

## NEW DRUG UPDATE

<b>Drug Name:</b>	mirabegron extended-release tablets
<b>Trade Name (Manufacturer):</b>	Myrbetriq™ (Astellas)
<b>Form:</b>	Oral tablets
<b>Strength:</b>	25 mg and 50 mg
<b>FDA Approval:</b>	June 28, 2012
<b>Market Availability:</b>	Available
<b>FDA Approval Classification:</b>	Standard review
<b>Classification:</b>	Specific Therapeutic Class (HIC3): Urinary Tract Antispasmodic/Anti-Incontinence Agent (R1A)

**Indication:**<sup>1</sup> Mirabegron (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.

**Contraindications/Warnings:** No contraindications have been reported.

Mirabegron may cause an increase in blood pressure. Periodic blood pressure monitoring is recommended, especially in patients with hypertension. Mirabegron is not recommended in patients with severe uncontrolled high blood pressure.

Urinary retention in patients with bladder outlet obstruction and in patients taking antimuscarinics for the treatment of OAB has been reported in postmarketing experiences in patients also taking mirabegron. Mirabegron should be used with caution in these patients.

Mirabegron is a moderate CYP2D6 inhibitor. Appropriate monitoring and adjustment of doses may be required with narrow therapeutic index drugs that are metabolized by CYP2D6 (e.g. thioridazine, flecainide and propafenone).

**Drug Interactions:** Drug interactions include drugs metabolized by CYP2D6 enzyme system such as metoprolol and desipramine and especially with narrow therapeutic index drugs, as noted in the warnings section. If a patient is concomitantly using digoxin and mirabegron, the lowest dose of digoxin should be prescribed. Serum digoxin concentrations should be monitored closely in order to titrate digoxin appropriately. Monitoring is also recommended when mirabegron is used concomitantly with warfarin as the drug's effect on INR and prothrombin time has not been fully investigated.

**Common Adverse Effects:** The most common adverse effects (greater than two percent of patients treated with mirabegron 25 mg and greater than placebo), based on pooled data from three placebo-controlled safety and efficacy studies in patients treated with mirabegron, included hypertension (11.3 percent), nasopharyngitis (3.5 percent), urinary tract infection (4.2 percent) and headache (2.1 percent).

### **Special Populations:**

**Pediatrics:** The safety and efficacy of mirabegron have not been established in the pediatric population.

**Pregnancy:** Pregnancy Category C

**Geriatrics:** During clinical studies, 36 percent of patients were 65 and older, while ten percent were 75 years of age and older. There were no differences in either effectiveness or tolerability between these patients and patients under the age of 65.

**Renal Impairment:** Specific guidelines for dosage adjustments in renal impairment are not available. Mirabegron has not been studied in patients with end stage renal disease or on hemodialysis and therefore is not recommended in these patients.

**Hepatic Impairment:** Specific guidelines for dosage adjustments in hepatic impairment are not available. Mirabegron has not been studied in patients with severe hepatic impairment and therefore is not recommended in these patients.

**Dosages:** The recommended starting dose of mirabegron is 25 mg once daily without regard to food. Mirabegron should be effective within eight weeks of therapy. The dose may be increased to 50 mg once daily depending on individual patient response and tolerability to the drug.

Mirabegron should be taken with water and swallowed whole; it should not be chewed, divided or crushed.

**Clinical Trials:** A literature search was performed using “mirabegron”.

Mirabegron was evaluated in three, 12-month, double-blind, randomized, placebo-controlled, parallel group clinical trials in patients with overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency. To be enrolled, patients had to present with symptoms of OAB for at least three months, at least eight micturitions per day and at least three episodes of urgency (with or without incontinence) over a three day period. Seventy-two percent of patients were female with a mean age of 59 years. Forty-eight percent of patients were antimuscarinic treatment-naïve; the remaining patients had received prior antimuscarinic treatment for OAB.

In Study 1, patients were randomized to placebo, mirabegron 50 mg, mirabegron 100 mg or an active control once daily. In Study 2, patients were randomized to placebo, mirabegron 50 mg or mirabegron 100 mg once daily. In Study 3, patients were randomized to placebo, mirabegron 25 mg or mirabegron 50 mg once daily. The efficacy endpoints in all three trials were change in baseline to end of treatment (week 12) in:

- mean number of incontinence episodes per 24 hours
- mean number of micturitions per 24 hours (based on a three-day micturition diary)

### **Results**

Change in baseline in mean number of incontinence episodes per 24 hours:

- Study 1:
  - mirabegron 50 mg: -1.57 (p=0.003)

- Study 2:
  - mirabegron 50 mg: -1.47 (p=0.026)
- Study 3:
  - mirabegron 25 mg: -1.36 (p=0.005)
  - mirabegron 50 mg: -1.38 (p=0.001)

Change in baseline in mean number of micturitions per 24 hours:

- Study 1:
  - mirabegron 50 mg: -1.93 (p=0.001)
- Study 2:
  - mirabegron 50 mg: -1.66 (p=0.001)
- Study 3:
  - mirabegron 25 mg: -1.65 (p=0.007)
  - mirabegron 50 mg: -1.60 (p=0.015)

Mirabegron 25 mg was effective in treating OAB symptoms within eight weeks and mirabegron 50 mg was effective in treating OAB symptoms within four weeks. Efficacy of both strengths was maintained through the 12 week treatment period.

**Other Drugs Used for Condition:**<sup>2</sup> Other FDA-approved pharmacological therapies indicated for the treatment of OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency in adult patients include the following antimuscarinics agents: darifenacin (Enablex®), fesoterodine (Toviaz®), oxybutynin (Ditropan®, Oxytrol™, Ditropan® XL), solifenacin (Vesicare®), tolterodine (Detrol®, Detrol® LA) and trospium (Sanctura®, Sanctura® XR).

**Place in Therapy:**<sup>3</sup> Mirabegron provides healthcare professionals with another option to treat OAB symptoms. According to the Agency for Healthcare Research and Quality (AHRQ), all antimuscarinic pharmacological treatments are effective at improving one or more OAB symptoms when compared to placebo and there is no single antimuscarinic agent that is superior to the other agents. Antimuscarinic agents treat OAB by binding to muscarinic receptors in the bladder and inhibiting involuntary bladder contractions.

Mirabegron offers an OAB treatment option with the first new mechanism of action in over 30 years. Mirabegron stimulates the beta-3 receptors in the detrusor muscle of the bladder, causing relaxation of the bladder muscle during the storage phase of the urination cycle. This improves the storage capacity of the bladder without decreasing bladder contraction during bladder voiding. Due to the new mechanism of action, mirabegron may be a treatment option for prescribers who have not been satisfied with previous antimuscarinic treatment results for OAB.

### ***Suggested Utilization Management:***

<b>Anticipated Therapeutic Class Review (TCR) Placement</b>	Bladder Relaxants
<b>Clinical Edit</b>	Prior authorization if product is determined to be non-preferred
<b>Quantity Limit</b>	30 tablets/30 days
<b>Duration of Approval</b>	Three months
<b>Drug to Disease Hard Edit</b>	Overactive bladder
<b>Retro-DUR</b>	Antimuscarinic drugs for overactive bladder
<b>Provider Profiling</b>	None

### ***References***

<sup>1</sup>Myrbetriq [package insert]. Northbrook, Illinois; Astellas Pharma Technologies, Inc; June 2012.

<sup>2</sup>Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2012. URL: <http://www.clinicalpharmacology.com>. Accessed July 20, 2012.

<sup>3</sup>Treatment for overactive bladder in women. August 2009. Agency for Healthcare Research and Quality. Rockville, MD. <http://www.ahrq.gov/clinic/tp/bladdertp.htm>. Accessed July 20, 2012.