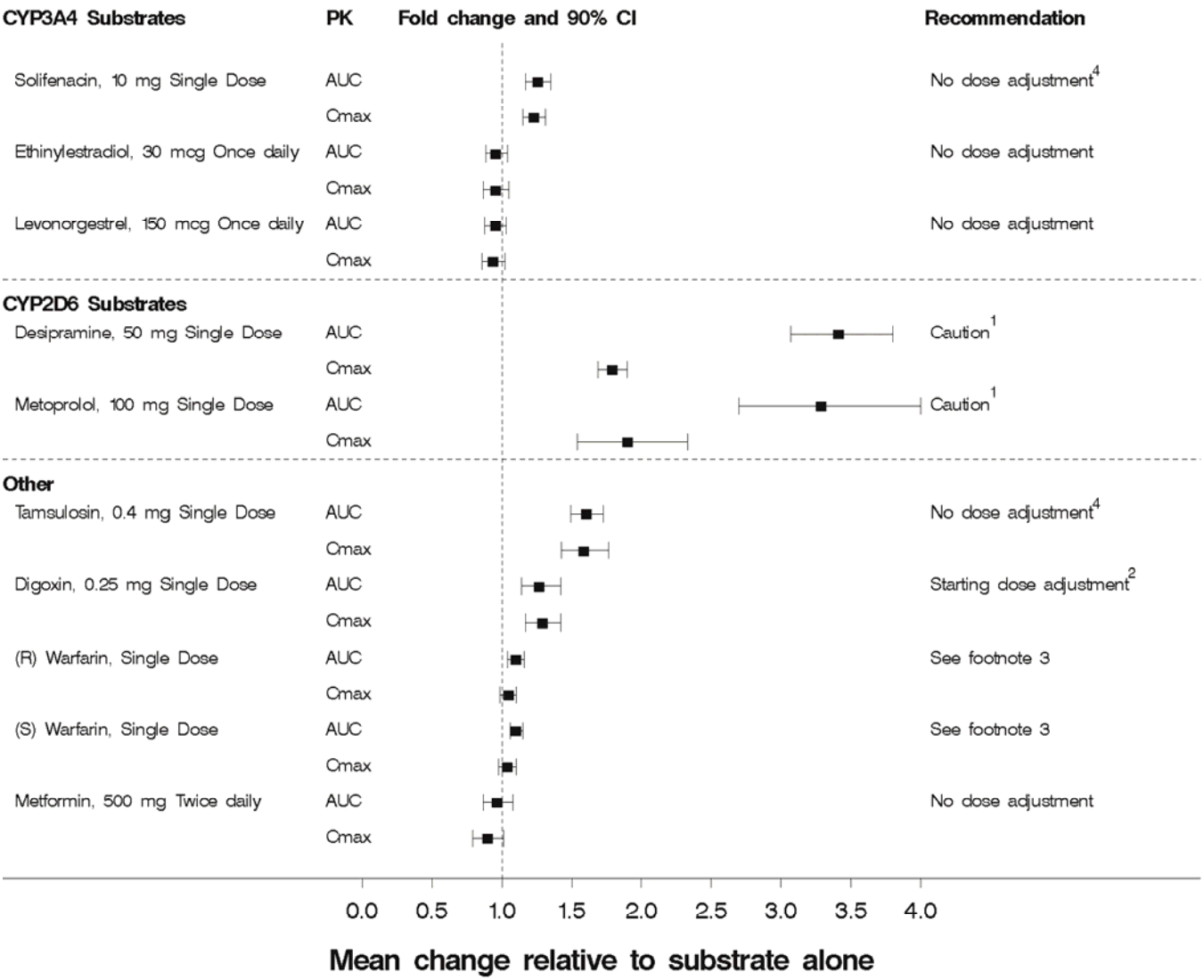
Figures 1 and 2 show the magnitude of these interactions on the pharmacokinetic parameters and the recommendations for dose adjustment, if any:

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 (5.2)]*.

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. Therefore, appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index CYP2D6 substrates, such as thioridazine, flecainide, and propafenone *[see Warnings and Precautions (5.4) and Drug Interactions (7.1)]*.

(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 (7.2)]*.

(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 (7.3)]*.

(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 (5.2)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity
Long-term carcinogenicity studies were conducted in rats and mice dosed orally with mirabegron for two years. Male rats were dosed at 0, 12.5, 25, or 50 mg/kg/day and female rats and both sexes of mice were dosed at 0, 25, 50, or 100 mg/kg/day. Mirabegron showed no carcinogenic potential at systemic exposures (AUC) 38 to 45-fold higher in rats and 21 to 38-fold higher in mice than the human systemic exposure at the 50 mg dose.

Mutagenesis
Mirabegron was not mutagenic in the Ames bacterial reverse mutation assay, did not induce chromosomal aberrations in human peripheral blood lymphocytes at concentrations that were not cytotoxic, and was not clastogenic in the rat micronucleus assay.

Impairment of Fertility
Fertility studies in rats showed that mirabegron had no effect on either male or female fertility at non-lethal doses up to 100 mg/kg/day. Systemic exposures (AUC) at 100 mg/kg in female rats was estimated to be 22 times the MRHD in women and 93 times the MRHD in men.

14 CLINICAL STUDIES

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 1, 2, and 3). 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 1, patients were randomized to placebo, MYRBETRIQ® 50 mg, MYRBETRIQ® 100 mg, or an active control once daily. In Study 2, patients were randomized to placebo, MYRBETRIQ® 50 mg or MYRBETRIQ® 100 mg once daily. In Study 3, 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. An important secondary endpoint was the change from baseline to end of treatment (Week 12) in mean volume voided per micturition.

Results for the co-primary endpoints and mean volume voided per micturition from Studies 1, 2, and 3 are shown in Table 3.

Table 3: Mean Baseline and Change from Baseline at Week 12‡ for Incontinence Episodes, Micturition Frequency, and Volume Voided per Micturition in Patients with Overactive Bladder in Studies 1, 2, and 3

Parameter	Study 1		Study 2		Study 3		
	Placebo	MYRBETRIQ® 50 mg	Placebo	MYRBETRIQ® 50 mg	Placebo	MYRBETRIQ® 25 mg	MYRBETRIQ® 50 mg
Number of Incontinence Episodes per 24 Hours^							
n	291	293	325	312	262	254	257
Baseline (mean)	2.67	2.83	3.03	2.77	2.43	2.65	2.51
Change from baseline (adjusted mean†)	-1.17	-1.57	-1.13	-1.47	-0.96	-1.36	-1.38
Difference from placebo (adjusted mean†)	--	-0.41	--	-0.34	--	-0.40	-0.42
95% Confidence Interval	--	(-0.72, -0.09)	--	(-0.66, -0.03)	--	(-0.74, -0.06)	(-0.76, -0.08)
p-value		0.003#		0.026#		0.005#	0.001#
Number of Micturitions per 24 Hours							
n	480	473	433	425	415	410	426
Baseline (mean)	11.71	11.65	11.51	11.80	11.48	11.68	11.66
Change from baseline (adjusted mean†)	-1.34	-1.93	-1.05	-1.66	-1.18	-1.65	-1.60
Difference from placebo (adjusted mean†)	--	-0.60	--	-0.61	--	-0.47	-0.42
95% Confidence Interval	--	(-0.90, -0.29)	--	(-0.98, -0.24)	--	(-0.82, -0.13)	(-0.76, -0.08)
p-value		< 0.001#		0.001#		0.007#	0.015#
Volume Voided (mL) per Micturition							
n	480	472	433	424	415	410	426
Baseline (mean)	156.7	161.1	157.5	156.3	164.0	165.2	159.3
Change from baseline (adjusted mean†)	12.3	24.2	7.0	18.2	8.3	12.8	20.7
Difference from placebo (adjusted mean†)	--	11.9	--	11.1	--	4.6	12.4
95% Confidence Interval	--	(6.3, 17.4)	--	(4.4, 17.9)	--	(-1.6, 10.8)	(6.3, 18.6)
p-value		< 0.001#		0.001#		0.15	< 0.001#

‡ Week 12 is last observation on treatment
† Least squares mean adjusted for baseline, gender, and geographical region
^For incontinence episodes per 24 hours, the analysis population is restricted to patients with at least 1 episode of incontinence at baseline.
#Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment

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 1, 2 and 3.

Figure 3: Mean (SE) Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours – Study 1

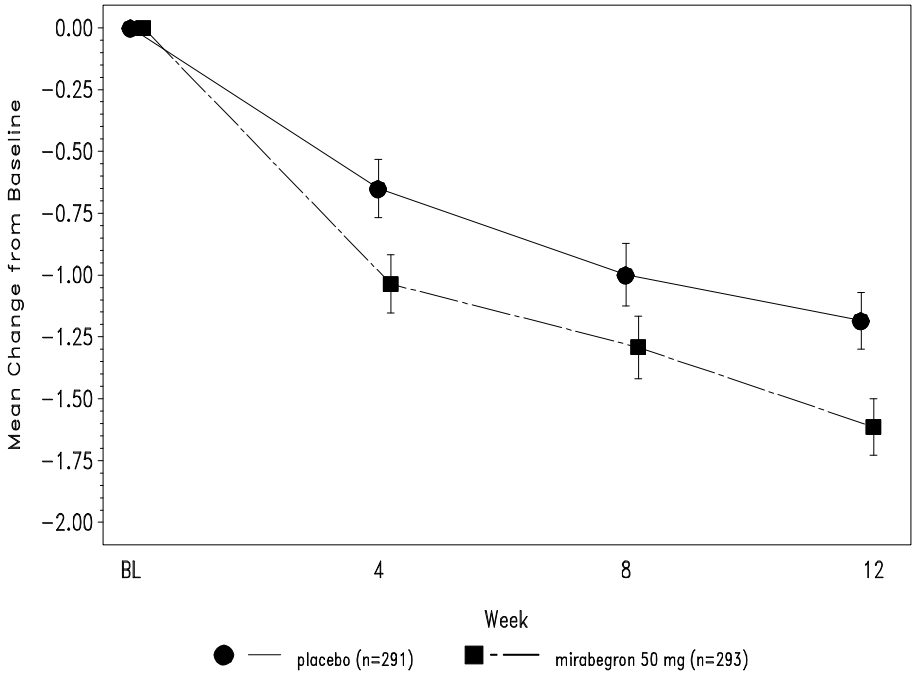


Figure 4: Mean (SE) Change from Baseline in Mean Number of Micturitions per 24 Hours - Study 1

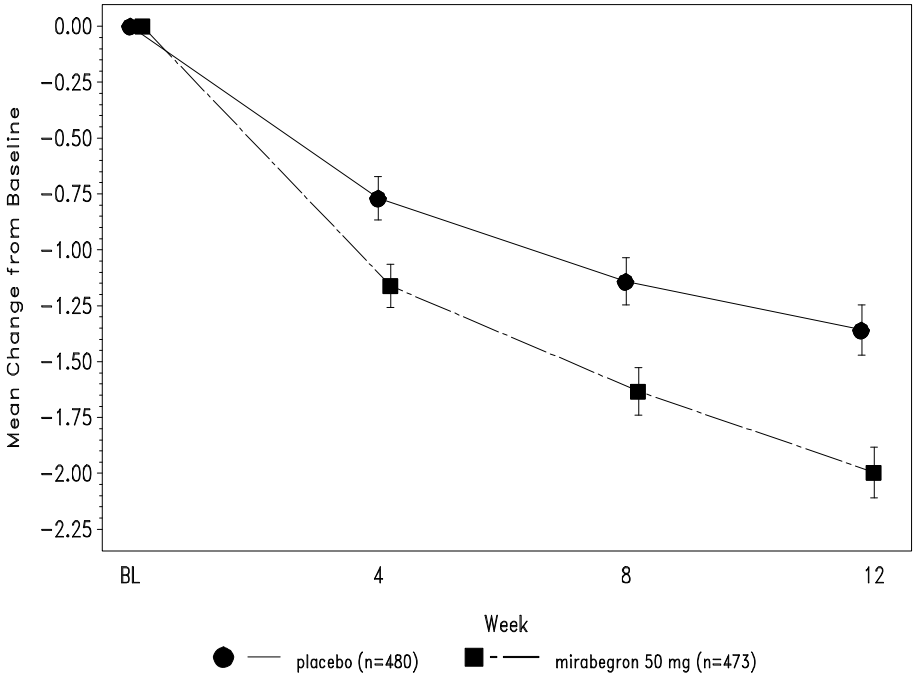


Figure 5: Mean (SE) Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours - Study 2

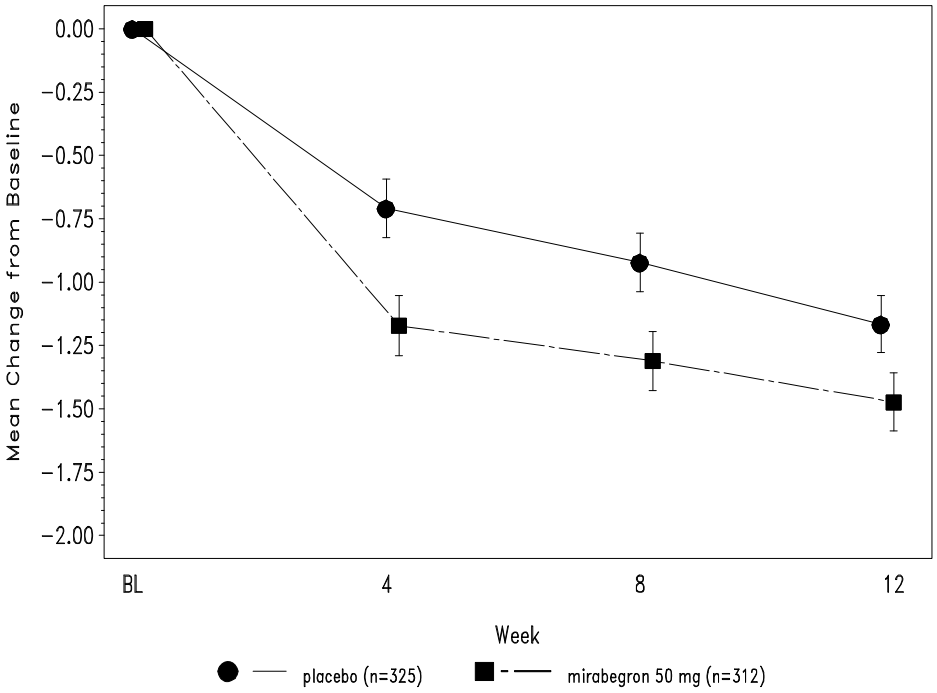


Figure 6: Mean (SE) Change from Baseline in Mean Number of Micturitions per 24 Hours - Study 2

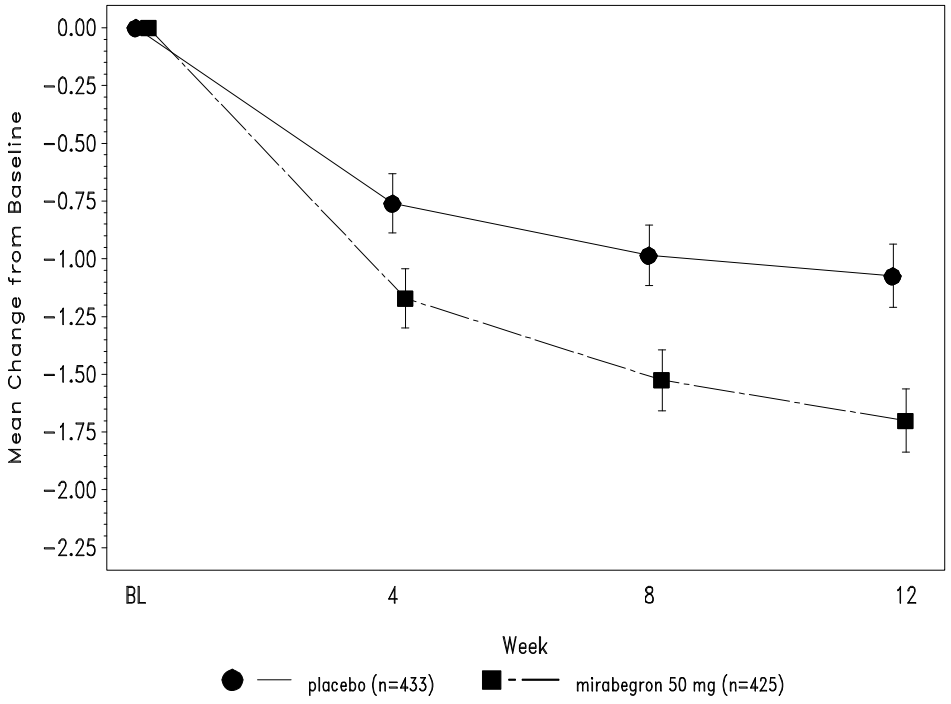


Figure 7: Mean (SE) Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours - Study 3

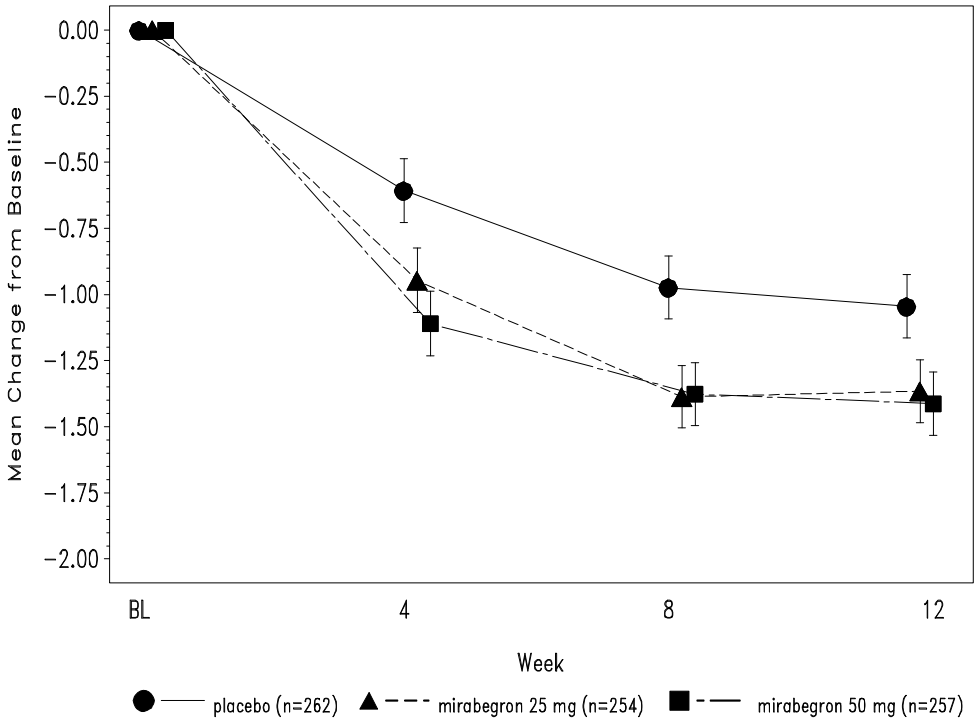
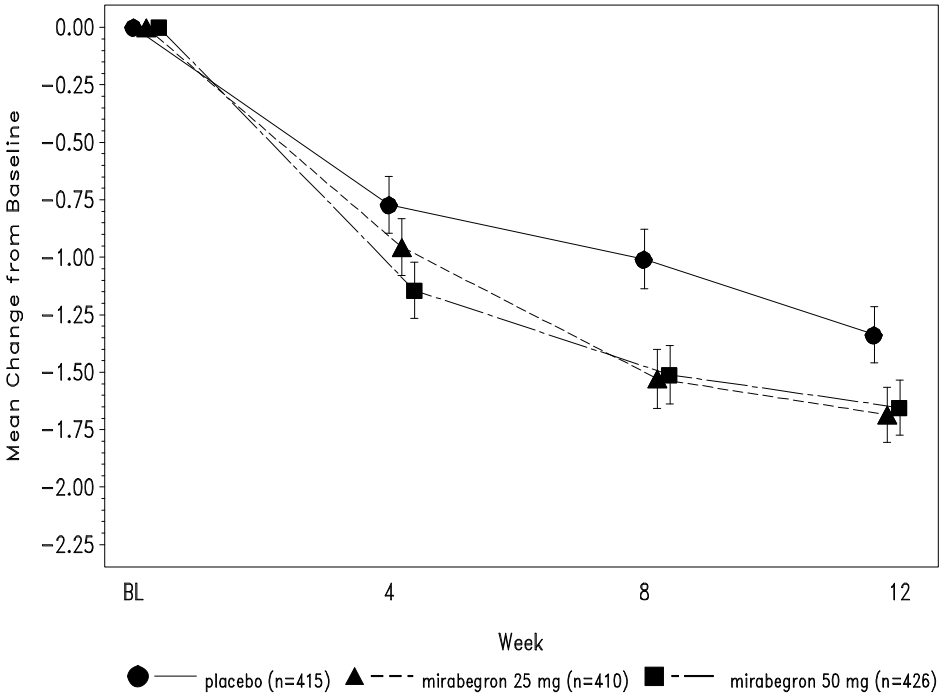


Figure 8: Mean (SE) Change from Baseline in Mean Number of Micturitions per 24 Hours - Study 3



16 HOW SUPPLIED/STORAGE AND HANDLING

MYRBETRIQ® is supplied as oval, film coated extended-release tablets, available in bottles and blister units as follows:

Strength	25 mg	50 mg
Color	brown	yellow
Debossed	logo, 325	logo, 355
Bottle of 30	NDC 0469-2601-30	NDC 0469-2602-30
Bottle of 90	NDC 0469-2601-90	NDC 0469-2602-90
Unit dose pack of 100	NDC 0469-2601-71	NDC 0469-2602-71

Store at 25°C (77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F) {see USP controlled Room Temperature}.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Inform patients that MYRBETRIQ® may increase blood pressure. Periodic blood pressure determinations are recommended, especially in patients with hypertension. MYRBETRIQ® has also been associated with infrequent urinary tract infections, rapid heartbeat, rash, and pruritus. Inform patients that urinary retention has been reported when taking mirabegron in combination with antimuscarinic drugs used in the treatment of overactive bladder. Instruct patients to contact their physician if they experience these effects while taking MYRBETRIQ®.

Patients should read the patient leaflet entitled “Patient Information” before starting therapy with MYRBETRIQ®.

Rx Only

PRODUCT OF JAPAN OR IRELAND – See bottle label or blister package for origin

Manufactured by:
Astellas Pharma Technologies, Inc.
Norman, Oklahoma 73072

Marketed and Distributed by:
Astellas Pharma US, Inc.
Northbrook, Illinois 60062

MYRBETRIQ® is a registered trademark of Astellas Pharma Inc. All other trademarks or registered trademarks are the property of their respective owners.

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Revised: July 2015
15F042-MIR-WPI

Patient Information

MYRBETRIQ® (meer-BEH-trick)

(mirabegron)

extended-release tablets

Read the Patient Information that comes with MYRBETRIQ® before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment.

What is MYRBETRIQ®?

MYRBETRIQ® is a prescription medicine for adults used to treat the following symptoms due to a condition called overactive bladder:

- Urge urinary incontinence: a strong need to urinate with leaking or wetting accidents
- Urgency: a strong need to urinate right away
- Frequency: urinating often

It is not known if MYRBETRIQ® is safe and effective in children.

Who should not use MYRBETRIQ®?

Do not use MYRBETRIQ® if you have an allergy to mirabegron or any of the ingredients in MYRBETRIQ®. See the end of this leaflet for a complete list of ingredients in MYRBETRIQ®.

What should I tell my doctor before taking MYRBETRIQ®?

Before you take MYRBETRIQ®, tell your doctor if you:

- have liver problems
- have kidney problems
- have very high uncontrolled blood pressure
- have trouble emptying your bladder or you have a weak urine stream
- are pregnant or plan to become pregnant. It is not known if MYRBETRIQ® will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if MYRBETRIQ® passes into your breast milk. You and your doctor should decide if you will take MYRBETRIQ® or breastfeed. You should not do both.

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.

Tell your doctor if you take:

- thioridazine (Mellaril™ or Mellaril-S™)
- flecainide (Tambocor®)
- propafenone (Rythmol®)
- digoxin (Lanoxin®)

How should I take MYRBETRIQ®?

- Take MYRBETRIQ® exactly as your doctor tells you to take it.
- You should take 1 MYRBETRIQ® tablet 1 time a day.
- You should take MYRBETRIQ® with water and swallow the tablet whole.
- Do not crush or chew the tablet.
- You can take MYRBETRIQ® with or without food.
- If you miss a dose of MYRBETRIQ®, begin taking MYRBETRIQ® again the next day. Do not take 2 doses of MYRBETRIQ® the same day.
- If you take too much MYRBETRIQ®, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of MYRBETRIQ®?

MYRBETRIQ® may cause serious side effects including:

- **increased blood pressure.** MYRBETRIQ® may cause your blood pressure to increase or make your blood pressure worse if you have a history of high blood pressure. It is recommended that your doctor check your blood pressure while you are taking MYRBETRIQ®.
- **inability to empty your bladder (urinary retention).** MYRBETRIQ® may increase your chances of not being able to empty your bladder if you have bladder outlet obstruction or if you are taking other medicines to treat overactive bladder. Tell your doctor right away if you are unable to empty your bladder.
- **angioedema.** MYRBETRIQ® may cause an allergic reaction with swelling of the lips, face, tongue, throat with or without difficulty breathing. Stop using MYRBETRIQ® and tell your doctor right away.

The most common side effects of MYRBETRIQ® include:

- increased blood pressure
- common cold symptoms (nasopharyngitis)
- urinary tract infection
- headache

Tell your doctor if you have any side effect that bothers you or that does not go away or if you have swelling of the face, lips, tongue, or throat, hives, skin rash or itching while taking MYRBETRIQ®.

These are not all the possible side effects of MYRBETRIQ®. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store MYRBETRIQ®?

- Store MYRBETRIQ® between 59°F to 86°F (15°C to 30°C). Keep the bottle closed.
- Safely throw away medicine that is out of date or no longer needed.

Keep MYRBETRIQ® and all medicines out of the reach of children.

General information about the safe and effective use of MYRBETRIQ®

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use MYRBETRIQ® for a condition for which it was not prescribed.

Do not give MYRBETRIQ® to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about MYRBETRIQ®. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about MYRBETRIQ® that is written for health professionals.

For more information, go to www.Myrbetriq.com website or call 1-800-727-7003.

What are the ingredients in MYRBETRIQ®?

Active ingredient: mirabegron

Inactive ingredients: polyethylene oxide, polyethylene glycol, hydroxypropyl cellulose, butylated hydroxytoluene, magnesium stearate, hypromellose, yellow ferric oxide and red ferric oxide (25 mg MYRBETRIQ® tablet only).

What is overactive bladder?
Overactive bladder occurs when you cannot control your bladder contractions. When these muscle contractions happen too often or cannot be controlled, you can get symptoms of overactive bladder, which are urinary frequency, urinary urgency, and urinary incontinence (leakage).

Rx Only

PRODUCT OF JAPAN OR IRELAND – See bottle label or blister package for origin

Manufactured by:
Astellas Pharma Technologies, Inc.
Norman, Oklahoma 73072

Marketed and Distributed by:
Astellas Pharma US, Inc.
Northbrook, Illinois 60062

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