CLINICAL UPDATE

Brand Name	Myrbetriq®
Generic Name	mirabegron
Drug Manufacturer	Astellas Pharma US, Inc

Clinical Update

TYPE OF CLINICAL UPDATE

New Indication and Dosage Form

FDA APPROVAL DATE

March 25, 2021

LAUNCH DATE

August 04, 2021

REVIEW DESIGNATION

Priority

TYPE OF REVIEW

Type 3 - New Dosage Form, New Drug Application (NDA): 213801

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Myrbetriq® is a beta-3 adrenergic agonist indicated for the treatment of:

- Overactive bladder (OAB) in adult patients with symptoms of urge urinary incontinence, urgency, and urinary frequency, either alone or in combination with the muscarinic antagonist solifenacin succinate.
- Neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 years and older and weighing 35 kg or more.

Myrbetriq® Granules is a beta-3 adrenergic agonist indicated for the treatment of NDO in pediatric patients aged 3 years and older.

MECHANISMS OF ACTION

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 which 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 FORM(S) AND STRENGTH(S)

- Extended-release tablets: 25 mg and 50 mg
- For extended-release oral suspension: 8 mg/mL of mirabegron after reconstitution

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DOSE & ADMINISTRATION

Myrbetriq® tables and granules are two different products and they are not substitutable on a milligram-per-milligram basis. Select the recommended product (Myrbetriq® or Myrbetriq® Granules) based on the indication and patient's weight. Do not combine Myrbetriq® and Myrbetriq® Granules to achieve the total dose.

A recommended dosage for Myrbetriq® Granules for adults has not been determined.

- OAB in Adults: The recommended starting dose of Myrbetriq® is 25 mg orally once daily, either alone or in combination with solifenacin succinate 5 mg orally once daily. After 4 to 8 weeks, the Myrbetriq® dose may be increased to 50 mg orally once daily.
- NDO in Pediatric Patients 3 Years and Older
  - Pediatric Patients weighing less than 35 kg: Use Myrbetriq® Granules: The recommended starting dose of Myrbetriq® Granules is weight-based and administered as an extended-release oral suspension once daily. After 4 to 8 weeks, increase to the lowest effective dose without exceeding the maximum recommended dose.
  - Pediatric Patients weighing 35 kg or more: Use Myrbetriq® or Myrbetriq® Granules:
    - The recommended starting dosage of Myrbetriq® is 25 mg orally once daily. After 4 to 8 weeks, the Myrbetriq® dose may be increased to 50 mg orally once daily.
    - The recommended starting dosage of Myrbetriq® Granules, administered as an extended-release oral suspension, is 6 mL (48 mg) orally once daily. After 4 to 8 weeks, increase to a maximum dosage of Myrbetriq® Granules 10 mL (80 mg) orally once daily.

EFFICACY

Myrbetriq®/Myrbetriq® Granules for Pediatric Neurogenic Detrusor Overactivity (NDO)

The efficacy of Myrbetriq® and Myrbetriq® Granules for the pediatric NDO indication was established in a study of 86 patients ages 3 to 17 years old. Improvements occurred in patients' maximum cystometric (bladder) capacity, number of detrusor (bladder wall muscle) contractions, volume of urine held until first detrusor (bladder wall muscle) contraction and number of daily urine leakage episodes after 24 weeks of treatment.

The efficacy of Myrbetriq®/Myrbetriq® Granules was evaluated in Study 9 (NCT02751931), a 52-week, open-label, baseline-controlled, multicenter, dose titration study in pediatric patients 3 years of age and older for the treatment of neurogenic detrusor overactivity (NDO).

Table 16: Change from Baseline in Maximum Cystometric Capacity (MCC) at 24 Weeks in Pediatric Patients with Neurogenic Detrusor Overactivity (NDO) Treated with MYRBETRIQ/MYRBETRIQ Granules in Study 9

Parameter	Children Aged 3 to Less than 12 Years (N=43)[1] Mean (SD)	Adolescents Aged 12 to 17 Years (N=25)[1] Mean (SD)
Maximum Cystometric Capacity (mL)		
Baseline	159 (95)	239 (99)
Week 24	231 (129)	352 (125)
Change from baseline	72 (87)	113 (83)
95% CI	(45, 99)	(79, 147)

1. N is the number of patients who took at least one dose and provided valid values for MCC at Baseline and Week 24.

Table 17: Changes from Baseline in Other Urodynamic Parameters at Week 24 in Pediatric Patients with Neurogenic Detrusor Overactivity (NDO) Treated with MYRBETRIQ/MYRBETRIQ Granules in Study 9

Parameter	Children Aged 3 to Less than 12 Years (N=43)[1] Mean (SD)	Adolescents Aged 12 to 17 Years (N=25)[1] Mean (SD)
Bladder Compliance (mL/cm H_2O)[2]		
Baseline	16.0 (55.8)	11.1 (10.7)
Change from baseline	14.6 (42.1)	13.6 (15.0)
	95% CI: -0.3, 29.5	95% CI: 6.7, 20.4
Number of Overactive Detrusor Contractions (> 15 cm H_2O)[2]		
Baseline	3.0 (4.0)	2.1 (3.1)
Change from baseline	-1.9 (4.2)	-0.8 (3.9)
	95% CI: -3.3, -0.4	95% CI: -2.5, 0.9
Bladder Volume Prior To First Detrusor Contraction (> 15 cm H_2O)[2]		
Baseline	115 (83)	177 (117)
Change from baseline	93 (88)	121 (160)
	95% CI: 64, 122	95% CI: 54, 189

1. N is the number of patients who took at least one dose and provided valid values for MCC at Baseline and Week 24.
2. Number of patients (Children/Adolescents) with data available for both Baseline and Week 24; Bladder Compliance: n=33/21; Number of Overactive Detrusor Contractions: n=36/22; Bladder Volume Prior To First Detrusor Contraction: n=38/24.

Table 18: Changes from Baseline in Maximum Catheterized Urine Volume and Number of Leakage Episodes at Week 24 in Pediatric Patients with Neurogenic Detrusor Overactivity (NDO) Treated with MYRBETRIQ/MYRBETRIQ Granules in Study 9

Parameter	Children Aged 3 to Less than 12 Years (N=43)[1] Mean (SD)	Adolescents Aged 12 to 17 Years (N=25)[1] Mean (SD)
Maximum Catheterized Urine Volume per Day (mL)[2]		
Baseline	304 (109)	360 (111)
Change from baseline	50 (104)	84 (122)
	95% CI: 17, 83	95% CI: 32, 137
Number of Leakage Episodes per Day[2]		
Baseline	2.8 (3.7)	1.8 (1.7)
Change from baseline	-2.0 (3.2)	-1.0 (1.1)
	95% CI: -3.2, -0.7	95% CI: -1.5, -0.5

1. N is the number of patients who took at least one dose and provided valid values for MCC at Baseline and Week 24.
2. Number of patients (Children/Adolescents) with data available for both Baseline and Week 24; Maximum Catheterized Urine Volume per Day: n=41/23; Number of Leakage Episodes per Day: n=26/21.

Myrbetriq® Monotherapy for Adult OAB

Myrbetriq® was evaluated in three, 12-week, double-blind, randomized, placebo-controlled, parallel group, multicenter clinical trials in patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency (Studies 1, 2, and 3).

Table 13: Mean Baseline and Change from Baseline at Week 12[1] for Incontinence Episodes, Micturition Frequency, and Volume Voided per Micturition in Patients with Overactive Bladder in Studies 1, 2, and 3

Parameter	Study 1		Study 2		Study 3		
	Placebo	MYRBETRIQ 50 mg	Placebo	MYRBETRIQ 50 mg	Placebo	MYRBETRIQ 25 mg	MYRBETRIQ 50 mg
Number of Incontinence Episodes per 24 Hours[2]							
n	291	293	325	312	262	254	257
Baseline (mean)	2.67	2.83	3.03	2.77	2.43	2.65	2.51
Change from baseline (adjusted mean[3])	-1.17	-1.57	-1.13	-1.47	-0.96	-1.36	-1.38
Difference from placebo (adjusted mean[3])	--	-0.41	--	-0.34	--	-0.40	-0.42
95% Confidence Interval	--	(-0.72, -0.09)	--	(-0.66, -0.03)	--	(-0.74, -0.06)	(-0.76, -0.08)
p-value	--	0.003[4]	--	0.026[4]	--	0.005[4]	0.001[4]
Number of Micturitions per 24 Hours							
n	480	473	433	425	415	410	426
Baseline (mean)	11.71	11.65	11.51	11.80	11.48	11.68	11.66
Change from baseline (adjusted mean[3])	-1.34	-1.93	-1.05	-1.66	-1.18	-1.65	-1.60
Difference from placebo (adjusted mean[3])	--	-0.60	--	-0.61	--	-0.47	-0.42
95% Confidence Interval	--	(-0.90, -0.29)	--	(-0.98, -0.24)	--	(-0.82, -0.13)	(-0.76, -0.08)
p-value	--	< 0.001[4]	--	0.001[4]	--	0.007[4]	0.015[4]
Volume Voided (mL) per Micturition							
n	480	472	433	424	415	410	426
Baseline (mean)	156.7	161.1	157.5	156.3	164.0	165.2	159.3
Change from baseline (adjusted mean[3])	12.3	24.2	7.0	18.2	8.3	12.8	20.7
Difference from placebo (adjusted mean[3])	--	11.9	--	11.1	--	4.6	12.4
95% Confidence Interval	--	(6.3, 17.4)	--	(4.4, 17.9)	--	(-1.6, 10.8)	(6.3, 18.6)
p-value	--	< 0.001[4]	--	0.001[4]	--	0.15	< 0.001[4]

1. Week 12 is the last observation on treatment.
2. For incontinence episodes per 24 hours, the analysis population is restricted to patients with at least 1 episode of incontinence at baseline.
3. Least squares mean adjusted for baseline, gender, and geographical region.
4. Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment.

Myrbetriq® Combination Therapy for Adult OAB

In Study 6 (NCT01972841), patients were randomized to placebo, solifenacin succinate 5 mg, Myrbetriq® 25 mg, Myrbetriq® 50 mg, solifenacin succinate 5 mg plus Myrbetriq® 25 mg, or solifenacin succinate 5 mg plus Myrbetriq® 50 mg once daily.

The co-primary efficacy endpoints in Study 6 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 7-day micturition diary. An important secondary endpoint was the change from baseline to end of treatment (week 12) in mean volume voided per micturition.

Table 14: Mean Baseline and Change from Baseline at Week 12[1] for Incontinence Episodes, Micturition Frequency, and Volume Voided per Micturition Overall Population with Overactive Bladder in Study 6

Parameter	Placebo	MYRBETRIQ 25 mg	MYRBETRIQ 50 mg	Solifenacin Succinate 5 mg	MYRBETRIQ 25 mg + Solifenacin Succinate 5 mg	MYRBETRIQ 50 mg + Solifenacin Succinate 5 mg
Number of Incontinence Episodes per 24 Hours						
n	412	409	406	413	823	816
Baseline (mean)	3.40	3.42	3.16	3.59	3.21	3.15
Change from baseline (adjusted mean[2])	-1.34	-1.70	-1.76	-1.79	-2.04	-1.98
Difference from Solifenacin Succinate (adjusted mean[2])	--	--	--	--	-0.25	-0.20
95% Confidence Interval	--	--	--	--	(-0.49, -0.01)	(-0.44, 0.04)
Difference from MYRBETRIQ (at the same MYRBETRIQ dose, adjusted mean[2])	--	--	--	--	-0.34	-0.23
95% Confidence Interval	--	--	--	--	(-0.58, -0.10)	(-0.47, 0.01)
Number of Micturitions per 24 Hours						
n	412	409	406	413	823	816
Baseline (mean)	10.97	10.81	11.19	10.74	10.72	10.72
Change from baseline (adjusted mean[2])	-1.64	-2.00	-2.03	-2.20	-2.49	-2.59
Difference from Solifenacin Succinate (adjusted mean[2])	--	--	--	--	-0.29	-0.39
95% Confidence Interval	--	--	--	--	(-0.57, -0.01)	(-0.67, -0.11)
Difference from MYRBETRIQ (at the same MYRBETRIQ dose, adjusted mean[2])	--	--	--	--	-0.48	-0.56
95% Confidence Interval	--	--	--	--	(-0.76, -0.21)	(-0.84, -0.28)
Volume Voided (mL) per Micturition						
n	413	407	408	411	821	821
Baseline (mean)	157.82	152.46	155.35	151.86	159.19	153.83
Change from baseline (adjusted mean[2])	8.44	13.32	21.99	30.99	34.84	39.73
Difference from Solifenacin Succinate (adjusted mean[2])	--	--	--	--	3.85	8.75
95% Confidence Interval	--	--	--	--	(-2.29, 10.00)	(2.61, 14.89)
Difference from MYRBETRIQ (at the same MYRBETRIQ dose, adjusted mean[2])	--	--	--	--	21.52	17.74
95% Confidence Interval	--	--	--	--	(15.35, 27.68)	(11.58, 23.90)

ANCOVA: Analysis of covariance

1. Week 12 is the last observation on treatment.
2. Least squares mean adjusted for baseline, gender, age group (< 65, ≥ 65 years), previous OAB medication (yes, no), and geographical region using an ANCOVA model.

Primary efficacy variables were change from baseline to end of treatment in mean number of incontinence episodes per 24 hours and change from baseline to end of treatment in mean number of micturitions per 24 hours. Combination treatment with Myrbetriq® and solifenacin succinate demonstrated statistically significant greater improvements from baseline compared to Myrbetriq® 50 mg and solifenacin succinate 5 mg for both efficacy endpoints. The improvements from baseline observed with coadministration of Myrbetriq® 50 mg and solifenacin succinate 5 mg compared to Myrbetriq® 50 mg and solifenacin succinate 5 mg were demonstrated at 3 months and were maintained throughout the 1-year treatment period. Also, for the secondary efficacy variable of change from baseline to end of treatment in mean volume voided (MVV) per micturition, the increase in MVV was

statistically significantly greater for combination treatment compared to the Myrbetriq® 50 mg and solifenacin succinate 5 mg groups.