**Mirabegron**
**(Myrbetriq)**

**Pharmacologic Category**  Beta₃ Agonist

**Indications**  Overactive bladder: Treatment of overactive bladder (OAB) with symptoms of urinary frequency, urgency, or urge urinary incontinence

**MOA**  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. This 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.

**Dosage and Administration**  Overactive bladder (OAB): Oral: Initial: 25 mg once daily; efficacy is observed within 8 weeks for 25 mg dose. May increase to 50 mg once daily based on individual patient efficacy and tolerability. Administer without regard to food. Swallow the tablet whole with water; do not chew, divide, or crush.

*Renal impairment*

CrCl 30 to 89 ml/minute or eGFR 30 to 89 ml/minute/1.73 m²: No dosage adjustment necessary

CrCl 15 to 29 ml/minute or eGFR 15 to 29 ml/minute/1.73 m²: Do not exceed 25 mg once daily

CrCl < 15 ml/minute or eGFR < 15 ml/minute/1.73 m²: Not recommended (has not been studied).

*Hepatic impairment*

Mild impairment (Child-Pugh class A): No dosage adjustment necessary

Moderate impairment (Child-Pugh class B): Do not exceed 25 mg once daily

Severe impairment (Child-Pugh class C): Not recommended (has not been studied).

**Pregnancy**  Risk factor 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. Adverse effects have been observed in some animal reproduction studies.

**Pharmacodynamics/Kinetics**

Onset of action: efficacy is seen within 8 weeks; steady state achieved within 7 days

Distribution: $V_{ss}$: $\sim 1670$ L (following IV administration), extensively distributed

Protein binding: $\sim 71\%$; binds mainly to albumin and alpha$_1$-acid glycoprotein

Metabolism: Substrate of CYP2D6 (minor), CYP3A4 (minor), P-glycoprotein; Inhibits CYP2D6 (moderate)

Bioavailability: 29% to 35% (following 25 mg and 50 mg oral dosing, respectively); $C_{max}$ and AUC are higher in females compared to males

Half-life elimination: $\sim 50$ hours

Time to peak: $\sim 3.5$ hours

Excretion: Urine (radiolabeled drug: 55%; unchanged drug: $\sim 25\%$); feces (radiolabeled drug: 34%; unchanged drug: 0%)

**Contraindications** Hypersensitivity to mirabegron or any component of the formulation. Canadian labeling: Severe uncontrolled hypertension (systolic blood pressure $\geq 180$ mm Hg and/or diastolic blood pressure $\geq 110$ mm Hg); pregnancy

**Warnings/Precautions**

Concerns related to adverse effects:

Angioedema: Angioedema of the face, lips, tongue, and/or larynx has been reported; some cases have occurred after the first dose. May be life-threatening. Immediately discontinue and institute supportive care if the tongue, hypopharynx, or larynx is involved.

BP effects: Dose-related increases in bp have been reported; monitor bp periodically during therapy. Not recommended in patients with severe uncontrolled hypertension (SBP $\geq 180$ and/or DBP $\geq 110$ mm Hg); if used in patients with controlled and less severe hypertension, use with caution and monitor bp closely; exacerbation of preexisting hypertension has been reported.
Disease-related concerns:

**Bladder flow obstruction:** Use with caution in patients with bladder outlet obstruction (BOO); the risk of urinary retention may be increased.

**Hepatic impairment:** Use with caution in patients with mild to moderate hepatic impairment; dosage adjustment is required in patients with moderate hepatic impairment. Use is not recommended in severe hepatic impairment.

**QT prolongation:** Use with caution in patients with a history of QT interval prolongation or those receiving medications known to prolong the QT interval. In one thorough QT study, supratherapeutic doses prolonged the QTc interval in females but not in males (Malik 2012). In general, mirabegron at the recommended dose has a low risk of QT interval prolongation (Sanford 2013).

**Renal impairment:** Use with caution in patients with renal impairment; dosage adjustment is required in patients with severe renal impairment. Use is not recommended in ESRD.

**Adverse-Reactions**

**Greater than 10%:** Cardiovascular: Hypertension (9% to 11%)

**1%-10%:**

Cardiovascular: Tachycardia (2%)

CNS: Headache (4%), dizziness (3%)

GI: Constipation (2-3%), xerostomia (3%), diarrhea (2%), abdominal pain (1%)

Genitourinary: UTI (3-6%), cystitis (2%)

Infection: Influenza (3%)

Neuromuscular & skeletal: Back pain (3%), arthralgia (2%)

Respiratory: Nasopharyngitis (4%), sinusitis (3%)

**Monitoring Parameters** Monitor blood pressure at baseline and then periodically during therapy.
Drug Interactions

The following are drug interactions for which monitoring is recommended:

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. Appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index CYP2D6 substrates, such as thioridazine, flecainide, and propafenone.

Digoxin

When given in combination, mirabegron increased mean digoxin AUC by 27% and mean C\text{max} from 1.01 to 1.3 ng/ml (29%). 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.

Efficacy

Herschorn et al. evaluated the efficacy and safety/tolerability of mirabegron 25 mg and 50 mg once-daily vs placebo in patients with OAB. Patients > 18 years with OAB symptoms for > 3 months entered a 2-week, single-blind, placebo run-in. At the end of the placebo run-in, potential enrollees completed a 3-day micturition diary. Those with an average of > 8 micturitions per 24 hours and > 3 urgency episodes (with or without incontinence) were randomized (1:1:1) to once-daily treatment with mirabegron 25 mg (n = 433), mirabegron 50 mg (n = 440), or placebo (n = 433) for 12 weeks. Urgency episodes were defined as a grade 3 or 4 on the 5-point Patient Perception of Intensity of Urgency Scale. Exclusion criteria included average total daily urine volume > 3000 ml and significant stress incontinence or mixed stress or urge incontinence, where stress was the main factor. Study visits occurred at baseline and weeks 4, 8, and 12; participants completed a 3-day micturition diary before each study visit. The two primary endpoints were changes from baseline to final visit in (1) mean number of incontinence episodes per 24 hours and (2) mean number of micturitions per 24 hours.

Compared to placebo, both mirabegron doses showed statistically significant improvements in coprimary efficacy endpoints. Average reductions in
incontinence episodes were 1.36, 1.38, and 0.96 for the mirabegron 25 mg, mirabegron 50 mg, and placebo groups, respectively. Average reductions in micturitions were 1.65, 1.60, and 1.18 for the mirabegron 25 mg, mirabegron 50 mg, and placebo groups, respectively.

Endpoints characterizing urgency (secondary endpoints) were more effectively treated with mirabegron 50 mg than mirabegron 25 mg. At weeks 4 and 8, mirabegron 50 mg showed statistically significant improvements vs placebo in average level of urgency, number of urgency incontinence episodes per 24 hours, and urgency episodes (grade 3 or 4). Compared to placebo, mirabegron 25 mg demonstrated numerically greater improvements on the three urgency assessments. The proportion of responders with zero incontinence episodes (100% dry rate) at final visit were as follows: 116 of 254 (45.7%) for mirabegron 25 mg; 121 of 257 (47.1%) for mirabegron 50 mg; 104 of 262 (39.7%) for placebo.

The protocol prespecified definition of a “hypertension event” was as follows: if the average SBP was ≥ 140 mm Hg and/or the average DBP was ≥ 90 mm Hg at two consecutive visits postbaseline in normotensive patients; average SBP increased ≥ 20 mm Hg and/or average DBP increased ≥ 10 mm Hg at two consecutive visits versus baseline in patients with hypertension at baseline; antihypertensive drugs were initiated, or if the dose of prior antihypertensive medication was increased due to BP increase.

Most TEAEs were mild or moderate in severity. Overall incidence of hypertension was 52 of 432 (12.0%), 49 of 440 (11.1%), and 37 of 433 (8.5%) in mirabegron 25 mg, 50 mg, and placebo groups, respectively. Adjusted average changes from baseline to final visit in SBP and DBP were comparable between mirabegron 25 mg and placebo groups. In the 50 mg group, the mean increase in morning and evening SBP (compared to placebo) was 1.5 mm Hg and the average increase in morning DBP was 1.0 mm Hg. Overall incidence of tachycardia was 7 of 432 (1.6%), 7 of 440 (1.6%) and 4 of 433 (0.9%) for mirabegron 25 mg, 50 mg, and placebo, respectively. Small increases from baseline in average pulse rate were seen for mirabegron versus placebo. At final visit, both doses of mirabegron increased pulse slightly compared to placebo. For AM measurements, average increase was 0.8 bpm for mirabegron 25 mg and 0.9 bpm for mirabegron 50 mg. For PM measurements, average increase was 0.6 bpm for 25 mg and 1.1 bpm for 50 mg.
Khullar et al. assessed the efficacy, safety, and tolerability of mirabegron 50 mg and 100 mg once daily in a 12 week randomized, double-blind, parallel-group, placebo- and tolterodine extended-release (ER)-controlled trial in patients with OAB (NCT00689104). The multicenter phase three trial was conducted in Europe and Australia. No statistical comparisons were performed for mirabegron versus tolterodine ER, which was included as an active control to evaluate the efficacy and safety of mirabegron in relation to that of a standard antimuscarinic OAB treatment.

Men and women > 18 years of age with symptoms of OAB for ≥ three months were included in the study. Inclusion criteria included an average micturition frequency of eight or more times per 24 hour period and at least three episodes of urgency (with or without incontinence) during a three day micturition diary period. Researchers excluded patients with the following conditions: stress incontinence; stress-predominant mixed incontinence; an average urine volume of > 3000 ml per day (as recorded in three day micturition diary period); clinically significant bladder outflow obstruction at risk of urinary retention (at discretion of investigator); indwelling catheter; diabetic neuropathy; severe hypertension (SBP ≥ 180 mm Hg and/or DBP ≥ 110 mm Hg); UTI; serum creatinine > 150 micromol/liter (1.7 mg/dL; AST/ALT > 2 times the ULN; GGT > 3 times ULN; interstitial cystitis; bladder stones; previous/current malignant disease of pelvic organs; uncontrolled narrow-angle glaucoma; urinary or gastric retention; severe colitis; toxic megacolon; myasthenia gravis; pregnant or breast-feeding or intending to become pregnant; anticholinergics; antispasmodics; CYP2D6 substrates with a narrow therapeutic index (thioridazine, flecainide, propafenone); strong CYP3A4 inhibitors. Patients were allowed to take CYP3A4 inducers, loop diuretics, alpha blockers, and 5 alpha-reductase inhibitors provided that the medication had been taken on a long-term basis at one dose and that the dose had not been adjusted in the month before entry in the study.

After screening, patients completed a two week single-blind (patients) placebo run-in period; those who met selection criteria were randomly assigned in a 1:1:1:1 ratio to a 12 week course of once daily placebo (n = 497), mirabegron 50 mg (n = 497), mirabegron 100 mg (n = 498), or tolterodine ER 4 mg (n = 495). For a three day period before baseline and at weeks 4, 8, and 12, patients filled out a paper micturition diary. The two co-primary efficacy endpoints were a change from baseline to final visit in the mean number of (1) incontinence episodes per 24 hours and (2) micturitions per 24 hours.
Compared with placebo, individuals in the mirabegron 50-mg and 100-mg groups demonstrated statistically significant reductions in the average number of incontinence episodes per 24 hours (average decreases of 1.57 and 1.46 for mirabegron 50 mg and 100 mg, respectively, vs 1.17 for placebo; p < 0.05 for both comparisons). Compared with placebo, individuals in the tolterodine ER group also improved but the difference was not statistically significant (average decrease of 1.27 vs 1.17; p = 0.11).

Compared with placebo, individuals in the mirabegron 50-mg and 100-mg groups demonstrated statistically significant reductions in the average number of micturitions per 24 hours (average decreases of 1.93 and 1.77 for mirabegron 50 mg and 100 mg, respectively, vs 1.34 for placebo; p < 0.05 for both comparisons). Compared with placebo, individuals in the tolterodine ER group also improved but the difference was not statistically significant (average decrease of 1.59 vs 1.34; p = 0.11).

The percentage of patients who were incontinent at baseline and “dry” at final visit was 45.1% for mirabegron 50 mg, 43.8% for mirabegron 100 mg, 47.3% for tolterodine ER 4 mg, and 40.5% for placebo. Compared to placebo, none of these differences was statistically significant.

The incidence of treatment-emergent AEs (TEAEs) was similar across all treatment groups. In all treatment groups, most TEAEs were mild or moderate. The incidence of dry mouth in the mirabegron 50-mg and 100-mg groups was similar to placebo (2.8%, 2.8%, and 2.6%, respectively). The incidence of dry mouth in patients receiving tolterodine ER was 10.1%.

The incidence of hypertension in each treatment group was as follows: 5.9% in mirabegron 50-mg; 5.4% in mirabegron 100-mg; 7.7% in placebo; 8.1% in tolterodine ER 4-mg. Compared with placebo, mirabegron demonstrated small dose-dependent increases in AM and PM pulse rates at the final visit (for mirabegron 50 mg and 100 mg, respectively AM: 0.8 bpm, 95% CI, 0.0-1.6 and 1.6 bpm, 95% CI, 0.8-2.4. PM: 0.7 bpm, 95% CI, -0.1 to 1.5 and 2.0 bpm, 95% CI, 1.2-2.8). Tolterodine ER 4 mg demonstrated similarly small increases in pulse rate compared to placebo. Across all treatment groups and in both the normotensive and hypertensive population, adjusted average changes from baseline in systolic and diastolic blood pressure measurements were < 1.5 mm Hg.

After a ≥ 30 day drug washout, some of the individuals enrolled in NCT00689104 entered a randomized, double-blind, active-controlled phase 3 study to assess mirabegron’s 12-month safety and efficacy (Chapple et al.).
After screening, patients completed a two-week single-blind placebo run-in period; inclusion and exclusion criteria were the same as in NCT00689104. Patients completed a three day micturition diary at the end of the two-week placebo run-in period (just before randomization) and before visits at months 1, 3, 6, 9, and 12. In total, 2444 patients were randomized and the study population was comprised of patients from NCT00689104, NCT00662909, and direct enrollers. About 80% of patients had participated in previous mirabegron phase 3 trials.

The primary outcome variable was the incidence and severity of TEAEs. Table 2 (below) lists the most frequent (> 2% in any treatment group) treatment-emergent adverse events and adverse events of interest. A "hypertension event" was defined using the same criteria as in Herschorn et al.

**Table 2**—Most frequent (> 2% in any treatment group) treatment-emergent adverse events and adverse events of interest

<table>
<thead>
<tr>
<th>MedDRA preferred term, n (%)</th>
<th>Mirabegron 50 mg (n = 812)</th>
<th>Mirabegron 100 mg (n = 820)</th>
<th>Tolterodine ER 4 mg (n = 812)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>485 (59.7)</td>
<td>503 (61.3)</td>
<td>508 (62.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>75 (9.2)</td>
<td>80 (9.8)</td>
<td>78 (9.6)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>48 (5.9)</td>
<td>45 (5.5)</td>
<td>52 (6.4)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>23 (2.8)</td>
<td>19 (2.3)</td>
<td>70 (8.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>33 (4.1)</td>
<td>26 (3.2)</td>
<td>20 (2.5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>23 (2.8)</td>
<td>25 (3.0)</td>
<td>22 (2.7)</td>
</tr>
<tr>
<td>Back pain</td>
<td>23 (2.8)</td>
<td>29 (3.5)</td>
<td>13 (1.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>22 (2.7)</td>
<td>13 (1.6)</td>
<td>21 (2.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 (1.8)</td>
<td>24 (2.9)</td>
<td>16 (2.0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17 (2.1)</td>
<td>19 (2.3)</td>
<td>16 (2.0)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>8 (1.0)</td>
<td>19 (2.3)</td>
<td>25 (3.1)</td>
</tr>
<tr>
<td>Cystitis</td>
<td>17 (2.1)</td>
<td>11 (1.3)</td>
<td>19 (2.3)</td>
</tr>
<tr>
<td><strong>Adverse events of interest, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrected QT interval prolongation</td>
<td>3 (0.4)</td>
<td>2 (0.2)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>89 (11.0)</td>
<td>83 (10.1)</td>
<td>86 (10.6)</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>32 (3.9)</td>
<td>34 (4.1)</td>
<td>49 (6.0)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Acute urinary retention</td>
<td>0</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>45 (5.5)</td>
<td>44 (5.4)</td>
<td>42 (5.2)</td>
</tr>
<tr>
<td>Syncope/seizure</td>
<td>1 (0.1)</td>
<td>0</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>17 (2.1)</td>
<td>19 (2.3)</td>
<td>15 (1.8)</td>
</tr>
</tbody>
</table>
Adjusted mean changes from baseline to final visit for SBP in mirabegron 50 and 100 mg and tolterodine were 0.2, 0.4, and -0.5 mm Hg for AM measurements and -0.3, 0.1, and -0.00 mm Hg for PM measurements. Adjusted mean changes for DBP were -0.3, 0.4, and 0.1 mm Hg for AM measurements and -0.0, 0.1, and 0.6 mm Hg for PM measurements. Across the 12-month period, adjusted mean change from baseline PR showed a small increase in each group. For the mirabegron 50 mg, 100 mg, and tolterodine groups, the changes in AM pulse were 0.9, 1.6, and 1.5 beats per minute (bpm). The changes in PM pulse were 0.4, 1.3, and 1.9 bpm.

With regard to efficacy, improvements were evident from month 1 (first time point) and were maintained throughout the year-long study. Reductions in the adjusted mean change from baseline for the mean number of micturitions per 24 h were as follows: -1.27 for mirabegron 50 mg, -1.41 for mirabegron 100 mg, and -1.39 for tolterodine ER 4 mg. Reductions in mean number of incontinence episodes per 24 h were -1.01 for mirabegron 50 mg, -1.24 for mirabegron 100 mg, and -1.26 for tolterodine ER 4 mg. Improvements in mean volume voided/micturition were 17.5 ml for mirabegron 50 mg, 21.5 ml for mirabegron 100 mg, and 18.1 ml for tolterodine ER 4 mg. The percentage of patients with zero incontinence episodes was 43.4%, 45.8%, and 45.1% for mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg, respectively.

Conclusions: Mirabegron (Myrbetriq) is a good treatment option for patients with OAB who do not respond to or cannot tolerate antimuscarinic agents. It was well tolerated in clinical trials and its efficacy was comparable to that of standard therapy.

Recommendation: Mirabegron (Myrbetriq) should be added to the formulary.
References:


Mirabegron (Lexi-Drugs), Lexicomp Online, Last Updated 6/1/17

Mirabegron (Myrbetriq), Highlights of Prescribing Information, Astellas Pharma Inc., revised August 2016

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