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

----------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: 7/2017

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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:

Gastrointestinal disorders: nausea, constipation, diarrhea

Nervous system disorders: dizziness, headache

There have been postmarketing reports of confusion, hallucinations, insomnia and anxiety in patients taking mirabegron. The majority of these patients had pre-existing medical conditions or concomitant medications that may cause confusion, hallucinations, insomnia and anxiety. A causal relationship between mirabegron and these disorders has not been established.

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

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

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