Drug Monograph

Drug/Drug Class:	**Myrbetriq™ (Mirabegron) extended-release tablets / beta-3 adrenergic agonist**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Each tablet of 25 mg Myrbetriq contains 25 mg extended-release mirabegron and each tablet of 50 mg Myrbetriq contains 50 mg extended-release mirabegron. Manufactured by: Astellas Pharma Technologies, Inc. Norman, Oklahoma 73072
Summary of Findings:	Mirabegron is a once-daily beta-3 adrenergic agonist that has demonstrated efficacy for the treatment of overactive bladder, with symptoms of urge urinary incontinence, urgency, and urinary frequency. Mirabegron relaxes the detrusor smooth muscle during the storage phase of the bladder fill-void cycle by activating beta-3 adrenergic receptors, which increases bladder capacity. It is the first beta-3 adrenergic agonist approved for the treatment of OAB and provides a new therapeutic option for this condition.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL Product
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Non-preferred Agent ☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

An estimated 33 million Americans suffer from this uncomfortable, disruptive, and potentially serious condition called overactive bladder.

Dosage Form(s)[1]

Each tablet of 25 mg Myrbetriq contains 25 mg extended-release mirabegron and each tablet of 50 mg Myrbetriq contains 50 mg extended-release mirabegron.

Manufacturer

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

Indication(s)[1]

Mirabegron is indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.

Clinical Efficacy[1-7] (mechanism of action/pharmacology, comparative efficacy)

Mirabegron is a once daily beta-3 adrenergic agonist and it relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of beta-3 adrenergic receptors, which increases bladder capacity.

	Myrbetriq
Protein binding	71%
Volume of distribution (steady-state)	1670 L
Metabolism	Dealkylation, oxidation, glucuronidation, and amide hydrolysis to inactive metabolites; CYP3A4 and CYP2D6 limited role; possibly butylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT), and alcohol dehydrogenase involved.
Excretion	Urine (55%)

	Feces (34%)
Half-life (terminal)	50 hours

The approval of mirabegron was primarily based upon 3 randomized, double-blind, placebo-controlled clinical trials involving 4116 patients with OAB. Results from the studies showed that patients receiving mirabegron 25 mg or 50 mg once daily experienced a significant decrease in the number of incontinence episodes and micturitions per 24 hours and a significant increase in the mean volume of urine voided per micturition compared with patients receiving placebo. Clinical comparisons between mirabegron and other agents used to treat OAB are not available.

Study 1 – Overactive Bladder

STUDY DESIGN	Three 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel- group clinical trials (n=4116).
INCLUSION CRITERIA	Patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. 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.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	In Study 1, patients were randomized to placebo, mirabegron extended-release 50 mg, mirabegron extended-release 100 mg, or an active control once daily. In Study 2, patients were randomized to placebo, mirabegron extended-release 50 mg, or mirabegron extended-release 100 mg once daily. In Study 3, patients were randomized to placebo, mirabegron extended-release 25 mg, or mirabegron extended-release 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	The adjusted mean difference from placebo in the number of incontinence episodes per 24 hours for mirabegron 50 mg in

	Studies 1, 2, and 3, respectively, was -0.41 (95% CI, -0.72 to -0.09), -0.34 (95% CI, -0.66 to -0.03), and -0.42 (95% CI, -0.76 to -0.08). In Study 3, this difference was -0.4 (95% CI, -0.74 to -0.06) for mirabegron 25 mg. The adjusted mean difference from placebo in the number of micturitions per 24 hours for mirabegron 50 mg in Studies 1, 2, and 3, respectively, was -0.6 (95% CI, -0.9 to -0.29), -0.61 (95% CI, -0.98 to -0.24), and -0.42 (95% CI, -0.76 to -0.08). In Study 3, this difference was -0.47 (95% CI, -0.82 to -0.13) for mirabegron 25 mg. The adjusted mean difference from placebo in the volume of urine voided per micturition for mirabegron 50 mg in Studies 1, 2, and 3, respectively, was 11.9 mL (95% CI, 6.3 to 17.4 mL), 11.1 mL (95% CI, 4.4 to 17.9 mL), and 12.4 mL (95% CI, 6.3 to 18.6 mL). In Study 3, this difference was 4.6 mL (95% CI, -1.6 to 10.8 mL) for mirabegron 25 mg. Mirabegron 25 mg was effective in treating the symptoms of OAB within 8 weeks, and mirabegron 50 mg was effective in treating the symptoms of OAB within 4 weeks. The efficacy of the 25 mg and 50 mg doses of mirabegron was maintained through the 12-week treatment period.
SAFETY	The most common side effects observed were hypertension, nasopharyngitis, urinary tract infection, headache, and upper respiratory infection.

Contraindications[1]

- None.

Warnings and Precautions[1]

- Elevated blood pressure may occur; blood pressure monitoring recommended; use not recommended in severe uncontrolled hypertension.
- Urinary retention possible with bladder outlet obstruction and concomitant use of antimuscarinic drugs; caution advised.
- Mirabegron is a moderate inhibitor of CYP2D6; monitoring recommended with concomitant use of CYP2D6 substrates.

Adverse Effects[1]

Most common >= 1%	Myrbetriq 25 mg (n=432)	Myrbetriq 50 mg (n=1375)
▪ Hypertension	11.3%	7.5%

▪ Nasopharyngitis	3.5%	3.9%
▪ Urinary tract infection	4.2%	2.9%
▪ Headache	2.1%	3.2%
▪ Constipation	1.6%	1.6%
▪ Upper respiratory infection	2.1%	1.5%
▪ Arthralgia	1.6%	1.3%
▪ Diarrhea	1.2%	1.5%
▪ Tachycardia	1.6%	1.2%

Drug Interactions[1]

- CYP2D6 substrates: desipramine, flecainide, metoprolol, propafenone, thioridazine
- Digoxin

Dosage and Administration[1]

The recommended starting dose is 25 mg orally once daily, with or without food. Swallow the tablet whole and with water. Physician may increase dose to 50 mg once daily after 8 weeks based on efficacy and tolerability. Severe renal impairment or moderate hepatic impairment: maximum dose, 25 mg once daily.

Cost Comparisons (at commonly used dosages)

COST (WAC)*

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ MONTH
Mirabegron extended-release	Myrbetriq	Astellas	25 mg tablets	1 tablet daily	$208.50
			50 mg tablets	1 tablet daily	$208.50
Fesoterodine	Toviaz	Pfizer	4 mg tablets	1 tablet daily	$ 149.10
			8 mg tablets	1 tablet daily	$ 149.10
Tolterodine extended-release	Detrol LA	Pharmacia	2 mg capsules	1 capsule daily	$ 170.10
			4 mg capsules	1 capsule daily	$ 170.40

Trospium chloride extended-release	Sanctura XR	Allergan	60 mg capsules	1 capsule daily	$ 187.20

* Wholesale Acquisition Cost (WAC)

Conclusion

Mirabegron is a once-daily beta-3 adrenergic agonist that has demonstrated efficacy for the treatment of OAB, with symptoms of urge urinary incontinence, urgency, and urinary frequency. While antimuscarinic agents are the current OAB treatment standard, and bind to muscarinic receptors in the bladder to inhibit involuntary bladder contractions, mirabegron relaxes the detrusor smooth muscle during the storage phase of the bladder fill-void cycle by activation of beta-3 adrenergic receptors, which increases bladder capacity. It is the first beta-3 adrenergic agonist approved for the treatment of OAB and provides a new therapeutic option for this condition.

Recommendation

This product is being considered for inclusion to the state specific Preferred Drug List and is currently under solicitation.

References

1. Product Information: Myrbetriq™, mirabegron extended-release tablets. Astellas Pharma US, Inc., Northbrook, IL, 06/2012.
2. Gras J: Mirabegron for the treatment of overactive bladder. Drugs Today 2012; 48(1):25-32.
3. Tyagi P, Tyagi V & Chancellor M: Mirabegron: a safety review. Expert Opin Drug Saf 2011; 10(2):287-294.
4. Andersson KE: Pharmacotherapy of the overactive bladder. Discov Med 2009; 8(42):118-124.
5. Bhide AA, Digesu GA, Fernando R et al: Use of mirabegron in treating overactive bladder. Int Urogynecol J 2012 Mar 13 (Epub ahead of print).
6. Tyagi P & Tyagi V: Mirabegron, a beta(3)-adrenoceptor agonist for the potential treatment of urinary frequency, urinary incontinence or urgency associated with overactive bladder. IDrugs 2010; 13(10):713-722.
7. Takusagawa S, Yajima K, Miyashita A et al: Identification of human cytochrome P450 isoforms and esterases involved in the metabolism of mirabegron, a potent and selective beta(3)-adrenoceptor agonist. Xenobiotica 2012 Apr 18 (Epub ahead of print).

Prepared by: Katie Wilbers, PharmD

Date: November 12, 2012