CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213801Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M
ADDENDUM

From: Shamir Tuchman, MD, MPH, Medical Officer
Division of Pediatric and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ORPURM, OND

John J. Alexander, MD, MPH, Deputy Director
DPMH, ORPURM, OND

To: Division of Urology, Obstetrics, and Gynecology (DUOG)

Subject: NDA and efficacy supplement review of cardiovascular data in pediatric patients with detrusor overactivity associated with a neurologic condition (NDO) treated with MYRBETRIQ[1]

Applicant: Astellas Pharma Global Development, Inc.[2]

Application number: NDA 213801, NDA 202611/S-17

[1] This review will refer to the drug product as "mirabegron"

[2] This review will refer to "Astellas Pharma Global Development, Inc." as the "Applicant"

Drug: Mirabegron

Drug Class: Beta-3 Adrenergic Agonist

Proposed Indication: Treatment of NDO in patients 3 to 17 years of age (b) (4) [redacted]

Approved Dosage Form: Tablet (25 mg and 50 mg)

Route of administration: Oral

Proposed Dosage Form(s): Granules for oral suspension (8 mg/mL)

Proposed Dosing Regimen: Tablet: Patients weighing more than or equal to 35 kg:
Initial 25 mg once daily up to 50 mg once daily
Granules for oral suspension:
11 kg to less than 22 kg: Initial 3 mL once daily up to 6 mL once daily
22 kg to less than 35 kg: Initial 4 mL once daily up to 8 mL once daily
35 kg or greater : Initial 6 mL once daily up to 10 mL once daily

Consult Request:
DUOG requests DPMH to provide an assessment of the overall adequacy of the Applicant's collection and analyses of the heart rate and blood pressure data in pediatric patients enrolled in studies that the Applicant has submitted as part of the NDA 213801 and NDA 202611/S-17. The Applicant has submitted the final reports for both studies to fulfill post-marketing requirements (PMRs) under the Pediatric Research Equity Act (PREA) and to fulfill a Written Request (WR). With submission of these data, the Applicant is seeking approval of mirabegron for treatment of NDO in patients 3 to 17 years of age.

Referenced Materials:

- The following documents included in the mirabegron NDA and efficacy supplement #17 entered into DARRTS under NDA 202611/S-17, September 28, 2020:

- DPMH Pediatric Clinical Review Memo in DAARTS on February 16, 2021

Addendum:

The following is a modification of the description of blood pressure (BP) category changes in children and adolescents from the DPMH Pediatric Clinical Review Memorandum entered into DARRTS on February 16, 2021 under NDA 213801. The information on changes in BP categories included in the memorandum cites proportions for children and adolescents calculated using the full patient population for which baseline BP measures were taken. However, a more appropriate population on which to base changes in BP category are those who had at least one BP measurement taken in a follow-up study visit. Therefore, the adjusted changes in BP categories referenced below are based on the cohort of patients in Study 178-CL-206A with at least one follow-up in-clinic BP measurement taken after the baseline study visit:

Using criteria from the National Heart, Lung and Blood Institute (NHLBI) 4th Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in children and Adolescents, 45 (82%), 3 (5%), and 7 (13%) of 55 patients 3 to less than 12 years of age (referred to as children for this analysis) were normotensive, pre-hypertensive, or had stage I hypertension (HTN), respectively, based on systolic blood pressure (SBP) criteria at the baseline in-clinic visit. The corresponding proportions for diastolic blood pressure (DBP) were similar in the same age group. For patients 12 to less than 18 years of age (referred to as adolescents for this analysis), the corresponding number of patients are 19 (61%), 8 (26%), and 4 (13%) for SBP at the baseline in-clinic visit. There was a slightly higher proportion of adolescents who were normotensive (71%) at baseline using DBP criteria. The baseline proportion of study patients that had pre-existing HTN was largely similar between children and adolescents using either the SBP or DBP criteria. Compared to children, there was a lower proportion of normotensive adolescents at baseline due to a larger proportion with pre-hypertension as defined by the NHLBI 4th Report.

Ten (24%) of the 41 children who were normotensive at baseline and had at least one follow-up BP measured at an in-clinic visit had a measured SBP at or above the 95th percentile based the NHLBI 4th Report while this occurred in only 1 of 19 (5%) adolescent patients who were normotensive at baseline. Six (15%) of the 41 children who were normotensive at baseline and had at least one follow-up BP measured at an in-clinic visit had a measured DBP at or above the 95th percentile based the NHLBI 4th Report during one of the clinic visits while this occurred in 2 (10%) of the 21 baseline normotensive adolescents. Overall 14% of children and 12% of adolescents changed

categories from either normotensive or pre-hypertensive at baseline to stage I HTN by either SBP or DBP criteria. One adolescent who had stage I systolic HTN at baseline developed stage II systolic HTN at the week 4 in-clinic visit and then subsequently returned to having stage I HTN at subsequent in-clinic visits without modification or discontinuation of mirabegron dosing. In children, 6 (60%) of the 10 patients who had a measured SBP at or above the 95th percentile continued to have sustained measurements above the 95th percentile at subsequent in-clinic visits (stage I HTN). For DBP, this proportion was 1 (17%) out of 6 children. Two of the 3 adolescents who developed stage I HTN were in the pre-hypertension category at baseline. No children developed stage II HTN by either SBP or DBP NHLBI 4th Report criteria at any point in the trial.

In addition, the * at the bottom of Tables 3, 4, and 5 denoting “children” as “patients 1 to less than 12 years of age” is modified to “patients 3 to less than 12 years of age”. This is consistent with the lower age of enrollment in Study 178-CL-206A.

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