PharmaNote®

VOLUME 28, ISSUE 6 MARCH 2013

MIRABEGRON: NEW OPTION FOR TREATMENT OF OVERACTIVE BLADDER

Richard Dance, Pharm.D. Candidate

Overactive bladder (OAB) affects 16.5% of American adults and is more frequent in females and the elderly.[1-3] Over 30-40% of individuals 75 years of age and older experience OAB.[4] Symptoms can become burdensome over time and can decrease quality of life due to disruption of daily activities, sleep, sexual function, and work productivity.[5,6] In 2007, OAB was responsible for $65.9 billion in medical costs which is expected to increase to $82.6 billion by 2020.[7]

OAB is a condition characterized by frequency, urgency, urge incontinence, and nocturia. The need to urinate 8 or more times in 24 hours is also associated with OAB. These voids are usually small in volume compared to regular or large volume voids seen in patients with polyuria.[8] Symptoms of OAB are caused by involuntary contractions of the detrusor muscle or by dysfunction of sensory neurons in the bladder. Acetylcholine and muscarinic type 3 receptors (M3) mediate the contractions of the detrusor muscle while norepinephrine and beta-3 receptors control relaxation.[9] First line treatment for OAB includes behavioral therapies such as bladder training, pelvic floor muscle strengthening, and fluid control. Pharmacological treatment is second line and includes anticholinergics such as oxybutynin, tolterodine, trospium chloride, solifenacin, and darifenacin.[8]

Astellas Pharma gained FDA approval for Mybetriq® (mirabegron) in June 2012. Mirabegron is a beta-3 agonist for the treatment of OAB in patients with symptoms of urge urinary incontinence, urgency, and urinary frequency. Mirabegron is the first beta-3 agonist approved for the treatment of OAB.[10] This article will overview the pharmacology, pharmacokinetics, clinical trials, adverse events, and dosing of mirabegron.

PHARMACOLOGY

Mirabegron functions as a beta-3 adrenergic receptor agonist. It is highly selective for the beta-3 receptor compared to the beta-1 and beta-2 receptor. In vitro studies of mirabegron demonstrated a half-maximal effective concentration (EC_{50}) of 22.4 nM at the beta-3 receptor and greater than10,000 nM at the beta-1 and beta-2 receptor.[10] Activation of the beta-3 adrenergic receptors result in relaxation of the detrusor muscle during the storage phase of the bladder fill-void cycle, increasing the bladder's ability to store urine.[11]

PHARMACOKINETICS

Two randomized, phase I pharmacokinetic studies were completed evaluating mirabegron (**Table 1**). The bioavailability of mirabegron increases with dose: 29% with 25 mg, 35% with 50 mg, and 45% with 150 mg. Peak concentration occurs after 3.5 hours and steady state concentrations were reached within 7 days with the extended release tablets; the half-life is

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Table 1 | Pharmacokinetic Properties of Mirabegron [4]

Property	Value
Bioavailability	29-25%
Peak Plasma Concentration	3.5 hours
Volume of Distribution	1670L (IV administration)
Protein Binding	71%
Metabolism	dealkylation, oxidation, glucuronidation, and amide hydrolysis
Clearance	Renal
Half-Life	50 hours

IV= Intravenous, L= liters

50 hours. Mirabegron is metabolized by a number of mechanisms including dealkylation, oxidation, glucuronidation, and amide hydrolysis.[4] As mirabegron is a moderate cytochrome P-450 enzyme (CYP) 2D6 inhibitor drugs metabolized by this route should be monitored when used concomitantly with mirabegron.[12] Twenty-five percent of mirabegron is excreted unchanged in the urine.[4]

Clinical Trials

The safety and efficacy of mirabegron was evaluated in three phase III clinical trials. All three studies were 12 week randomized, double blind, placebo controlled, parallel group, multicenter trials (**Table 2**). The two primary outcomes measured for all 3 studies were: 1) change from baseline to final visit in the mean number of incontinence events per 24 hours; and 2) the change from baseline to final visit in the mean number of urinations every 24 hours (**Table 3**). An important secondary outcome was the change from baseline to week 12 visit in the average volume voided per urination. Patients recorded the volume of each urination for a 3 day period at baseline and likewise before the final clinic visit. Results are represented as a least square mean (LSM) for each outcome, which are averages adjusted for treatment group, gender, and geographic region using an analysis of covariance (ANCOVA) with baseline results as the covariate.[13-15] The adjustments are made to increase the precision between outcomes measured and for imbalances between the groups such as differences in age, gender, and geographic region. Limitations common in all trials included the short duration of the trials (12 weeks), a gender and racially narrow group study subjects, and the fact that patients who had discontinued anticholinergic therapy in past due to lack of efficacy were included.

The study to Test the Efficacy and Safety of the Beta-3 Agonist Mirabegron (YM178) in Patients With Symptoms of Overactive Bladder (SCORPIO) took place in Europe, Australia, and South Africa.[13] SCORPIO was conducted at 219 facilities and involved 1,978 patients, of which 72% were female and 99% were Caucasian. Patients were randomized to receive placebo (N = 494), mirabegron 50 mg (N =493), mirabegron 100 mg (N=496), or tolterodine SR (N = 495) for 12 weeks. Comparisons were made between baseline and results from the week 12 clinic visit.

The result of the primary outcome, change from baseline mean number of incontinence episodes every 24 hours (calculated by LSM), was -1.17 for placebo, -1.57 for mirabegron 50 mg (compared to placebo, p = 0.003), -1.46 for mirabegron 100 mg (compared to placebo, p = 0.01), and -1.27 for tolterodine SR 4 mg (compared to placebo, p = 0.11). The second primary outcome, change from baseline mean number of urinations every 24 hours, was decreased from baseline by -1.34 with placebo, by -1.93 with mirabegron 50 mg (compared to placebo, p < 0.001), by -1.77 with mirabegron 100 mg (compared to placebo, p = 0.005), and by -1.59 with tolterodine SR (compared to placebo, p

Table 2 | Exclusion, Inclusion Criteria, and Outcomes for Clinical Trials [13-15]

Inclusion Criteria	Ability to complete urination diary and questionnaires correctly Have symptoms of OAB for ≥ 3 mo Experience an average of ≥ 8 urinations every 24 hrs during the 3 day urination period Experience 3 episodes of urgency with or without incontinence during the 3 day urination period
Exclusion Criteria	Pregnant, stress incontinence, indwelling catheter, urinary tract infection, chronic inflammation of interstitial cystitis, bladder stones, pelvic radiation therapy, pervious or current cancer of pelvic organs, electro-stimulation therapy, severe hypertension, hypersensitivity to tolterodine or other anticholinergics, treated with any investigation drug within 30 days (within 90 days for UK patients), average total daily urine volume > 3000 ml during the 3 day urination period
Primary Outcomes	Change from baseline to final visit the mean number of incontinence events per 24 hrs Change from baseline to final visit the mean number of urinations every 24 hrs
Secondary Outcome	Change from baseline to the week 12 clinic visit the average volume voided per urination

hrs: hours, mo: months

=0.11).[13]

The mean volume of urine voided per urination increased by 12.3 mL with placebo, 24.2 mL with mirabegron 50 mg, 25.6 mL with mirabegron 100 mg, and 25 mL with tolterodine SR 4 mg (compared to placebo, p < 0.001 for all). One limitation to the study was that tolterodine was used as an active control and was not compared directly against mirabegron.[13]

The Efficacy and Safety of Beta-3 Agonist Mirabegron (YM178) in Patients With Symptoms of Overactive Bladder (ARIES) study was conducted in the United States and Canada at 125 facilities. Overall 1,328 patients were randomized to 12 weeks of once daily placebo (N = 453), mirabegron 50 mg (N = 442), or mirabegron 100 mg (N = 433). The ARIES study population was primarily composed of women (74%) and Caucasians (87%). Outcomes were measured by comparing baseline data to week 12 data.[14]

Compared to baseline, at 12 weeks the mean number of incontinence events every 24 hours (calculated by LSM) decreased by 1.13 for placebo, 1.47 for mirabegron 50 mg, and 1.63 for mirabegron 100 mg. Compared to placebo mirabegron 50 mg and 100 mg resulted in a decrease of mean incontinence events every 24 hours by -0.34 (p = 0.026) and -0.50 (p < 0.001), respectively. When compared to placebo, mirabegron 50 mg and 100 mg decreased the mean number of urinations per 24 hours by -0.61 (p = 0.001) and -0.70 (p < 0.001). Compared to placebo, mirabegron 50 mg and 100 mg increased the mean volume of urine voided by 11.1 mL (p = 0.001) and 11 mL (p = 0.002), respectively. Researchers concluded that by week 12 mirabegron 50 mg and 100 mg showed statistically significant improvements in symptoms of OAB measured compared to placebo.[14]

The Study to Test the Efficacy and Safety of the Beta-3 Agonist Mirabegron (YM178) in Patients With Symptoms of Overactive Bladder (CAPRICORN) was conducted in the United States, Canada, and Europe. CAPRICORN involved 151 facilities and 1,305 patients with 68% being female and 90% being Caucasian. Patients were randomized to placebo (N=433), mirabegron 25 mg (N = 432), or mirabegron 50 mg (N = 440) once daily for 12 weeks. Results were calculated by comparing baseline and week 12 data.[15]

At week 12 the mean number of incontinence events per 24 hours decreased by 0.96 for placebo, 1.36 for mirabegron 25 mg, and 1.38 for mirabegron 50 mg. Compared to placebo, mirabegron 25 mg and 50 mg resulted in a difference of incontinence events by -0.40 (p = 0.005) and -0.42 (p = 0.001), respectively. The mean number of urinations every 24 hours was decreased by 1.18 for placebo, 1.65 for mirabegron 25 mg (compared to placebo, p = 0.007), and 1.60 for mirabegron 50 mg (compared to placebo, p = 0.015). The mean volume of urine voided per urination was increased by 8.3 mL with placebo, by 12.8 mL with mirabegron 25 mg (compared to placebo, p = 0.15), and by 20.7 mL with mirabegron 50 (compared to placebo, p < 0.001). Improvements of the 2 primary outcomes were statically significant by week 8 for mirabegron 25 mg and by week 4 for mirabegron 50 mg.[15]

Adverse Events

The safety of mirabegron was evaluated through adverse event reporting that occurred in SCORPIO[13], ARIES[14], and CAPRICORN[15] as well as a fourth study

Table 3 | Summary of Clinical Trial Results for Mirabegron

Study	Intervention	Outcomes*		
		Change from BL to wk 12 clinic visit mean # of incontinence episodes Q 24 H	Change from BL to wk 12: mean # of urinations Q 24 H	Change from BL to wk 12: mean volume voided/ urination
SCORPIO [13]	M 50 mg (N=493), M 100 mg (N=496), T SR 4 mg (N=495)	M 50 mg: -0.41 (p=000.3) M 100 mg: -0.29 (p=0.010) T SR 4 mg: -0.10 (p=0.10)	M 50 mg: -0.60 (p<0.001) M 100 mg: -0.44 (p=0.005) T SR 4 mg: -0.25 (p=0.11)	M 50 mg: 11.9 mL (p<0.001) M 100 mg: 13.2 mL (p<0.001) T SR 4 mg: 12.6 mL (p<0.001)
ARIES [14]	M 50 mg (N=442), M 100 mg (N=433)	M 50 mg: -0.34 (p=0.026) M 100 mg: -0.50 (p<0.001)	M 50 mg: -0.61 (p=0.001) M 100 mg: -0.70 (p=0.001)	M 50 mg: 11.1 mL (p=0.001) M 100 mg: 11 mL (p=0.002)
CAPRICORN [15]	M 25 mg (N=432), M 50 mg (N=440)	M 25mg: -0.40 (p=0.005) M 50 mg:-0.42 (p=0.001)	M 25mg: -0.47 (p=0.007) M 50 mg: -0.42 (p=0.015)	M 25mg: 4.6 mL (p=0.15) M 50 mg: 12.4 mL (p<0.001)

#= Number, BL= Baseline, H= Hours, M=Mirabegron, mL= milliliters, PCB= Placebo, Q= Every, SR= Sustained Release, T= Tolterodine, VL= Volume, Wk= Week
*Values reported represent the difference compared to placebo, calculated by LSMD

Table 4 | Number of Patients With Adverse Events in TAURUS [16]

	Mild	Moderate	Severe
Mir 50 mg	222 (27%)	212 (26%)	51 (0.06%)
Mir 100 mg	240 (29%)	211 (25%)	52 (0.06%)
Tol SR 4 mg	251 (31%)	218 (26%)	39 (0.04%)

M= Mirabegron, T= Tolterodine sustained release

TAURUS[16] which was used to identify safety, tolerability and long term effects of a daily mirabegron. In TAURUS, 2,444 patients were randomized to mirabegron 50 (N=812), mirabegron 100 mg (N=820), or tolterodine SR 4 (N=812) once daily for 12 months; patients were evaluated at months 1, 3, 6, 9, 12, and 13 one month after discontinuing study medications. The primary outcome was measured as the number of patients with an adverse events classified as mild (no disruption of normal day activities), moderate (affected normal day activities), or severe (inability to preform daily activities) (**Table 4**).[16]

Adverse reactions occurring more frequently than 2% in TAURUS included hypertension, urinary tract infection, headache, nasopharyngitis, back pain, constipation, dry mouth, dizziness, sinusitis, influenza, arthralgia, and cystitis (**Table 5**).[16]

Adverse events occurring more frequently than 0.2% from SCORPIO[13], ARIES[14], and CAPRICORN[15] leading to study drug discontinuation included nausea, headache, hypertension, diarrhea, constipation, dizziness, and tachycardia. The most common adverse reactions were hypertension, nasopharyngitis, urinary tract infection, and headache (**Table 6**).[13-15]

Table 5 | Adverse Reactions Reported in TAURUS By More Than 2% of Patients [16]

	Mir 50 mg (%)	Mir 100 mg (%)	Tol SR 4 mg (%)
Hypertension	9.2	9.8	9.6
Urinary Tract Infection	5.9	5.5	6.4
Headache	4.1	3.2	2.5
Nasopharyngitis	3.9	4.3	3.1
Back Pain	2.8	3.5	1.6
Constipation	2.8	3.0	2.7
Dry Mouth	2.8	2.3	8.6
Dizziness	2.7	1.6	2.6
Sinusitis	2.7	2.2	1.5
Influenza	2.6	3.0	3.4
Arthralgia	2.1	2.3	2.0
Cystitis	2.1	1.3	2.3

Mir: mirabegron; tol SR: tolterodine sustained release

Dosage

Mirabegron is available in a 25 mg or 50 mg extended release tablet to be taken once daily. It can be taken with or without food and should be swallowed whole with water.[11] Patients should see results within 8 weeks of treatment for the 25 mg dose and within 4 weeks with the 50 mg dose.[15] For patients with mild hepatic impairment (Child-Pugh class A) no dose adjustments are needed. For patients with moderate hepatic impairment (Child-Pugh class B) the dose should not exceed 25 mg. Mirabegron is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C). In patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] 30-89 mL/min/1.73 m^2) no dose adjustments are needed. In patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) the daily dose should not exceed 25 mg. Mirabegron is not recommended in end stage renal disease (eGFR <15 mL/min/1.73 m^2). No dosage adjustments are needed specifically for geriatric patients.[11]

Cost

The average retail price is $248.99 for a 30-day supply of mirabegron 25 mg or 50 mg. With the Myrbetriq® savings program, insured patients are responsible for the first $15 plus any cost over $50 each month for a year; the savings program does not apply

Table 6 | Adverse Reactions From Mirabegron Clinical Trials [13-15]

	Pcb (%)	Mir 25 mg (%)	Mir 50 mg (%)
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

Mir: mirabegron; pcb: placebo

to individuals who have government sponsored insurance. Myrbetriq® is also available via the Astellas Access Program free for those uninsured and below the federal poverty line.[17]

Summary

Myrbetriq® (mirabegron) is the first beta-3 agonist for the treatment of OAB symptoms. It provides patients with a new treatment option alongside the anticholinergics commonly used today. It can potentially be used after anticholinergic medication failure or a as fist line pharmacologic treatment. The CAPRICORN, AIRES, and SCORPIO trials combined efficacy and safety of mirabegron in 3,231 patients with symptoms of OAB. All 3 trials showed improvements in OAB symptoms by decreasing the number of incontinence episodes per 24 hours, decreasing the number of urinations per 24 hours, and increasing the average volume voided per urination when compared to placebo. Adverse events were similar when compared to active control in the safety trial TAURUS. As the most common adverse reaction is increased blood pressure patients should monitor blood pressure periodically when prescribed mirabegron. Mirabegron has not been studied in patients with end stage renal disease or severe hepatic impairment, there for should not be used in this patient population.

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Clinical Trial Update

Update on alpha-1 antitrypsin deficiency: clinical relevance and diagnosis— alpha-1 antitrypsin (AAT) is a serine protease inhibitor that provides protective effects against proteolytic enzymes. [1]

AAT is normally produced in the liver and is transported by the circulatory system to other organ systems. AAT deficiency (AATD) is caused by genetic polymorphisms which can lead to polymerization of AAT and accumulation in hepatocytes, reducing serum levels to less than 20 microM. Clinically AATD can cause hepatitis, cirrhosis, and hepatoma in individuals with genetic phenotypes that cause AAT polymerization and accumulation. Emphysema is the most common lung-related manifestation caused by unchecked proteolyltic activity by neutrophil elastase, which is normally inactivated by AAT; the protective effects of AAT are thought to be lost when serums levels decrease below 11 microM. Skin manifestations such as panniculitis can also occur but respiratory failure is the most common cause of death in AATD (45-72% of deaths).[1]

Patients with AATD often experience a delay between symptom onset and diagnosis. Delays in diagnosis have ranged from 5.6 (+/- 8.5) years to 8.3 (+/- 6.9) years in surveys of patients with AATD; many also reported seeing at least 3 physicians before the diagnosis was established.[1]

One potential reason for the delay in diagnosis is the perceived rarity of AATD. Using population based estimates there are an estimated 33,088 PI*ZZ individuals in the US. In contrast, direct approaches to estimate prevalence based on population-based screening studies estimates about 70,000 people in the US have AATD; this equates to 1/4,455 individuals.[1]

Treatment of AATD involves standard therapy for the disease (for respiratory disease, bronchodilators, lung rehabilitation, oxygen, etc.) combined with infusing purified pooled human plasma AAT (augmentation therapy) to raise AAT levels above the required protective threshold. In the US six different AAT preparations are commercially available. AAT testing should be offered to targeted individuals only. Serum AAT testing followed by genotypic characterization is the most common method to establish the diagnosis of AATD.

According to the ATS/ERS Guidelines[2] patients with persistent airflow limitation on spirometry should be tested. Additional clinical features suggesting AAT testing include: emphysema in a young individual (≤ 45 years of age); emphysema in a non– or minimal smoker; emphysema characterized by predominant basilar changes on chest x-ray; family history of emphysema or liver disease; clinical findings or history of panniculitis; or clinical findings or history of unexplained chronic liver disease. Diagnosis is confirmed by an AAT serum level less than 11 microM plus a severe deficient genotype.[1]

The international reference laboratory for AAT levels and phenotype and genotype analysis is located at the University of Florida in Gainesville, FL. In the state of Florida finger-stick screening tests are free to patients if administered at doctor's offices. Additionally, Grifols Inc. is supporting a nationwide targeted detection program by offering free finger stick tests that can be administered at doctor's offices. Providers interested in obtaining a test kit may call 1-800-562-7222. Tests are shipped in a supplied preaddressed envelope; results are sent to the prescribing physician in approximately 2 weeks.

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The PharmaNote is Published by:
The Department of Pharmacy Services, UF Family Practice Medical Group, Departments of Community Health and Family Medicine and Pharmacotherapy and Translational Research
University of Florida