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APPLICATION NUMBER:

213801Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 213801 and NDA 202611/S-017
Link to EDR	\\CDSESUB1\evsprod\NDA213801\0001 \\CDSESUB1\evsprod\NDA202611\0017
Submission Date	9/28/2020
Submission Type	Priority
Brand Name	MYRBETRIQ and MYRBETRIQ GRANULES
Generic Name	Mirabegron extended-release tablets and mirabegron extended-release granules for oral suspension
Dosage Form and Strength	Tablets: 25 mg and 50 mg Granules for oral suspension: 8.3 g of granules containing 830 mg mirabegron per bottle
Route of Administration	Oral
Proposed Indication	Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 years and older
Applicant	Astellas Pharma Global Development, Inc.
Associated IND	IND 069416
OCP Review Team	Peng Zou, PhD; Yun Wang, PhD; Jingyu Yu, PhD; Yanhui Lu, PhD
OCP Final Signatory	Yanhui Lu Team Leader Office of Clinical Pharmacology

Table of Contents

1. EXECUTIVE SUMMARY 3
   1.1 Recommendations 3
   1.2 Post-Marketing Requirements and Commitments 4
2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT 4
   2.1 Pharmacology and Clinical Pharmacokinetics 4
   2.2 Dosing and Therapeutic Individualization 6
      2.2.1 General dosing 6
      2.2.2 Therapeutic individualization 6
   2.3 Outstanding Issues 6
   2.4 Summary of Labeling Recommendations 6
3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW 7
   3.1 Overview of the Product and Regulatory Background 7
   3.2 General Pharmacology and Pharmacokinetic Characteristics 7
   3.3 Clinical Pharmacology Review Questions 9
      3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness? 9
      3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought? 9
      3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors? 14
      3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy? 15
      3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation 17
4. APPENDICES 17
   4.1 Summary of Bioanalytical Method Validation and Performance 17
   4.2 Clinical BA/BE Assessments 18
      4.2.1 Study 178-CL-201 19
      4.2.2 Study 178-CL-208 21
      4.2.3 Study 178-CL-202 23
      4.2.4 Study 178-CL-203 25
   4.3 Population PK Analyses 26
   4.4 Additional Analysis (Issue-based analysis) 37
   4.5 Exposure-Response Analyses 46

1. EXECUTIVE SUMMARY

Myrbetriq® (mirabegron, 25 mg and 50 mg extended-release tablets) is currently approved in the US for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and urinary frequency in adults (NDA 202611) in 2012. In the NDA approval letter dated June 28, 2012, to satisfy the Pediatric Research Equity Act (PREA) requirements, FDA requested the Applicant Astellas Pharma Global Development, Inc. (Astellas) to develop mirabegron ER microgranule-based suspension in children from 5 to < 18 years of age with neurogenic detrusor overactivity (NDO) as a postmarketing requirement (PMR). FDA requested two PMR studies:

- PMR 1898-1: Open label, multicenter single ascending dose study to evaluate pharmacokinetics, safety and tolerability of mirabegron modified release microgranule based suspension in children from 5 to < 18 years of age with NDO or OAB (178-CL-202 and 178-CL-203).
- PMR 1898-2 Open label, baseline-controlled, multi-center, sequential dose titration study followed by a fixed dose observation period to evaluate pharmacokinetics, safety and efficacy of mirabegron modified release microgranule-based suspension in children from 5 to < 18 years of age with NDO (178-CL-206/206A).

On March 18, 2016, FDA issued a written request thereby lowering the minimum age in the pediatric population from 5 years to 3 years for the pivotal phase 3 study 178-CL-206A.

The final reports for Studies 178-CL-202 and 178-CL-203 were submitted to IND 069416 on February 24, 2016 and March 31, 2017, respectively. The applicant received the fulfillment of PMR 1898-1 letter on December 27, 2018. NDA 213801 and concurrent efficacy supplement-17 (S-17) to NDA 202611 were filed on September 28, 2020 to fulfill the PMR 1898-2 and to satisfy the written request dated March 18, 2016. The proposed indication in current submission is for the treatment of pediatric patients aged 3 to < 18 years with NDO. In addition to the approved Myrbetriq® extended-release (ER) tablets, Astellas has developed mirabegron ER granules (mirabegron for oral suspension) for pediatric patients.

1.1 Recommendations

The Office of Clinical Pharmacology Division of Cardiometabolic and Endocrine Pharmacology and Division of Pharmacometrics have reviewed the information contained in NDA 213801 and NDA 202611/S-017 recommend approval of this NDA. The information also satisfies the PREA requirements 1898-1 and 1898-2 outlined in the approval letter for NDA 202611 dated Jun 28, 2012 and the written requests issued on Mar 18, 2016.

Key clinical pharmacology review issues with specific recommendations/comments are summarized in the table below:

Review Issue	Recommendations and Comments
Supportive evidence of effectiveness	Based on cross-study comparison, population pharmacokinetic (popPK) analysis showed that steady-state AUC_{0-t} values of mirabegron for pediatric subjects receiving the proposed maximum dose (PED50, defined at the bottom of this table) fell within the range (42 – 854 ng*h/mL) of observed adult exposures receiving approved mirabegron tablets 50 mg once daily. Median steady-state AUC_{0-t} values in children aged 3 to < 12 years (277 ng*h/mL) and adolescents aged 12 to < 18 years (260 ng*h/mL) receiving PED50 were slightly higher than that in adults (188 ng*h/mL) receiving 50 mg once daily. Similarly, steady-state AUC_{0-t} values of mirabegron for pediatric subjects receiving the proposed starting dose (PED25,

	defined at the bottom of this table) fell within the range (17 – 578 ng*h/mL) of observed adult exposures receiving approved mirabegron tablets 25 mg once daily.
General dosing instructions	MYRBETRIQ Tablet or Granules should be taken with food in pediatric patients. The body weight-based doses are listed below: • Patients with body weight ≥ 35 kg: tablets 25 - 50 mg once daily (QD); granules 48 – 80 mg QD • Patients with body weight ≥ 22 kg and < 35 kg: granules 32 – 64 mg QD • Patients with body weight < 22 kg: granules 24 – 48 mg QD
Dosing in patient subgroups (intrinsic and extrinsic factors)	The daily dose of MYRBETRIQ Tablet or Granules should not exceed the recommended starting dose in the following populations: • Pediatric patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2). • Pediatric patients with moderate hepatic impairment (Child-Pugh Class B). MYRBETRIQ Tablet or Granules is not recommended for use in pediatric patients with end-stage renal disease (ESRD) or in pediatric patients with severe hepatic impairment (Child-Pugh Class C). No dose adjustment is needed for pediatric patients with mild-to-moderate renal impairment and pediatric patients with mild hepatic impairment.
Labeling	Refer to Section 2.4 for the review team's recommendations.
Bridge between the to-be-marketed and clinical trial formulations	To-be-marketed (TBM) formulations of mirabegron ER granules for oral suspension and the approved mirabegron tablets were used in the pivotal clinical trial (Study 178-CL-206A).
Other (specify)	None.

PED50: pediatric dose targeted to achieve steady-state exposures similar to those of adults administered the mirabegron 50 mg tablet once daily.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mirabegron, also known as YM178, is an agonist of the human beta-3 adrenergic receptor (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. For pediatric patients ≥ 35 kg, the recommended starting dose is 25 mg once daily (QD) or 6 mL (8 mg/mL) QD with food, for mirabegron ER tablets and granules, respectively. The ER granules were reconstituted with water to prepare a suspension with a concentration of 8 mg/mL oral suspension. Based on individual patient efficacy and tolerability, the dose may be increased to 50 mg or 10 mL (i.e. 80 mg) once daily after 4-8 weeks for mirabegron ER tablets and oral suspension, respectively. For patients with body weight ≥ 22 kg and < 35 kg, the recommended starting dose and maximum doses are 4 mL and 8 mL of oral suspension QD, respectively, orally administered with food. For patients with body weight ≥ 11 kg and < 22 kg, the recommended starting dose and maximum doses are 3 mL and 6 mL of oral suspension QD, respectively, orally administered with food.

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