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
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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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SHAMIR TUCHMAN
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MONA K KHURANA
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 24, 2021
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 213801
Product Name and Strength:	Myrbetriq granules (mirabegron for extended release oral suspension), 8 mg/mL, 100 mL
Applicant/Sponsor Name:	Astellas Pharma Global Development, Inc. (Astellas)
OSE RCM #:	2020-2062-3
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Acting Team Leader:	Celeste Karpow, PharmD, MPH

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on March 24, 2021 for Myrbetriq. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised carton labeling for Myrbetriq (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[a] and two label and labeling memorandums[b,c].

2 CONCLUSION

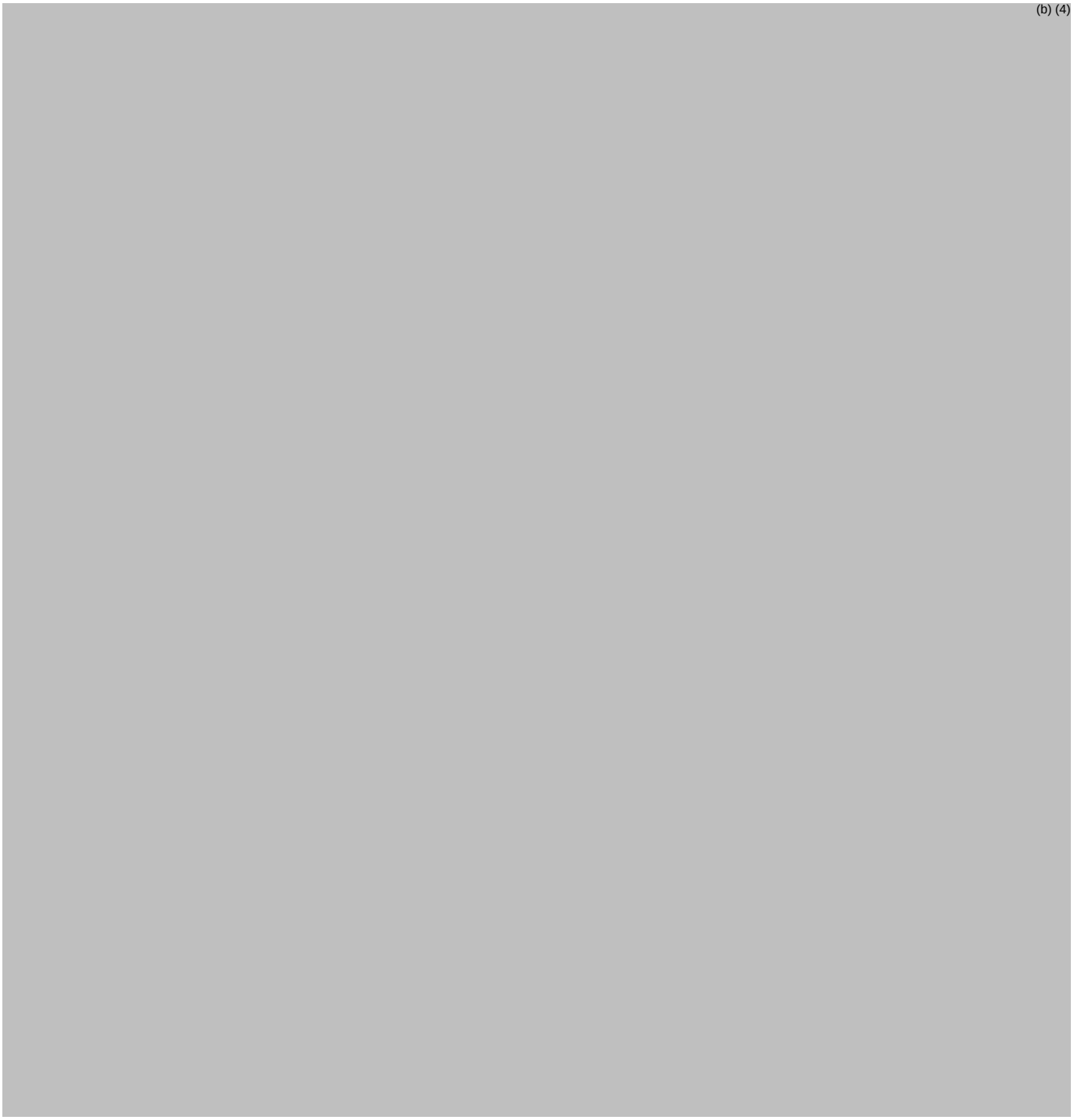
The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Baugh D. Label and Labeling Review for Myrbetriq granules (NDA 213801). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 22. RCM No.: 2020-2062-2.
[b] Baugh, D. Label and Labeling Memorandum for mirabegron granules (NDA 213801) and Myrbetriq (NDA 202611/S-017). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 17. RCM No.: 2020-2062-1 and 2020-2168-1.
[c] Baugh, D. Label and Labeling Memorandum for mirabegron granules (NDA 213801). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 22. RCM No.: 2020-2062-2.

APPENDIX A. IMAGE OF LABELING RECEIVED ON MARCH 24, 2021

Carton labeling

(b) (4)



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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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Date of This Review:	March 22, 2021
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 213801
Product Name and Strength:	Myrbetriq granules (mirabegron for extended release oral suspension), 8 mg/mL, 100 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Astellas Pharma Global Development, Inc. (Astellas)
FDA Received Date:	March 17, 2021 and March 19, 2021
OSE RCM #:	2020-2062-2
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Acting Team Leader:	Celeste Karpow, PharmD, MPH

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, carton labeling, and prescribing information (PI) received on March 19, 2021 and revised pouch labels received on March 17, 2021 for Myrbetriq Granules (extended release for oral suspension). The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised PI, container labels, pouch labels, and carton labeling (Appendices A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[a] and memorandum[b].

2 FINDINGS AND RECOMMENDATIONS

Our evaluation of the proposed Myrbetriq Granules PI and carton labeling identified areas of vulnerability that may lead to medication errors. Below, Table 2 includes our recommendations for the proposed Myrbetriq Granules PI for DUOG and Table 3 includes our recommendation for the carton labeling for Astellas. We ask that the Division convey Table 2 in its entirety to Astellas so that the recommendation is implemented prior to approval of this NDA.

Our recommendations to the container labels and pouch labels were implemented and we have no additional recommendations at this time.

The following table (Table 2) outlines issues and recommendations for the Division:

Table 1. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Astellas proposed further revisions to Section 2.6 (Preparation Instructions). We agreed to these additional statements during labeling discussions.	Astellas proposed these revisions to further emphasize the importance of shaking the suspension to achieve complete dispersion.	The third bullet in Section 2.6 was revised from "Measure 100 mL of water, add the total amount to the bottle, and immediately shake vigorously for 1 minute, then let it stand for 10 to 30 minutes." to read "Measure 100 mL of water, add the total amount to the

[a] Baugh, D. Label, Labeling, and Packaging Review for mirabegron granules (NDA 213801) and Myrbetriq (NDA 202611/S-017). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 17. RCM No.: 2020-2062-1 and 2020-2168-1.

[b] Baugh, D. Label and Labeling Memorandum for mirabegron granules (NDA 213801) and Myrbetriq (NDA 202611/S-017). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 17. RCM No.: 2020-2062-1 and 2020-2168-1.

Table 1. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			bottle, and immediately shake vigorously for 1 minute, then let it stand for 10 to 30 minutes. Shake vigorously again for 1 minute." The fourth bullet was revised from "If granules have not dispersed, shake vigorously for 1 minute." to read "If granules have not dispersed, shake vigorously for another 1 minute."
Full Prescribing Information – Section 17 Patient Counseling			
1.	During discussions between DMEPA and the Division of Medical Policy Programs (DMPP), we agreed to add statements regarding proper administration of Myrbetriq Granules to Section 17 (Patient Counseling) of the Full Prescribing Information (FPI).	These statements were added to align the FPI with the Patient Package Insert (PPI).	The statements added to Section 17 of the FPI were: "*MYRBETRIQ Granules* Advise pediatric patients and/or their caregivers to use an appropriate measuring device and instructions for measuring the correct dose of MYRBETRIQ Granules for extended-release oral suspension. Instruct patients or their caregivers that patients should take MYRBETRIQ Granules for extended-release oral suspension orally within 1 hour after preparation with food once daily and not save the dose for later. The bottle should be shaken for 1 minute each day if the suspension will not be used for 2 or more days. When ready

Table 1. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			to use, shake the bottle vigorously for 1 minute then let it stand until the foam on top of the suspension is gone (approximately 1 to 2 minutes)."

The following table (Table 3) outlines issues and recommendations to convey to the Applicant:

Table 2. Identified Issues and Recommendations for Astellas Pharma Global Development, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Carton Labeling			
1.	We note the statement, 'Pharmacist: reconstitute product prior to dispensing and dispense with dosing device' on the principal display panel lacks prominence.	As currently presented, we are concerned this statement may be overlooked. As a result, the product might be dispensed to the patient as granules without reconstitution by the pharmacist.	Improve the prominence of the statement 'Pharmacist: reconstitute product prior to dispensing and dispense with dosing device' on the principal display panel by increasing its font size, changing the font color from black to red, boxing the statement, or by other means.

APPENDIX A. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Myrbetriq Granules labels and labeling submitted by Astellas Pharma Global Development, Inc.

- Pouch Label received March 17, 2021 (one for Ireland and one for Japan)
- Container Label(s) received on March 17, 2021 and March 19, 2021
- Carton labeling received on March 17, 2021 and March 19, 2021
- Prescribing Information (Image not shown) received on March 17, 2021 at the following link: \\CDSESUB1\evsprod\nda213801\0036\m1\us\114-labeling\draft-labeling\draft-labeling-text\myrbetriq-uspi-clean-17mar21.docx

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 17, 2021
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 213801 (mirabegron granules), NDA 202611/S-017 (Myrbetriq)
Product Name and Strength:	Myrbetriq granules (mirabegron for extended release oral suspension), 8 mg/mL, 100 mL Myrbetriq (mirabegron extended release tablets), 25 mg and 50 mg
Applicant/Sponsor Name:	Astellas Pharma Global Development, Inc. (Astellas)
OSE RCM #:	2020-2062-1 (Myrbetriq Granules) and 2020-2168-1 (Myrbetriq)
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Acting Team Leader:	Celeste Karpow, PharmD, MPH

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label, pouch and carton labeling received on March 4, 2021 for Myrbetriq Granules (extended release for oral suspension) and revised container labels and carton labeling on March 11, 2021 and March 15, 2021 for Myrbetriq (extended release tablets). The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container label, pouch label, and carton labeling (Appendices C and D) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[a] and in response to an information request sent on March 5, 2021[b].

[a] Baugh, D. Label, Labeling, and Packaging Review for mirabegron granules (NDA 213801) and Myrbetriq (NDA 202611/S-017). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 22. RCM No.: 2020-2062 and 2020-2168.

[b] Roule, J. FDA Communication: Carton and Container for NDA 202611 for Myrbetriq. Silver Spring (MD): FDA, CDER, Division of Urology, Obstetrics, and Gynecology (US); 2021 MAR 04. NDA 202611 Supplement-17.

Additionally, during the course of our review of the label and labeling for Myrbetriq granules (NDA 213801) and Myrbetriq (NDA 202611/S-017)[c], the Office of Pharmaceutical Quality (OPQ) identified a discrepancy in the presentation of the established name for Myrbetriq (NDA 202611). Specifically, the presentation of the name on the approved Myrbetriq container label and carton labeling was determined to be inconsistent with the Prescribing Information (PI) for Myrbetriq Granules (mirabegron for extended-release oral suspension). As such, the Agency requested Astellas submit revised container and carton labeling for Myrbetriq (mirabegron) extended release tablets[d] (Appendix D) and the Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revisions to the Myrbetriq container label and carton labeling.

[c] Baugh D. Label, Labeling, and Packaging Review for Myrbetriq (NDA 213801) and mirabegron granules (NDA 202611/S-017). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 22. RCM No.: 2020-2062 and 2020-2168.

[d] Roule, J. FDA Communication: Carton and Container for NDA 202611 for Myrbetriq. Silver Spring (MD): FDA, CDER, Division of Urology, Obstetrics, and Gynecology (US); 2021 MAR 04. NDA 202611 Supplement-17.

2 CONCLUSION

We provide additional recommendations for the Division to consider in the Myrbetriq Granules Prescribing Information (Table 2).

Although the Applicant implemented or considered all of our Myrbetriq Granules container label and carton labeling recommendations (Appendix A), we have additional recommendations in Table 3 below.

In addition, the sponsor submitted revised container labels and carton labeling for Myrbetriq extended-release tablets in response to the Agency's March 5, 2021 request. The revised container labels and carton labeling submitted for the Myrbetriq extended-release tablets revised the established name from 'Myrbetriq (mirbegron) extended release tablets' to 'Myrbetriq (mirabegron extended release tablets)' which was recommended to the sponsor by OPQ. We have no concerns with the revisions to the established name based on the recommendations from OPQ.

3 RECOMMENDATIONS FOR ASTELLAS PHARMA GLOBAL DEVELOPMENT, INC.

We recommend the following recommendations in Table 3 be implemented prior to approval of this NDA:

Table 1. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	We note the statement in section 16.2 of the PI,, 'Store the (b) (4) suspension at 20˚C to 25˚C (68˚F to 77˚F) . . .'	Use of the word '(b) (4)' is not commonly used when referring to compounding activities and it may cause confusion.	Revise the storage statement, 'Store the (b) (4) suspension at 20˚C to 25˚C (68˚F to 77˚F) . . . 'to read 'Store the reconstituted suspension at 20˚C to 25˚C (68˚F to 77˚F) . . . '

Table 2. Identified Issues and Recommendations for Astellas Pharma Global Development, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Myrbetriq Granules Container Label(s) and Carton Labeling			
1.	We note the statement on the container label and carton labeling (italics added for emphasis), 'Store the (b) (4) suspension at 20˚C to 25˚C (68˚F to 77˚F) . . . '	Use of the word '(b) (4)' is not commonly used when referring to compounding activities and it may cause confusion.	Revise the storage statement, 'Store the (b) (4) suspension at 20˚C to 25˚C (68˚F to 77˚F) to read 'Store the reconstituted suspension at 20˚C to 25˚C (68˚F to 77˚F) . . . '
Myrbetriq Granules Carton Labeling			
1.	For pharmacist compounding instructions, we note that the pharmacist is instructed to measure 100 mL of (b) (4) water.	Reference to (b) (4) .	Consider revising the statement '(b) (4) ' to read 'Measure 100 mL of water . . .' so that the pharmacist can decide which water source is appropriate for compounding purposes.
2.	The statement 'Pharmacist: reconstitute product prior to dispensing and dispense with dosing device" lacks prominence and is located at the bottom of the principal display panel in small black font.	We are concerned that this statement may be overlooked and the pharmacist will dispense the product without adding water and mixing the contents.	Move the statement, 'Pharmacist: Reconstitute product prior to dispensing and dispense with dosing device' to appear before the 'Rx only' and net quantity statements. Additionally, increase the prominence of this statement taking into account all pertinent factors, including typography, layout, contrast, and other printing features. See also recommendation # 4.
3.	The statement (b) (4) is presented in red, bold	The statement (b) (4) competes in prominence	Delete the statement '(b) (4) from the principal display panel.

Table 2. Identified Issues and Recommendations for Astellas Pharma Global Development, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	font on the principal display panel.	with more important information on the principal display panel. In addition, this statement appears under pharmacist preparation instructions as well as in the patient/caregiver instructions and is redundant.	
4.	On the principal display panel, the statement 'shake vigorously for 1 minute before each use' is located below the 'Rx only' statement and the net quantity '100 mL'.	We are concerned that this statement may be overlooked.	We recommend relocating the statement 'shake vigorously for 1 minute before each use' to appear after the statement, 'Pharmacist: Reconstitute product prior to dispensing and dispense with dosing device' and to appear before the 'Rx only' and 'net quantity statement'. Therefore, we recommend the following sequence of information appear below the drug identifying information on the principal display panel: 'Pharmacist: Reconstitute product prior to dispensing and dispense with dosing device' Discard after __/__/___ 'Shake vigorously for 1 minute before each use' We recommend the Rx Only and net quantity statements appear below the aforementioned statements on the principal display panel.

Table 2. Identified Issues and Recommendations for Astellas Pharma Global Development, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
5.	Since the Prescribing Information (PI) has been revised, the Preparation instructions for the pharmacist on the carton labeling submitted March 4, 2021 are not the same as Section 2.6 (Preparation and Storage Instructions for Myrbetriq Granules) PI.	We are concerned that differences between the pharmacist preparation instructions on the carton labeling and Section 2.6 (Preparation and Storage Instructions for Myrbetriq Granules) of the Prescribing Information may cause confusion and may cause important steps to be overlooked.	Ensure the side panel of the carton labeling, titled, 'PHARMACIST:' aligns with Section 2.6 of the 'to-be-marketed' PI.

DMEPA preliminarily agreed with the proposed pharmacist preparation instructions below for Section 2.6 of the PI submitted by email to the Agency on March 12, 2021,:

- Discard the pouch and desiccant prior to reconstitution. Do not dispense.
- Tap the closed bottle several times to loosen the granules.
- Measure 100 mL of water, add the total amount to the bottle, and immediately shake vigorously for 1 minute, then let it stand for 10 to 30 minutes.
- If granules have not dispersed, shake vigorously for (b) (4) 1 minute.
- Record the 28 day expiration date on the container and carton based on the reconstitution date.
- Give the patient an appropriate dosing device.
- Store the reconstituted suspension at 20°C to 25°C (68°F to 77°F) for up to 28 days.
- Discard the unused portion after 28 days.

After reconstitution with 100 mL water, the suspension contains 8 mg/mL of mirabegron.

APPENDIX A. ASTELLAS' RESPONSE TO FEBRUARY 23, 2021 INFORMATION REQUEST (RECEIVED FROM SPONSOR MARCH 5, 2021)

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APPENDIX B. ASTELLAS' RESPONSE TO MARCH 5, 2021 INFORMATION REQUEST (RECEIVED FROM SPONSOR MARCH 15, 2021)

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 4, 2021
To:	Nenita Crisostomo, RN Regulatory Health Project Manager **Division of Urology, Obstetrics, and Gynecology (DUOG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Elvy Varghese, PharmD. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name), Dosage Form and Route and Application Type/Number :	MYRBETRIQ GRANULES (mirabegron for extended-release oral suspension), NDA 213801 MYRBETRIQ (mirabegron extended-release tablets) for oral use, NDA 202611/S-017
Applicant:	Astellas Pharma Global Development, Inc.

1 INTRODUCTION

On September 23, 2020, Astellas Pharma Global Development, Inc. submitted for the Agency's review an Original New Drug Application (NDA 213801): Request for Priority Review Designation, for MYRBETRIQ GRANULES (mirabegron for extended-release oral suspension). The proposed indication for MYRBETRIQ GRANULES (mirabegron for extended-release oral suspension) is for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients.

On September 28, 2020, Astellas Pharma Global Development, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS): Labeling Exclusivity Determination Requested/Request for Priority Review Designation, to the Original New Drug Application (NDA 202611/S-017) for MYRBETRIQ (mirabegron extended-release tablets) for oral use. The purpose of this submission is to support the use of MYRBETRIQ (mirabegron extended-release tablets) for oral use for the treatment of NDO in pediatric patients.

MYRBETRIQ (mirabegron extended-release tablets) for oral use was approved on June 28, 2012 and is indicated for the treatment of overactive bladder (OAB) in adult patients with symptoms of urge urinary incontinence, urgency, and urinary frequency. MYRBETRIQ GRANULES (mirabegron for extended-release oral suspension) and MYRBETRIQ (mirabegron extended-release tablets) for oral use will share labeling for the two formulations.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Urology, Obstetrics, and Gynecology (DUOG) on October 6, 2020 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for MYRBETRIQ GRANULES (mirabegron for extended-release oral suspension) and MYRBETRIQ (mirabegron extended-release tablets) for oral use.

2 MATERIAL REVIEWED

- Draft MYRBETRIQ GRANULES (mirabegron for extended-release oral suspension) and MYRBETRIQ (mirabegron extended-release tablets) for oral use PPI received on September 23, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 24, 2021.
- Draft MYRBETRIQ GRANULES (mirabegron for extended-release oral suspension) and MYRBETRIQ (mirabegron extended-release tablets) for oral use Prescribing Information (PI) received on September 23, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 24, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 3, 2021

To: Elena N. Boley, Clinical Reviewer, M.D.
Division of Urology, Obstetrics, and Gynecology (DUOG)

Nenita Crisostomo, RN,
Regulatory Project Manager, DUOG

From: Elvy Varghese, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for MYRBETRIQ® GRANULES (mirabegron for extended-release oral suspension) and MYRBETRIQ® (mirabegron extended-release tablets) for oral use

NDA: 213801 and 202611/S-17

In response to DUOG's consult requests dated October 6, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI) and carton and container labeling for the original NDA submission for MYRBETRIQ® GRANULES (mirabegron for extended-release oral suspension) (Myrbetriq Granules) and MYRBETRIQ® (mirabegron extended-release tablets) for oral use (Myrbetriq). Myrbetriq supplement (S-17) is an efficacy supplement for the new indication- treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 3 years of and older and weighing 35 kg or more.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DUOG (Nenita Crisostomo) on February 24, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling for Myrbetriq Granules submitted by the Sponsor to the electronic document room on January 4, 2021, and our comments are provided below. We note that the consult request asks for comments on carton and container labeling for Myrbetriq, however no revised carton and container labeling was submitted.

Thank you for your consult. If you have any questions, please contact Elvy Varghese at (240) 402-0080 or Elvy.Varghese@fda.hhs.gov.

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ELVY M VARGHESE
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LABEL, LABELING, AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 22 2021
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 213801 (mirabegron granules), NDA 202611/S-017 (Myrbetriq)
Product Name and Strength:	mirabegron granules (mirabegron for extended release oral suspension), 8 mg/mL, 100 mL Myrbetriq (mirabegron) extended release tablets, 25 mg and 50 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Astellas Pharma Global Development, Inc. (Astellas)
FDA Received Date:	September 28, 2020, December 15, 2020, and February 5, 2021
OSE RCM #:	2020-2062 (mirabegron granules) and 2020-2168 (Myrbetriq)
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Acting Team Leader:	Celeste Karpow, PharmD, MPH

1 REASON FOR REVIEW

On September 28, 2020, Astellas Pharma Global Development, Inc. submitted an efficacy supplement (NDA 202611/S-017) for Myrbetriq and the container label, carton labeling, and prescribing information (PI) for mirabegron granules, NDA 213801. The supplement (NDA 202611/S-017) provides for an additional indication which includes the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 3 years of age and older and mirabegron granules (NDA 213801) will have the same indication.

Subsequently the Division of Bone, Reproductive, and Urologic Products (DBRUP) requested the Division of Medication Error Prevention and Analysis (DMEPA) evaluate the container label, carton labeling, and prescribing information (PI) for NDA 213801 and the PI for NDA 202611/S-017 for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

Myrbetriq (mirabegron extended release tablets) 25 mg and 50 mg was approved June 28, 2012 under NDA 202611. The indications for Myrbetriq are for the treatment of overactive bladder (OAB) in adults with symptoms of urge urinary incontinence, urgency, and urinary frequency; and, in combination with solifenacin succinate, for the treatment of OAB in adults with symptoms of urge urinary incontinency, urgency, and urinary frequency.

The approval letter for NDA 202611 contained a Pediatric Research Equity Act (PREA) post-marketing requirement (PMR) for a study in pediatric patients with neurogenic detrusor overactivity (NDO). In parallel, Astellas submitted sNDA 202611/017 which proposes the addition of the same pediatric indication (NDO) as a Request for Pediatric Exclusivity.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Information Requests Sent to Astellas	C
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

4 FINDINGS AND RECOMMENDATIONS

Myrbetriq

The Applicant proposes to add an indication which includes pediatric patients 3 years of age and older. We note that the Myrbetriq extended release tablets should be taken with water, swallowed whole and should not be chewed, divided, or crushed. We are concerned that pediatric patients may chew the extended release tablets, and this was communicated to the DUOG review team at the filing meeting on October 28, 2020. In our follow up discussions, we were told that based on the weight-based dosing for the mirabegron tablets, the patient would be about 11 years old which minimizes the possibility for biting, chewing, or crushing the tablet. Therefore, our concerns are minimized.

As part of our evaluation, we considered whether the proposed changes to the Myrbetriq PI require updates to the container labels and carton labeling to ensure consistency, decrease the risk of medication error, and minimize the risk of confusion. We find the revisions do not require changes to the presentation of the name, strength, or route of administration. As such, our evaluation did not identify any necessary changes for the container labels and carton labeling.

Myrbetriq Granules

Tables 2 and 3 below include the medication error issues identified with the submitted mirabegron granules pouch, container label, carton labeling, prescribing information (PI), and patient information, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

The role of the submitted labeling titled 'pouch' in the medication use process was unclear which hindered our ability to review and comment on this label. We sent an Information Request (IR) to the Sponsor December 10, 2020. In their December 15, 2020 reply (Appendix C), the Sponsor stated that the role of the pouch was (b) (4) . The pouch has no role in the dispensing or the administration of the mirabegron granule product and we provide our comments regarding the 'pouch' in Table 3.

We note the patient and caregiver preparation instructions on the side panel of the carton labeling (b) (4) lists multiple steps which need to be completed prior to administration of the product. To inform our review, we sent an Information Request (IR) to Astellas on January 29, 2021 to address our specific areas of concern related to the patient and caregiver preparation instructions on the side panel of the carton labeling. We acknowledge Astellas' February 5, 2021 response. We find Astellas' revisions to the patient and caregiver preparation instructions decrease the number of steps required prior to administration. However, we propose further revisions to the patient and caregiver preparation instructions in Table 3 to achieve word efficiency and clarity. Additionally, we propose these revisions to the patient and caregiver

preparation instructions be repeated in Patient Information under the heading 'How should I take Myrbetriq (b) (4) Granules (b) (4) ?'.

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Prescribing Information – General Issues			
1.	We note the use of 'MYRBETRIQ (b) (4) Granules' throughout the Prescribing Information.	MYRBETRIQ (b) (4) Granules is not the proprietary name found to be acceptable by DMEPA.	Change the proprietary name for this product from 'MYRBETRIQ (b) (4) Granules' to read 'MYRBETRIQ Granules' throughout the Prescribing Information.
2.	There is no statement in Section 2 of the PI to indicate if an adult patient who cannot swallow tablets would be able to take (or switch to) Myrbetriq granules.	The absence of an explicit statement in the PI to address whether adults can take Myrbetriq granules might lead readers to assume it is acceptable for an adult patient who cannot swallow tablets to take (or switch to) Myrbetriq granules.	The review team indicated via email on February 5, 2021 that the Agency has not received information on dosing of the oral suspension in the adult population. As such, we recommend the review team consider adding a statement similar to: 'The use of Myrbetriq Granules in adults has not been evaluated.'
Highlights of Prescribing Information			
1.	In the section titled, 'Dosage and Administration', there is no statement indicating the oral suspension is not substitutable with the currently marketed tablets.	The absence of a substitutability statement may lead the reader to erroneously assume the oral suspension is substitutable with the currently marketed tablets and vice versa.	We recommend adding a statement similar to, "To avoid substitution errors and overdosage, do not substitute the oral suspension for the extended-release tablet on a milligram-per-milligram basis because the oral suspension and extended-release tablet are not substitutable.'
2.	In the section titled 'Dosage Forms and Strengths' (Section 3), we note that the strength statements for the extended release tablets and for the oral suspension are	Only the dosage form and strength should be stated in this section of the HPI.	Remove (b) (4) from these statements.

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	immediately followed by (b) (4) .		
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The statement (b) (4) in Section 2.6 ((b) (4)) does not state where the expiration date should be written. Additionally, (b) (4)' is not a term commonly used and may cause confusion.	We are concerned that this step might be skipped in the preparation of the product if the pharmacist is not instructed to record the 28-day expiration date on the container and carton.	Revise the statement (b) (4) ' in Section 2.6 (b) (4) to read 'Discard bottle 28 days from reconstitution.'
2.	We note the following statement located after Table 1 (b) (4)	This statement may be overlooked because it appears *after* the table and is not stated at the point at which this decision may be made.	Consider revising the statement, " (b) (4) " to a statement similar to " (b) (4) ." Consider adding a 'General Comments' section after Section 2 (Dosing and Administration) *and* before Section 2.1 (Dosing Information for Adult Patients with OAB) to increase the

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			prominence of this important information.
3.	(b) (4)		
4.	The pediatric dosing for Myrbetriq granules does not include the 'mg' strength.	We are concerned 'wrong dose' medication errors may occur should the prescriber order dosing in 'mg' units of measure.	We recommend adding the 'mg' strength to all pediatric dosing where 'mL' occur.
5.	Section 2.6 (Preparation Instructions for MYRBETRIQ Granules) does not include storage directions after reconstitution.	We are concerned deteriorated drug errors might occur in the absence of this information.	Add the storage temperatures to Section 2.6 (Preparation Instructions of MYRBETRIQ Granules) so that this product is properly stored after reconstitution.
6.	Weight-based pediatric dosing in Section 2.2 (Dosing Information for Pediatric Patients Aged 3 years and older with Neurogenic Detrusor Overactivity [NDO]) is stated as '≥ 35 kg and < 35 kg'.	The use of ≥ and < are dangerous and ambiguous abbreviations that may be misinterpreted and cause over- or underdoses.	We recommend using the statements 'less than' or 'more than' wherever appropriate throughout the labeling.
7.	We note in Section 2.2 (Dosing Information for Pediatric Patients Aged 3 years and older with Neurogenic Detrusor Overactivity [NDO]) the subheading titled (b) (4)	This subheading requires references to dosing with both the tablet and granules and may mislead the reader to substitute tablets for granules and vice versa even though the dosage forms are not substitutable.	We recommend separating weight based dosing into 2 separate groups ('less than 35 kg' and '35 kg or more') to better present the dosing for these different weight groups.

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	(b) (4)		
8.	We note the statement, "Tap the closed bottle several times to loosen the granules." was deleted from Section 2.6 of the PI, titled, "Preparation and Storage Instructions for MYBETRIQ Granules."	This statement is helpful for pharmacists who are not familiar with reconstitution.	Consider including a statement similar to, "Tap the closed bottle several times to loosen the granules." to Section 2.6 of the PI.
Full Prescribing Information – Section 17 Patient Counseling			
1.	There are detailed patient/caregiver instructions for how to mix and administer the granules.	Giving the patient/caregiver details of how to mix the product at the point of prescribing may be overwhelming and cause confusion. It is not realistic to expect the patient to understand or remember the details of preparation and administration at this point in the medication use process.	Consider abbreviating these instructions such that the patient is made aware that the product they are getting will be a liquid and will require an oral dosing device which can be obtained from the pharmacist.
Patient Information			
2.	The instructions under the heading, 'How should I take MYRBETRIQ (b) (4) Granules (b) (4) ?' are unclear, overly complex, and impractical for patients and caregivers to follow.	We are concerned the complexity of the 'How should I take MYRBETRIQ (b) (4) Granules (b) (4) ?' section may lead to 'wrong technique' medication errors.	For clarity, revise the (b) (4) steps under the 'How should I take MYRBETRIQ (b) (4) Granules (b) (4) ?' section to the following or similar statements: **NOTE**: If Myrbetriq Suspension will not be used for 2 or more days, shake the bottle vigorously for 1 minute each day to ensure the granules are suspended. Step 1. Shake the bottle vigorously for 1 minute then let stand until foam on the

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			surface of the suspension is gone (approximately 1 to 2 minutes). If the granules have not dispersed, repeat shaking and standing. Step 2. Using the dosing device provided by the pharmacist, place the dose into the dosing device and take the suspension within one hour with food. Disregard any bubbles. Step 3. After each use, wash the oral dosing device with mild household detergent, rinse under running tap water and allow to air dry. To avoid confusion, ensure the patient and caregiver instructions included in the Prescribing Information is identical to the instructions on the carton labeling.

Table 3. Identified Issues and Recommendations for Astellas Pharma Global Development, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Label and Carton Labeling for mirabegron granules			
1.	The Office of Pharmaceutical Quality (OPQ) stated the established name is 'mirabegron for extended release oral suspension' during the February 4, 2021 labeling meeting. However, we note that the	All labeling should consistently reflect the proper established name for this product to avoid confusion.	We defer to OPQ's final decision. Ensure all labeling reflects the correct established name.

Table 3. Identified Issues and Recommendations for Astellas Pharma Global Development, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	carton labeling states 'oral suspension'.		
2.	The established name lacks prominence commensurate with the proprietary name.	Important drug information may be overlooked.	Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
3.	The format for the expiration date is not defined.	Clearly define the expiration date to minimize confusion and the risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
4.	We note the statement (b) (4), appears on the principal display panel.	This statement clutters the label, is redundant, and detracts from other more important information.	Remove the statement '(b) (4)' from the label and labeling wherever it appears.
Container Label for mirabegron granules			
1.	The statement, 'Recommended dosage: see prescribing	The (b) (4) in the recommended dosage	Delete the statement, (b) (4)' from the recommended dosage statement.

Table 3. Identified Issues and Recommendations for Astellas Pharma Global Development, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	information. (b) (4)	statement is redundant and therefore unnecessary.	
2.	We note the statement, (b) (4) "	We are concerned patients/caregivers might not know what instructions to reference.	Revise (b) (4) to read 'Patient/Caregiver: Refer to Patient Information or carton on how to give this product.'
Carton Labeling for mirabegron granules			
1.	The patient and caregiver preparation instructions on the side panel of the carton labeling, received February 5, 2021, are unclear and complex.	We are concerned the complexity of the patient and caregiver preparation instructions may lead to 'wrong technique' medication errors.	Revise the (b) (4) steps titled, "PATIENTS AND CAREGIVERS" to include the following or similar statements: **NOTE**: If Myrbetriq Suspension will not be used for 2 or more days, shake the bottle vigorously for 1 minute each day to ensure the granules are suspended. Step 1. Shake the bottle vigorously for 1 minute then let stand until foam on the surface of the suspension is gone (approximately 1 to 2 minutes). If the granules have not dispersed, repeat shaking and standing. Step 2. Using the dosing device provided by the pharmacist, place the dose into the dosing device and take the suspension within one hour with food. Disregard any bubbles.

Table 3. Identified Issues and Recommendations for Astellas Pharma Global Development, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			Step 3. After each use, wash the oral dosing device with mild household detergent, rinse under running tap water and allow to air dry. To avoid confusion, ensure the patient and caregiver preparation instructions on the carton labeling is identical to the instructions included in the Patient Information document.
2.	There is no indication on the PDP to alert pharmacists to reconstitute the product prior to dispensing.	We are concerned pharmacists might not reconstitute the oral suspension at the time of dispensing.	Consider adding the following or a similar statement to the principal display panel: "Attention pharmacists: reconstitute product prior to dispensing and dispense with dosing device".
3.	We note the absence of a linear bar code on the carton labeling.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	We request you add the product's linear barcode to the carton labeling as required by 21 CFR 201.25 (c)(2). The barcode should be surrounded by enough white space to allow scanners to read the bar code properly (see 21 CFR 201.25(c)(i)). Print density should be consistent to allow for an accurate scan. The bar code should be placed in a conspicuous location (e.g., not on the bottom of a carton) where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation) in accordance with 21 CFR 201.25 (c)(ii).

Table 3. Identified Issues and Recommendations for Astellas Pharma Global Development, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
4.	As currently presented, there appears to be incomplete product identifier information presented on the carton labeling.	The Drug Supply Chain Security Act (DSCSA) requires manufacturers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. If you determine that the product identifier requirements apply to your product's labeling, add a placeholder for the human-readable and machine-readable (2-D data matrix barcode) product identifier to the carton labeling. The DSCSA guidance on product identifiers recommends the format of the human-readable portion be located near the 2D data matrix barcode and recommends the following format: NDC: [insert NDC] Serial: [insert serial number] LOT: [insert lot number] EXP: [insert expiration date]
5.	The patient/caregiver is not told how to store the	The absence of storage instructions for the	Consider adding the statement 'store the bottle upright and at

Table 3. Identified Issues and Recommendations for Astellas Pharma Global Development, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	product in the home. We note this information is included in Section 17 (Patient Counseling) of the PI.	patient/caregiver may contribute to 'deteriorated drug' medication errors.	room temperature' to the side panel of the carton labeling to inform the patient/caregiver of this important information.
6.	The (b) (4) appears after the strength statement on the principal display panel, competes with important drug information on the principal display panel.	The location of the (b) (4) may lead to confusion with product strength. In addition, the (b) (4) competes with important drug information (i.e., proprietary name, established name, dosage form and strength statement), and clutters the principal display panel.	We recommend re-locating the (b) (4) away from the product strength, such as the side or back panel.
7.	We note the statement 'Shake vigorously for 1 minute before each use' highlighted in red font on the principal display panel (PDP).	This statement competes with important drug information (i.e., proprietary name, established name, dosage form and strength statement), and not reflective of the complete instructions on the side panel for patients and caregivers.	Remove the statement 'Shake vigorously for 1 minute before each use' from the principal display panel (PDP).
8.	Storage instructions are not provided for patients and caregivers.	We are concerned 'deteriorated drug' errors may occur as a result of the absence of storage instructions.	Add the following statement after step (b) (4): 'Store at 20˚C to 25˚C (68˚F to 77˚F) with excursions permitted from 15˚C to 30˚C (59˚F to 86˚F) [See USP Controlled Room Temperature].
Pouch Label			
1.	The pouch label includes drug information similar to the container label.	The inclusion of drug information on the pouch may lead the pharmacist to believe that the pouch should be included in the dispensing process. This may also cause	Revise the information included on the pouch label to clearly reflect its purpose. For example, consider deleting the detailed drug information and adding the following statement: 'This pouch is to be used for storage of

Table 3. Identified Issues and Recommendations for Astellas Pharma Global Development, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		confusion for the patient or caregiver if dispensed.	mirabegron granules bottle prior to reconstitution. Dispense enclosed bottle only.' Alternatively, consider other language that would clearly reflect the purpose of the pouch.

5 CONCLUSION

Our evaluation of the proposed Myrbetriq pouch label, container label, carton labeling, Prescribing Information (PI), and Patient Information identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Astellas Pharma Global Development, Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Error! Reference source not found. presents relevant product information for Myrbetriq and mirabegron Granules that Astellas Pharma Global Development, Inc. submitted on September 28, 2020.

Table 2. Relevant Product Information for Myrbetriq and Myrbetriq (b) (4) Granules		
Product Name	**Myrbetriq**	**mirabegron granules**
Initial Approval Date	June 28, 2012	N/A
Active Ingredient	mirabegron	
Indication	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency; and In combination with solifenacin for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency <u>Proposed</u>: treatment of neurogenic detrusor overactivity in pediatric patients aged 3 years of age and older	Treatment of neurogenic detrusor overactivity in pediatric patients aged 3 years and older
Route of Administration	oral	
Dosage Form	Extended release tablets	For extended release oral suspension
Strength	25 mg and 50 mg	8 mg/mL (after reconstitution)
Dose and Frequency	Initially 25 mg once daily, alone or in combination with solifenacin succinate 5 mg once daily	The recommended dose is determined based on patient weight and should be administered once daily with food. Treatment should be initiated at the recommended starting dose. Thereafter, the dose may be increased to the lowest effective dose. The maximum dose should not be

		exceeded. Patients who reach 35 kg while on treatment may be switched from oral suspension to tablet formulation, if they can swallow tablets. However, the extended release tablets and the extended release oral suspension are not bioequivalent and should not be substituted on a mg per mg basis.
How Supplied	Bottle of 30 count; bottle of 90 count	One carton containing one bottle with a child-resistant cap
Storage	25˚C (77˚F) with excursions permitted form 15˚C to 30˚C (59˚F to 86˚F); [see USP Controlled Room Temperature]	20˚C to 25˚C (68˚F to 77˚F) with excursions permitted form 15˚C to 30˚C (59˚F to 86˚F) [see USP Controlled Room Temperature] Store reconstituted oral suspension at room temperature (b) (4) for up to 28 days (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 25, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, 213801, 202611, and Myrbetriq. Our search identified 3 previous reviews[a,b,c] and we considered our previous recommendations to see if they are applicable for this current review.

[a] (b) (4)

[b] Siahpoushan, M. Label and Labeling Review for Myrbetriq (NDA 202611). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 MAY 31. RCM No.: 2012-398-2.

[c] Baugh, D. Label, Labeling, and Packaging Review for Myrbetriq (NDA 202611/S-011). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 04. RCM No.: 2017-1451.

APPENDIX C. INFORMATION REQUESTS SENT TO ASTELLAS

Information Request Response from Astellas Received December 15, 2020 (regarding the role of the pouch in the dispensing and administration process)

\\CDSESUB1\evsprod\nda213801\0009\m1\us\1-11-1-response-2020-dec-10.pdf

Information Request Response from Astellas Received February 5, 2021 (regarding patient/caregiver preparation instructions on the carton labeling)

\\CDSESUB1\evsprod\nda213801\0025\m1\us\111-information-amendment\multiple-module-information-amendments\1114-information-amendment.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with post-market medication error data, we reviewed the following mirabegron granules labels and labeling submitted by Astellas Pharma Global Development, Inc.

- Container label for mirabegron granules received on September 28, 2020
- Carton labeling for mirabegron granules received on September 28, 2020 and February 5, 2021
- Prescribing Information (Image not shown) received on September 28, 2020 \\CDSESUB1\evsprod\nda213801\0001\m1\us\myrbetriq-uspi-clean.doc
- Patient Information (image not shown) received September 28, 2020 (attached to Prescribing Information [PI]) \\CDSESUB1\evsprod\nda213801\0001\m1\us\myrbetriq-uspi-clean.doc

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DENISE V BAUGH
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02/22/2021 07:47:59 PM

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

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

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[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.

Materials Reviewed:

- The following documents entered into DARRTS under NDA 213801, September 28, 2020:

- Introduction to the Clinical Summary for the Indication of Neurogenic Detrusor Overactivity in Pediatric Patients, Module 2.2 (eCTD #1)
- Clinical Overview for the Indication of Neurogenic Detrusor Overactivity in Pediatric Patients, Module 2.5 (eCTD #1)
- Summary of Clinical Efficacy, Module 2.7.3 (eCTD #1)
- Summary of Clinical Safety, Module 2.7.4 (eCTD #1)
- Integrated Summary of Efficacy, Module 5.3.5.3 (eCTD #1)
- Integrated Summary of Safety, Module 5.3.5.3 (eCTD #1)
- Non-clinical Overview, Module 2.4 (eCTD#1)
- Summary of Clinical Pharmacology Studies, Module 2.7.2 (eCTD#1)
- Population PK Study Report for Study 178-206, Module 5.3.3.5 (eCTD#1)
- Study 178-CL-206A Protocol, Module 16.1.1 (eCTD #1)
- Study 178-CL-206A Study Report, Module 5.3.5.1 (eCTD #1)

- The following documents included in the mirabegron NDA and efficacy supplement #17 entered into DARRTS under NDA 202611/S-17, September 28, 2020:
  - Mirabegron WR dated March 18, 2016.
  - Mirabegron Proposed Pediatric Study Request (PPSR), Module 1.9.4 (eCTD #179)

I. Background

A. Pediatric NDO:

The most common neurologic disorders leading to bladder dysfunction in children are congenital neural tube defects such as myelomeningoceles. As a result of abnormal innervation, the detrusor muscle in the bladder may become overactive (e.g. NDO) and the external urethral sphincter will reflexively contract instead of relaxing in response to detrusor contraction. This pathologic dyssynergia is termed neurogenic bladder-sphincter dysfunction (NBSD). NBSD may lead to high pressure incontinence with the risk of diminished bladder capacity and compliance. In addition, this bladder dysfunction carries risks of recurrent urinary tract infections, high pressure voiding, and resultant renal parenchymal and upper urinary tract injury.

NDO is the most common diagnosis in pediatric patients with NBSD.[3] NDO has been identified as one of the risk factors for deterioration in renal function in patients with

[3] Korzeniecka-Kozerska A, Porowski T, Bagińska J, Wasilewska A. Urodynamic Findings and Renal Function in Children with Neurogenic Bladder after Myelomeningocele. Urol Int. 2015;95(2):146-152

spina bifida.[4] Patients with congenital neural tube defects have shown evidence of renal injury, dilatation of the upper urinary tracts, and urinary retention within the first 6 months of life. Furthermore, children without urinary tract dilatation or urinary retention at birth develop these abnormalities at an average age of 3 years.[5] The natural history of untreated NBSD is one of progressive deterioration in renal function in up to 58% of children by the age of 3 years.[6] With early evaluation and institution of appropriate therapy, most of these children will age with preservation of renal function.[7] With this said, up to 26% of patients with neurogenic bladder will have some degree of permanent renal damage present with 1.3% progressing to end-stage renal disease in adulthood.[8] Treatments aimed at improving NDO therefore have implications for long-term preservation in renal function in patients with NBSD.

Pediatric patients with NDO are treated with a combination of scheduled clean intermittent catheterization (CIC) to limit distention and pressure build-up in the bladder and oral anticholinergic agents to inhibit intermittent detrusor contractions (IDC).[9] Oral anticholinergic therapy is associated with adverse effects including dry mouth, constipation, and sedation. In children where oral anticholinergic agents are sub-optimally effective or not tolerated, intravesicular administration of anticholinergics has been used with similar results and potentially less systemic adverse reactions.[10]

Approximately 10% of pediatric patients with NDO are not successfully managed with the combination of CIC and anticholinergic therapy.[11,12] Surgical treatment with either urinary diversion or reconstructive bladder augmentation with its attendant risks and long-term sequelae may be undertaken in these patients. In addition, bladder

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[4] Thorup J, Biering-Sorensen F, Cortes D. Urological outcome after myelomeningocele: 20 years of follow-up. BJU Int. 2011;107(6):994-999

[5] Hopps CV, Kropp KA. Preservation of renal function in children with myelomeningocele managed with basic newborn evaluation and close followup. J Urol. 2003;169(1):305-308.

[6] Smith ED. Urinary prognosis in spina bifida. J Urol. 1972;108(5):815-817.

[7] See footnote 6

[8] Veenboer PW, Bosch JL, van Asbeck FW, de Kort LM. Upper and lower urinary tract outcomes in adult myelomeningocele patients: a systematic review. PLoS One. 2012;7(10):e48399

[9] Hernandez RD, Hurwitz RS, Foote JE, Zimmern PE, Leach GE. Nonsurgical management of threatened upper urinary tracts and incontinence in children with myelomeningocele. J Urol. 1994;152(5 Pt 1):1582-1585.

[10] Reitz A, Schurch B Intravesical therapy options for neurogenic detrusor overactivity. Spinal Cord 2004; 42:267–272

[11] Verpoorten C, Buyse GM. The neurogenic bladder: medical treatment. Pediatr Nephrol. 2008;23(5):717-725.

[12] Lehnert T, Weisser M, Till H, Rolle U. The effects of long-term medical treatment combined with clean intermittent catheterization in children with neurogenic detrusor overactivity. Int Urol Nephrol. 2012;44(2):335-341

augmentation may be performed in older children to facilitate continence and independence irrespective of changes to the urinary tract or renal function.[13] Short and long-term complications of bladder augmentation may include malignancies of the bladder; metabolic complications including hypokalemic, hyperchloremic metabolic alkalosis; urinary calculi; bladder perforation; urinary tract infections; small bowel obstruction; and deterioration of the upper urinary tract.[14] Since the intestine used for bladder augmentation does not contract with the bladder in a coordinated fashion, patients who undergo bladder augmentation often must remain on CIC.[15]

B. Approved Oral Drug Products for Pediatric NDO:

There are currently two FDA approved oral drugs for the treatment of NDO in pediatric patients. Oxybutynin chloride is approved for the treatment of NDO in pediatric patients 5 years of age and older.[16] Solifenacin succinate is approved for the same indication in pediatric patients 2 years of age and older.[17]

II. NDA 213801, NDA 202611/S-17

A. Drug Product:

Mirabegron is a first-in-class, selective beta-3 adrenoceptor agonist. Mirabegron, is approved under the trade name MYRBETRIQ in adults for the treatment of overactive bladder (OAB).[18] Mirabegron leads to an improvement in OAB by stimulating beta-3 adrenergic receptors resulting in bladder smooth muscle relaxation leading to increased bladder compliance. The Applicant purports that mirabegron offers a potential alternative treatment for pediatric patients with NDO who are either intolerant of or have a sub-optimal clinical response to anticholinergic therapy.

[13] Snow-Lisy DC, Yerkes EB, Cheng EY. Update on Urological Management of Spina Bifida from Prenatal Diagnosis to Adulthood. J Urol. 2015;194(2):288-296.

[14] Ibid

[15] Ibid

[16] Found under DITROPAN at Drugs@FDA.gov

[17] Found under VESICARE LS at Drugs@FDA.gov

[18] Found under MYRBETRIQ at Drugs@FDA.gov

B. Regulatory History of Mirabegron for NDO:

DUOG approved Mirabegron in 2012 for the treatment of adults with OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency.[19] Two double-blind, placebo-controlled, randomized, multi-center trials conducted in 691 adult patients with urinary incontinence due to NDO served as the basis for this approval.

Safety findings of concern that were evaluated by review teams during the adult development program for mirabegron included a potential clinical signal of dose-dependent increases in blood pressure (BP) and heart rate (HR). Non-clinical data in adult rats, rabbits, and dogs, revealed that elevated HR at exposures similar to the maximum recommended human dose were partially reversed by metoprolol, suggesting that this is at least partially due to off target beta-1 adrenergic receptor agonism.

The currently approved MYRBETRIQ prescribing information includes increased BP as an adverse reaction with mirabegron use in Section 5 (Warnings and Precautions) and recommends that prescribers monitor periodic BPs during mirabegron treatment and avoid use in patients with severe uncontrolled hypertension (HTN).[20] Adults who received 50 mg mirabegron had higher mean increases in systolic BP (SBP; 3.5 mmHg) and diastolic BP (DBP; 1.5 mm Hg) than those who received placebo in placebo-controlled, multidose, phase 1 studies in healthy volunteers. In the adult OAB placebo-controlled, multidose, phase 3 trials, the mean increases in SBP and DBP in the mirabegron arm relative to placebo were in the range of 0.5 to 1 mm Hg with infrequent worsening of pre-existing HTN.[21]

Approximately 1.2% to 1.6% of patients treated with mirabegron monotherapy reported tachycardia in the adult clinical trials.

As mirabegron represents a new active ingredient for treatment of OAB for which PREA is applicable, DUOG granted a partial waiver for pediatric studies in patients less than 5 years of age on the basis that OAB is not a condition in infants or young children who are not yet bladder trained and therefore necessary studies are not possible or highly impracticable. DUOG granted a deferral of pediatric studies in patients 5 to 17 years of age due to the drug product being ready for approval in adults. Upon initial US approval

[19] FDA Approval letter found at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=202611 under NDA 202611

[20] Ibid

[21] Ibid

of mirabegron in adults for OAB, DUOG issued the following two post-marketing requirements (PMR):

1) PMR-1 (1898-1): An 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 less than 18 years of age with NDO or OAB.
2) PMR-2 (1898-2): An open label, baseline-controlled, multicenter, 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 less than 18 years of age with NDO.

DUOG issued a Written Request (WR) on March 18, 2016, requesting studies that mirrored the PREA PMR issued with the mirabegron approval in adults. Unlike the PREA PMR which required enrollment down to 5 years of age, the WR requested that these studies include enrollment of pediatric patients down to 3 years of age. Safety endpoints to be collected in the studies included vital signs; specifically increased HR, tachycardia, and increased BP given that these findings had been noted in the adult OAB program and were also potential drug safety concerns in the target pediatric population that required active monitoring. The WR specified that the safety endpoints, including vital signs, were to be summarized using descriptive statistics with respect to age-, height-, and sex-specific percentiles.

To facilitate dosing in studies conducted to satisfy the PREA PMR and the WR, the Applicant developed an age-appropriate granules for oral suspension formulation. Pediatric population pharmacokinetic modeling based on data from two phase 1 pediatric trials (Study 178-CL-202 in NDO, Study 178-CL-203 in OAB) and one phase 3 pediatric trial (Study178-CL-206A) predicted a formulation effect on the bioavailability of mirabegron. The ratio of the mean exposure of mirabegron oral suspension to extended-release tablets calculated from the model was 42.9%. This value is consistent with the ratio of 48% between mirabegron oral suspension and extended-release tablets in the fasted state in Study 178-CL-201.

C. Clinical Studies Supporting Mirabegron Efficacy and Safety in Pediatric Patients:

Studies 178-CL-202, 178-CL-203, and 178-CL-206A assessed the efficacy and safety of mirabegron in pediatric patients. Studies 178-CL-202 and 178-CL-203 assessed the

exposure and safety from a single dose of mirabegron in a total of 43 pediatric patients 3 to 17 years of age.

1. Study 178-CL-206A

Study 178-CL-206A was a phase 3, open-label, baseline-controlled, multicenter, dose-titration study followed by a fixed-dose observation period in pediatric patients from 3 to less than 18 years of age with NDO on CIC. The schedule of mirabegron study visits is shown in **Table 1**:

Table 1: Schedule of Mirabegron Treatment and Assessments in Study 178-CL-206A

Study Period (56 weeks)									
Pre-Treatment Period (4 weeks)			Efficacy Treatment Period (24 weeks)					Safety Period (28 weeks)	
Visit 1*	Visit 2**	Visit 3*	Visit 4** Week 2	Visit 5* Week 4	Visit 6** Week 8	Visit 7* Week 12	Visit 8* Week 24	Visit 9** Week 36	Visit 10* Week 52
Screening	Start of washout for prohibited medications	Baseline	1st dose titration possibility	2nd dose titration possibility	3rd dose titration possibility	Fixed dose	Fixed dose	Fixed dose	End of Study

* In-clinic study visit
** Telephone encounter study visit
Source: Table adapted from the flow chart and schedule of assessments from the study protocol for Study 178-CL-206 (Module 16.1.1, eCTD #1)

The study had a pretreatment period for up to 4 weeks before the baseline visit, an efficacy treatment period from the day after the baseline visit to week 24, and a long-term safety period after week 24 and continuing to week 52 or the end of treatment. Patients who received oral drug treatment for NDO or other prohibited medication underwent a 2-week washout period. Treatment with mirabegron began with an initial dose based on the patient's weight and that predicted to achieve plasma concentrations equivalent to those of the steady state exposure with 25 mg of mirabegron administered and approved for once daily use in adults with OAB (e.g. pediatric equivalent dose of 25 mg (PED25)). Patients were up-titrated at weeks 2, 4, or 8 to the pediatric equivalent dose of 50 mg (PED50) once daily unless the investigator considered the patient to be effectively treated with PED25, based on urodynamics and the recorded catheterized urine volumes on electronic diaries. In addition to the eligibility age minimum of 3 years and use of CIC, patients had to weigh more than or equal to 11 kg to participate in the trial. The trial excluded patients with a mean resting HR above the 99th percentile for age as defined from published reference distributions.[22] The trial also excluded patients with established

[22] Fleming S, Thompson M, Stevens R, Heneghan C, Plüddemann A, Maconochie I, Tarassenko L, Mant D. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet. 2011 Mar 19;377(9770):1011-8

HTN and a SBP or DBP greater than the 99th percentile plus 5 mm Hg (e.g. stage II HTN) using the NIHLBI 4th Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (NHLBI 4th Report).[23] Enrolled patients received mirabegron once daily in the morning within one hour before or after breakfast except during study visits when pharmacokinetic (PK) samples were planned to be taken at the visit. No formal discontinuation criteria were provided in the study protocol relating to changes from baseline in HR or BP.

a. Pharmacokinetic Assessment

Samples of venous blood for PK assessment were taken after at least 10 days of daily stable dosing. A total of 4 PK samples were collected, divided over 2 sampling days. These 2 days were selected around two of the scheduled study visits (i.e. week 4, week 8, week 12, week 24, week 36, or week 52) and did not have to be in a specific (i.e. consecutive) order.

b. Vital Signs Measurements

In-clinic measurement of BP and HR occurred at the screening, baseline, week 4, 12, 24, and 52 study visits prior to phlebotomy and urodynamic studies. Study investigators performed in-clinic BP and HR measurements in triplicate with an interval of 2 minutes between measures in the sitting (or supine) position using the right arm with the patient calm for at least 5 minutes. The preferred method of BP measurement was via auscultation or alternatively per standard clinic practice if auscultation was not available. Study investigators determined the correct cuff size at each clinic visit. Patient positioning, right arm preference, and the method of BP measurement remained consistent throughout the trial in each patient.

Parents/caregivers performed home BP measurements (SBPM) and HR on enrolled patients at the start of washout (where applicable), baseline, and prior to the week 2, 4, 8, 12, 24, 36, and 52 study visits. Study investigators provided devices for measuring BP and HR to patients for home measurements as well as provided detailed on-site training to use the SBPM device and a booklet with operating instructions in local language to the patient and the patient's parent(s)/caregiver(s). For each patient, study investigators determined the correct cuff size by measuring the circumference of the patient's upper

[23] The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. U.S. Department of Health and Human Services, National Institutes of Health National Heart, Lung, and Blood Institute. NIH Publication No. 05-5267 Originally printed September 1996 (96-3790) Revised May 2005. Available at: https://www.nhlbi.nih.gov/files/docs/resources/heart/hbp_ped.pdf

arm in order to give the patient the device with most appropriate cuff. The goal bladder length of the cuff was 80% to 100% and the width approximately 40% of the arm's circumference. Parents/caregivers measured patients' BP in triplicate in the morning and evening in the right arm with an interval of 2 minutes between measures in the sitting (or supine) position with the patient calm for at least 5 minutes.

c. Vital Signs Assessment

Predefined cardiovascular treatment emergent adverse events (TEAE's) of Special Interest monitored in the pediatric phase 1 and 3 trials of mirabegron included increased BP, increased HR, tachycardia, and cardiac arrhythmias including QT prolongation.

The Applicant assessed changes in BP and HR in the safety analysis set (SAF), which consisted of all patients who took at least one dose of mirabegron, using the following approach:

- Reported SBP and DBP values obtained via repeated measures from both SBPM and in-clinic measurements (e.g. 2, 4, 8, 12, 24, 36, and 52 weeks) from all enrolled patients who received at least one dose of mirabegron
- Calculated SBP and DBP percentiles for each patient using the NHLBI 4th Report.[24]
- Assigned BP categories for individual patient BP measurements based on thresholds established in the 2005 NHLBI 4th Report and the 2017 clinical practice guidelines established by the American Academy of Pediatrics Subcommittee on Screening and Management of High Blood Pressures in Children (AAP HTN Subcommittee) as shown in the **Table 2**:[25]
    - Normal BP
    - Elevated BP (or pre-hypertension)
    - Stage I HTN
    - Stage II HTN

This reviewer focused on BP changes with mirabegron therapy that occurred with in-clinic measurements given the likelihood that BP measures obtained by trained personnel using standardized measurement methods during the in-clinic study visits would be more

[24] Ibid

[25] Flynn JT, Kaelber DC, Baker-Smith CM, et al; SUBCOMMITTEE ON SCREENING AND MANAGEMENT OF HIGH BLOOD PRESSURE IN CHILDREN. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. *Pediatrics*. 2017; 140(3):e20171904. Pediatrics. 2017 Dec;140(6):e20173035. doi: 10.1542/peds.2017-3035. Erratum for: Pediatrics. 2017 Sep;140(3)

reliable than those collected by parents and caregivers at home. Where study populations were identified with BP elevations, this reviewer compared BPs from in-clinic study visits with SBPM for the same visit to assess for the presence of anxiety as a contributing factor to in-clinic BP elevations.

Table 2 highlights the differences in criteria for establishing categories of BP in pediatric patients with HTN. An important difference between the criteria established by the NHLBI 4th Report and AAP HTN Subcommittee guidelines is the reference population values used to establish BP percentiles. The AAP HTN Subcommittee guidelines established updated normative BP values based on the reference population used in the NHLBI 4th Report with obese children and adolescent values removed with the resultant effect of lowering the BP associated with each percentile in the normative tables. Because the Applicant generated BP percentiles for each study patient based on the NHLBI 4th Report, this reviewer used the BP categories from the NHLBI 4th Report to evaluate changes in BP categories with mirabegron use.

Table 2: Blood Pressure Category Criteria for the NHLBI 4th Report and AAP HTN Subcommittee Clinical Practice Guidelines

BP Category	NHLBI 4h Report	AAP HTN Subcommittee
Normal BP	SBP and/or DBP < 90th percentile	*Children: SBP and DBP < 90th percentile **Adolescents: SBP < 120 and DBP < 80 mmHg
Pre-hypertension/Elevated BP	SBP and/or DBP 90th percentile to < 95th percentile, or > 120/80 mmHg even if below 90th percentile up to 95th percentile	Children: SBP and/ or DBP ≥ 90th percentile to < 95th percentile or SBP 120 and DBP 80 mmHg to < 95th percentile (whichever is lower) Adolescents: SBP 120 to 129 and DBP < 80 mmHg
Stage I HTN	SBP and/or DBP 95th percentile to 99th percentile + 5 mmHg	Children: SBP and/or DBP ≥ 95th percentile to < 95th percentile + 12 mmHg, or SBP 130 to 139 and/or DBP 80 to 89 mmHg (whichever is lower) Adolescents: SBP 130 to 139 and/or DBP 80 to 89 mmHg
Stage II HTN	SBP and/or DBP > 99th percentile + 5 mmHg	Children: SBP and/or DBP ≥ 95th percentile + 12 mmHg, or SBP ≥ 140 and/or DBP ≥ 90 mmHg (whichever is lower) Adolescents: SBP ≥ 140 and/or DBP ≥ 90 mmHg

* Patients aged 1 to less than 13 years of age
** Patients 13 years to 17 years of age

The Applicant defined potentially clinically relevant (PCR) changes in BP in the analyses as either of the following scenarios:

1) the occurrence of stage II HTN defined in either the NHLBI 4th report or AAP HTN Subcommittee at any point in the trial and/or
2) a change in blood pressure category from normotensive or prehypertensive at baseline to either Stage I or II HTN at any point in the trial

The Applicant calculated HR percentiles for each patient measurement using published reference data[26] and defined abnormal HR as a value greater than the 99th percentile compared with age-related norms and a PCR change in HR as one that results in a HR above the 99th AND greater than or equal to a 15 beats per minute (bpm) change from baseline.

This reviewer assessed HR elevations based on criteria established in the published source by Fleming et al. to generate the HR percentiles in children and adolescents in Study 178-CL-206A.[27] This reviewer assessed changes relative to increases raising the HR above the 90th and 99th percentiles to provide an assessment of the range of HR increases leading to both mild and more severe changes in percentiles. The Applicant's definition of a PCR HR change as that above the 99th percentile AND greater than or equal to a 15 bpm change is an arbitrary cutoff and not endorsed in the publication from which HR percentiles were generated.[28]

D. Cardiovascular Safety Results of Mirabegron for Pediatric NDO:

Study 178-CL-206A enrolled 91 pediatric patients, and the SAF consisted of 86 patients who received at least one dose of mirabegron. Seventy-eight percent (67/86) of the SAF completed the full 52-weeks of follow-up in the trial. Forty one (61%) of these patients were 3 to 11 years of age. The racial distribution of the SAF included 62 (72%) white, 20 (23%) Asian, and 4 (5%) other patients. Three patients (3%) were of Hispanic or Latino ethnicity. Eight-four percent (46/55) of patients 3 to less than 12 years of age [29] and 94% (29/31) of adolescent patients 12 to less than 18 years of age[30] had BP and HR measured via oscillometric devices at in-clinic visits. Eight patients discontinued mirabegron before

[26] See footnote 22

[27] Ibid

[28] Ibid

[29] This review will refer to study patients less than 12 years of age as "children"

[30] This review will refer to study patients 12 to 17 years of age as "adolescents"

the first post-baseline BP and HR measurement. The percentage of patients treated with mirabegron tablets remained consistent between 53% and 55% thru the study.

1. Blood Pressure

Baseline BP and subsequent changes in the absolute BP and percentile with mirabegron exposures from in-clinic BP measurements in Study 178-CL-206A are shown in **Table 3**.

In children, SBP and SBP percentile increased through the study visits. This also occurred for DBP which had a comparable rise of 3.4% from baseline at the week 12 study visit with smaller increases from baseline compared with SBP after the week 12 study visit. Increases in BP were less pronounced and sustained through study visits in adolescents. As a whole, children had higher mirabegron exposures expressed as area under the curve (AUC) and larger baseline increases in BP compared with adolescents after the week 4 in-clinic visit.

Table 3: Changes in Blood Pressure Relative to Mirabegron Exposure from in-Clinic Study Visits in Study 178-CL-206A

Study Visit	***Children**				****Adolescents**			
	n	**AUC**	*****SBP (Percentile)**	**% Normal**	**n**	**AUC**	*****SBP (Percentile)**	**% Normal**
Baseline	55	-	102.1 (60.9)	81.8%	31	-	112.8 (61.2)	61.3%
Week 4	50	259.8	+ 1.1 (+ 2.1)	82.0%	28	256.8	+ 0.2 (- 1.5)	67.9%
Week 12	46	306.9	+ 3.9 (+ 9.8)	67.4%	27	270.0	- 0.4 (- 1.5)	70.4%
Week 24	45	298.4	+ 2.9 (+ 6.4)	73.3%	27	247.1	+ 0.9 (- 0.5)	70.4%
Week 52	41	267.4	+ 6.4 (+10.5)	63.4%	26	203.3	+ 0.3 (- 3.0)	65.4%
	n	**AUC**	*****DBP (Percentile)**		**n**	**AUC**	*****DBP (Percentile)**	
Baseline	55	-	65.4 (69.9)	81.8%	31	-	69.8 (65.8)	71%
Week 4	50	259.8	+ 0.8 (+ 3.1)	80%	28	256.8	+ 0.9 (+ 1.9)	71.4%
Week 12	46	306.9	+ 2.2 (+ 5.6)	73.9%	27	270.0	+ 1.0 (+ 0.9)	74.1%
Week 24	45	298.4	+ 1.3 (+ 1.5)	73.3%	27	247.1	+ 1.2 (- 0.4)	66.7%
Week 52	41	267.4	+ 1.5 (- 0.6)	75.6%	26	203.3	- 0.2 (- 4.7)	76.9%

* Patients 1 to less than 12 years of age

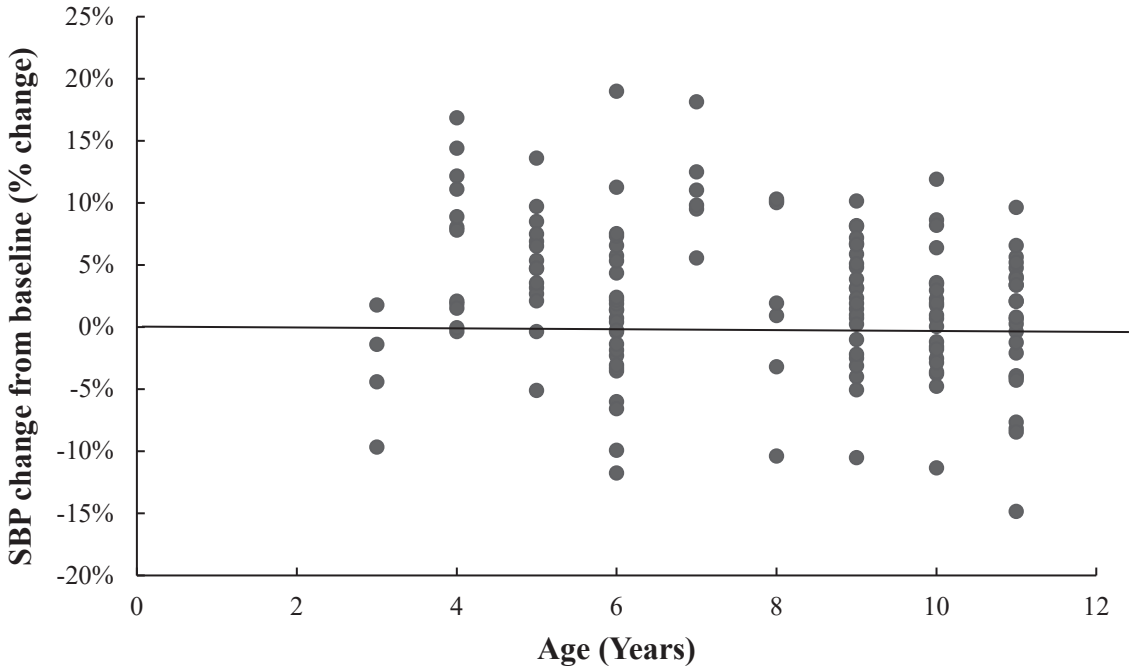
** Patients 12 years to 17 years of age

*** SBP and DBP in mmHg and expressed as the mean for the baseline in-clinic study visit and mean change from baseline for subsequent in-clinic study visits (mean percentile change from baseline in parentheses)

Source: Table abstracted, in part, from Table 15 in the Summary of Clinical Safety (Module 2.7.4, eCTD #1)

As shown in **Figure 1**, analysis of the SBP changes in children reveals that most of the BP elevations are driven by increases in the 4 to 7-year old age group.

Figure 1: Changes in Systolic Blood Pressure by Age in Children in Study 178-CL-206A

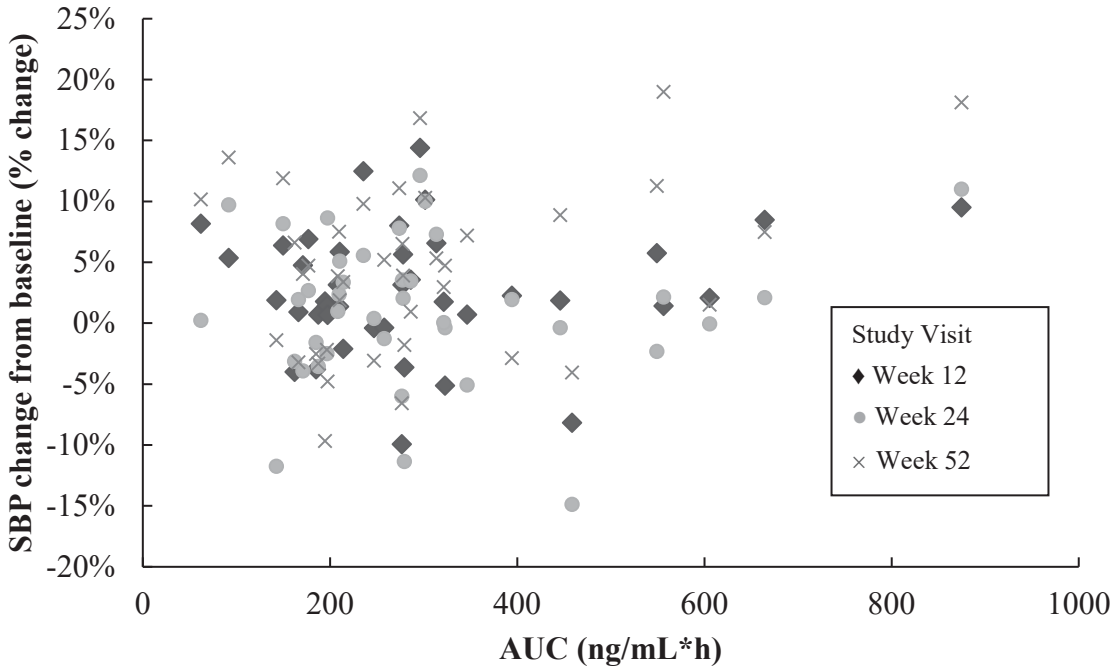


Source: Figure generated from vital sign (ADVS) datasets submitted under Study 178-CL-206A (Module 5.3.5.1, eCTD #1)

In children, the SBP increased by 4.3 mm Hg and the DBP by 1.7 mm Hg from baseline after the week 4 in-clinic visit. Within this group, the SBP increased by 5.9 mm Hg and the DBP increased by 2.3 mm Hg from baseline after the week 4 in-clinic visit in patients less than 8 years of age.

The mean AUC for mirabegron was 14% to 32% higher at each in-clinic visit after the week 4 visit in children compared with adolescents. The reason for this increase was largely due to five children with AUC's greater than 500 ng/mL*hr. No adolescents had AUC's greater than 500 ng/mL*hr. Despite a higher overall mirabegron exposure, there was not a clear exposure-response relationship in children with larger blood pressure elevations. See **Figure 2**.

Figure 2: Exposure-Response for SBP Change in Children in Study 178-CL-206A



Source: Figure generated from PK (ADPC) and vital sign (ADVS) datasets submitted under Study 178-CL-206A (Module 5.3.5.1, eCTD #1)

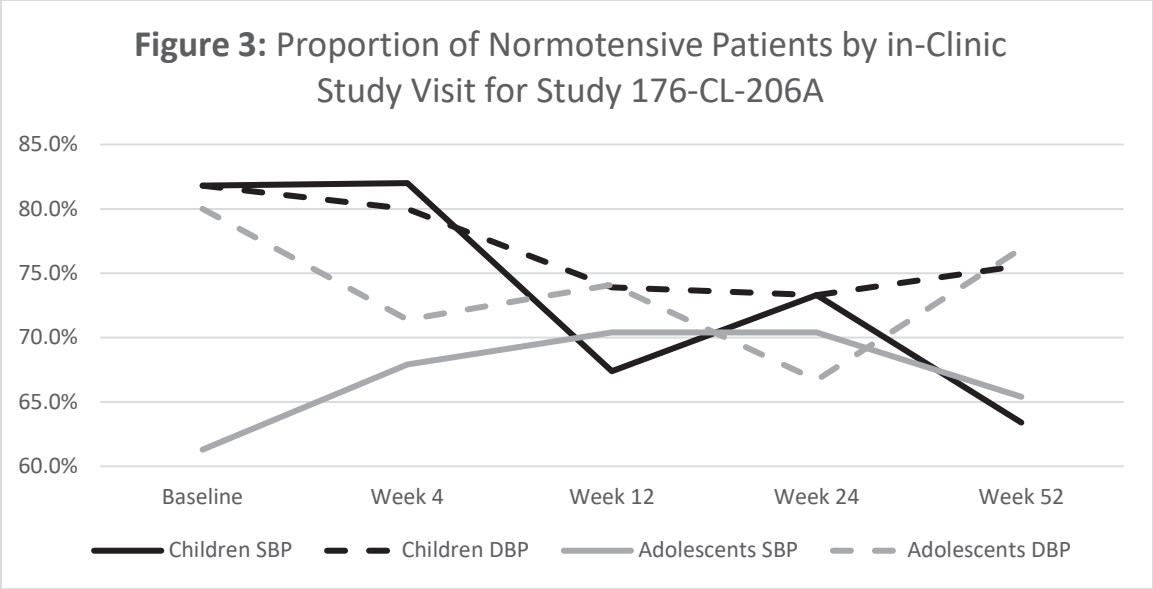
Using criteria from the NHLBI 4th Report, 45 (82%), 3 (5%), and 7 (13%) of 55 patients 3 to less than 12 years of age (referred to as children for this analysis) were normotensive, pre-hypertensive, or had stage I HTN, based on either SBP or DBP criteria, at the baseline in-clinic visit. For patients 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%) at the baseline in-clinic visit. The baseline proportion of study patients that had pre-existing HTN was largely similar between children and adolescents. 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 (22%) of the 45 children who were normotensive at baseline had a measured SBP at or above the 95th percentile based the NHLBI 4th Report during one of the in-clinic study visits while this occurred in only one adolescent patient (5%). Six (13%) of the 45 children who were normotensive at baseline 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 (11%) of the baseline normotensive adolescents. Overall 22% of children and 14% of adolescents changed categories from either normotensive or pre-hypertensive at baseline to stage I HTN by either SBP or DBP criteria at least once during the trial. 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). Three of the 4 adolescents who developed stage I HTN were in the pre-hypertension category at baseline. The single adolescent that had a measured BP at or above the 95th percentile from a normotensive baseline did not persist with BP elevations during subsequent in-clinic visits. Three of the 6 (50%) children who had normal DBP at baseline developed stage I HTN based on DBP criteria during the study. No children developed stage II HTN by either SBP or DBP NHLBI 4th Report criteria at any point in the trial.

For children and adolescents with complete follow-up thru 52 weeks in the study, the proportion at the baseline visit that were normotensive, pre-hypertensive, or had stage I HTN, based on either SBP or DBP criteria, was similar to that for patients who did not complete all study visits thru 52 weeks (e.g. full safety analysis population). Similarly, the proportion of children and adolescents, that completed all study visits, that changed categories from either normotensive/pre-hypertension to stage I HTN is similar to the full safety analysis population. In general, of patients with complete 52-week follow-up, children were more likely to change from normotensive to having at least one BP measured at or above the 95%ile (24%) compared with adolescents (8%).

As shown in **Figure 3**, for SBP the proportion of children who remained normotensive declined over the 52-week study period with the largest decrease occurring at the week 12 in-clinic visit. For DBP, and for both SBP and DBP in adolescents, the declines were relatively modest, if present, and not sustained thru the study period.



Source: Figure generated, in part, from Table 15 in the Summary of Clinical Safety (Module 2.7.4, eCTD #1)

For BP measured via oscillometric methods (e.g. automated cuffs), 20% percent of patients had study clinic visit PCR BP changes compared with 22% of patients with BP measured using auscultation. None of the SBP or DBP elevations appeared to be associated with adverse events, such as headaches, which can present as a symptom of acute HTN in the study population.

2. Heart Rate

Baseline HR and subsequent changes in the absolute and percent change in HR with mirabegron exposures from in-clinic HR measurements in Study 178-CL-206A are presented in **Table 4.**

Table 4: Changes in Heart Rate from in-Clinic Study Visits in Study 178-CL-206A

Study Visit	***Children**			****Adolescents**		
	n	**AUC**	**HR*****	**n**	**AUC**	**HR*****
Baseline	55	-	93.4	31	-	85.4
Week 4	50	259.8	+ 1.9 (+2%)	28	256.8	+ 2.8 (+3.3%)
Week 12	46	306.9	+ 0.7 (+0.8%)	27	270.0	- 1.1 (-1.3%)
Week 24	45	298.4	- 0.5 (-0.5%)	27	247.1	+ 1.8 (+2.1%)
Week 52	41	267.4	+ 2.3 (+2.5%)	26	203.3	+ 0.9 (+1.1%)

* Patients 1 to less than 12 years of age

** Patients 12 years to 17 years of age
*** HR in beats per minute and expressed as the mean for the baseline in-clinic study visit and mean change from baseline for subsequent in-clinic study visits (Percent change from baseline in parenthesis.
Source: Table abstracted from Table 15 in the Summary of Clinical Safety (Module 2.7.4, eCTD #1)

As shown in **Table 4**, Mirabegron treatment was associated with minimal increases in HR in both children and adolescents.

As defined by the Applicant, 3 of 50 (6%) children and 2 of 28 (7.1%) adolescents developed PCR HR changes during the in-clinic study visits. When HR was measured using oscillometric methods, 7% percent of patients had PCR HR changes compared with 0% of patients with HR measured using auscultation.

As shown in **Table 5**, at baseline, a larger proportion of adolescents had HR's above the 90th percentile compared with children. With this said, a consistent trend in the proportion of study patients with HR's above the 90th percentile did not occur at subsequent in-clinic study visits in either children or adolescents. No more than two study patients at each study visit developed HR's greater than the 99th percentile which were not sustained at subsequent study visits.

Table 5: Heart Rate Parameters from in-Clinic Study Visits in Children and Adolescents in Study 178-CL-206A

Study Visit	***Children**				****Adolescents**			
	n	**AUC**	**Proportion > 90%ile*****	**Proportion > 99%ile*****	**n**	**AUC**	**Proportion > 90%ile*****	**Proportion > 99%ile*****
Baseline	55	-	9.1%	0%	31	-	22.6%	0%
Week 4	50	259.8	14%	2%	28	256.8	35.7%	7.1%
Week 12	46	306.9	8.7%	0%	27	270.0	14.8%	0%
Week 24	45	298.4	6.7%	0%	27	247.1	33.3%	3.7%
Week 52	41	267.4	12.2%	2.4%	26	203.3	15.4%	3.8%

* Patients 1 to less than 12 years of age
** Patients 12 years to 17 years of age
***HR Percentiles abstracted from Figure 4: Centiles of heart rate for normal children from birth to 18 years of age from Fleming et al.[31]
Source: Table generated from vital sign (ADVS) datasets submitted under Study 178-CL-206A (Module 5.3.5.1, eCTD #1)

[31] See footnote 22

There were similar proportions of patients with HR's greater than the 90th and 99th percentiles in the population of patients with complete follow-up at all in-clinic study visits compared to the full safety analysis population.

3. Comparison of Vital Signs from Home and In-Clinic Measurements

As shown in **Table 6**, a more detailed analysis of BP and HR measures in children between the ages of 4 and 7 years reveals that home measures were generally higher than in-clinic measurements for both BP and HR. In addition, changes in BP were similar in direction and magnitude at subsequent study visits when comparing home and in-clinic readings. The HR did not increase appreciably in children with subsequent clinic visits and is less pronounced than that seen with home measures. This suggests that anxiety was not an important contributing factor to the in-clinic BP elevations noted with mirabegron therapy in the 4 to 7 year old patients.

Table 6: Home and in-Clinic Vital Signs in Children 4 to 7 Years of Age in Study 178-CL-206A

Study Visit	**Children 4 to 7 years of age**						
	n	**Home SBP***	**In-Clinic SBP***	**Home DBP***	**In-Clinic DBP***	**Home HR***	**In-Clinic HR***
Baseline	22	99.8	97.7	67.7	63.8	99.5	98.2
Week 4	21	98.9 (-0.9)	97.7(0)	65.2(-2.5)	63.8(0)	98.5(-1)	99.4(+1.2)
Week 12	20	103.4(+3.6)	102.3(+4.6)	68.2(+0.5)	66.8(+3.0)	101(+1.5)	98.1(-0.1)
Week 24	19	100.5(+0.7)	101.3(+3.6)	66.3(-1.4)	64.3(+0.5)	98.2(-1.3)	96.6(-1.6)
Week 52	19	106.2(+6.4)	105.5(+7.8)	70.8(+3.1)	67.2(+3.4)	100.3(+0.8)	98.6(+0.4)

* Expressed as mean and mean change from baseline in parentheses
Source: Table generated from vital sign (ADVS) datasets submitted under Study 178-CL-206A (Module 5.3.5.1, eCTD #1)

III. Discussion

For both consistency and accuracy, this reviewer analyzed in-clinic study visit BPs. The in-clinic BP measurements were standardized in the protocol and measured consistently in the same manner by trained study personnel during in-person study clinic visits.

The analysis of BP shifts provided in this review is based solely on criteria established by the NHLBI 4th Report. The Applicant calculated BP percentiles using the NHLBI 4th Report reference standards but used criteria from AAP HTN Subcommittee Clinical

Practice Guidelines to identify and categorize PCR BP changes. This approach to categorize abnormal BPs during the trial is inappropriate as the AAP HTN Subcommittee Clinical Practice Guidelines use reference BP standards that exclude obese children and adolescents from the reference "healthy" population and as a result have overall lower BP associated with each percentile.[32]

The absolute increase in both SBP and DBP in children is higher than that previously reported in the MYRBETRIQ prescribing information from clinical trials in healthy adults and adults with OAB. Unlike the adult program, the pediatric trials did not include a placebo control. A BP elevation at or above the 95th percentile occurred in approximately 22% of the children in Study 178-CL-206A who were previously normotensive at baseline. These BP elevations were sustained at subsequent in-clinic study visits in approximately 60% of these children (e.g. stage I HTN). The magnitude of the observed SBP and DBP increases in adolescents from Study 178-CL-206A were similar to those already reported in the approved adult population. The normotensive adolescent who developed elevated BP at one in-clinic study visit did not develop sustained HTN at subsequent study visits.

Baseline changes in HR over the study were small in both children and adolescents and did not result in an appreciable number of study patients developing HR's above the 99th percentile. There were a greater proportion of adolescents at baseline with HR's above the 90th percentile for age, but mirabegron treatment did not result in significant increases in this group.

The more pronounced changes in BP in children were driven by observed BP increases in the 4 to 7 year old age group. The increases cannot be explained by increased mirabegron exposures in these children even though the largest initial BP increases occurred at the week 12 study visit after titration of mirabegron dosing to the PED50.

In order to exclude the possibility of anxiety as a potential confounder of the increased BPs observed in the 4 to 7 year age cohort, this reviewer compared in-home (SBPM) and in-clinic BP and HR values in this age group and, in general, the SBPM BP and HR values taken at home were higher than the in-clinic measures. This is not the expected pattern in cases where anxiety with the in-clinic study visits would be responsible for BP and HR elevations.

[32] See footnote 25

IV. Conclusions:

Mirabegron appears to have increased BP disproportionately in children compared with adolescents participating in Study 178-CL-206A. The reasons for this occurrence are unclear based on review of the vital sign data. Approximately 22% of the children who were normotensive at baseline developed at least one measured BP at or above the 95th percentile in Study 178-CL-206A, and HTN was sustained in approximately 60% of these children. The magnitude of the observed SBP and DBP increases seen in adolescents from Study 178-CL-206A were similar to those already reported in the approved adult population. None of the observed BPs in children led to stage II HTN, and one adolescent developed stage II HTN which was not sustained. No patients required discontinuation from the trial because of changes in BP or HR.

Mirabegron appeared to impact SBP more than DBP after the 12 week study visit in enrolled children, but the precise reason for mirabegron's discrepant effect on BP in the pediatric study population is unclear. An exploratory study of the role of off-target mirabegron beta-1 adrenergic activation in healthy adults showed that mirabegron increased HR and SBP but not DBP or cardiac output.[33] The increase in SBP was attenuated by co-administration of select beta-1 and beta-1/2 adrenergic antagonists. A potential explanation in the preferential increase in SBP relative to DBP with mirabegron use may include off-target beta-1 adrenergic effects that caused increased cardiac inotropic and chronotropic effects without changes in peripheral vascular resistance.

The increases in BP, which caused sustained shifts in BP categories in more than half of the children, do not represent a barrier to approvability of mirabegron but should be described in mirabegron labeling. Symptoms, such as headaches, which may be attributable to BP increases were uncommon in Study 178-CL-206A and did not lead to discontinuation of mirabegron. Furthermore, monitoring for an adverse reaction of HTN is readily possible with mirabegron use and approved anti-hypertensive drug products can be used to lower BP in children where chronic use is needed. If DUOG plans to approve the dosages administered in Study 178-CL-206A for use in patients 3 to less than 12 years of age labeling should reflect changes in BP associated with use at the approved dosages, particularly in younger children (e.g. 3 to 7 years of age).

Mirabegron did not cause clinically meaningful changes from baseline in HR in children and adolescent patients in Study 178-CL-206A. Amended labeling regarding

[33] van Gelderen M, Stölzel M, Meijer J, Kerbusch V, Collins C, Korstanje C. An Exploratory Study in Healthy Male Subjects of the Mechanism of Mirabegron-Induced Cardiovascular Effects. J Clin Pharmacol. 2017 Dec;57(12):1534-1544

WARNINGS AND PRECAUTIONS relative to changes in HR is not warranted based on these findings.

V. Recommendations:

- The BP data collected in Study 178-CL-206A should not preclude approvability of this product in the pediatric NDO population down to 3 years of age.
- Describe BP and HR findings from Study 178-CL-206A in Sections 5, 6, and 8.4 of product labeling with pediatric approval for NDO.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHAMIR TUCHMAN
02/16/2021 11:09:44 AM

MONA K KHURANA
02/16/2021 11:21:26 AM

JOHN J ALEXANDER
02/16/2021 01:08:00 PM

Memo to File

Date	January 28, 2021
From	Ling Yang, M.D., Ph.D. Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Elena Boley, M.D., M.B.A., Clinical Reviewer Mark Hirsch, M.D., Clinical Team Leader Samantha Bell, B.S., Regulatory Project Manager Division of Urology, Obstetrics and Gynecology (DUOG)
NDA	213801
Applicant	Astellas Pharma Global Development, Inc.
Drug	Myrbetriq (mirabegron) (b) (4) Granules
NME	No
Review Priority	Priority
Proposed Indication	Treatment of Neurogenic Detrusor Activity in Pediatric Patients aged 3 Years and Older
Consultation Request Date	October 28, 2020
Summary Goal Date	February 26, 2021
Action Goal Date	March 28, 2021
PDUFA Date	March 28, 2021

A consult to conduct inspections was received from the Division of Urology, Obstetrics, and Gynecology (DUOG) on 10/28/2020 that identified the sponsor Astellas Pharma and the following two clinical investigators (CIs) for good clinical practice (GCP) inspections:

- Dr. David Bolong (Site 63001; Philippines)
- Dr. Sang Won Han (Site 82001; Korea)

An inspection assignment was issued by the Office of Scientific Investigations (OSI) on 11/04/2020 and the plans to conduct GCP inspections of the sponsor and the CIs were scheduled by the Office of Regulatory Affairs (ORA).

The ongoing COVID-19 global pandemic has significantly limited ORA's ability to conduct onsite GCP inspections. Following discussions between OSI and DUOG, a decision was made that assessment of the application could proceed without GCP inspections if they were not possible before the action due date. At this time, following guidelines to protect the health, safety, and welfare of FDA employees and study staff, and with repeated evaluations of the current situation and mission-critical priorities, the planned inspections in support of NDA 213801 have been cancelled.

As a result, OSI will not be able to determine if Study 178-CL-206A was conducted adequately nor whether the study data are reliable in support of the proposed indication at this time.

{See appended electronic signature page}

Ling Yang, M.D., Ph.D.
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OSI/DCCE/GCPAB/Team Leader/Min Lu
OSI/DCCE/GCPAB Reviewer/Ling Yang
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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01/28/2021 02:02:40 PM

MIN LU
01/28/2021 02:07:49 PM

KASSA AYALEW
01/28/2021 03:00:07 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: January 27, 2021

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst, DCN

To: Nenita Crisostomo
DRUP

Subject: QT Consult to NDA 213801 (SDN 001 / New NDA)

Note: Any text in the review with a light background should be inferred as copied from the consult request.

This memo responds to your consult to us dated 1/7/2021 regarding the division's QT related question. We reviewed the previous IRT review(s) for NDA 202611 dated 01/24/2012 in DARRTS and the 9 individual cases of potential QT prolongation.

1 Responses for the Division

Question 1: Mirabegron is known to increase heart rate. In this setting, what is the preferred QT interval correction method?

IRT's response: We recommend Fridericia's correction for HR unless there are significant increases in HR, which is generally defined as a mean increase of > 10 bpm. We do not recommend the use of Bazett's correction for QT because it has been shown to be inferior for adults (ICH E14 Q&A (R3) section 1.5) and has been shown to be associated with false positive increases in QTc particularly if the heart rate is elevated[1]. In the thorough QT study for mirabegron the observed mean HR increase at 50 mg was less than 10 bpm and it therefore seems reasonable to use Fridericia's correction method for doses not associated with significantly higher exposure than 50 mg.

[1] Andrsova et al. *Problems with Bazett QTc correction in pediatric screening of prolonged QTc interval*. BMC Pediatrics 2020.

Question 2: Do the 9 individual cases above, reported either as TEAE of QT prolongation (n=3) or as ECG abnormality (n=6), raise concerns about the risk of QT prolongation?

IRT's response: The 9 individual cases reported in the consult request do not elevate the risk of QT prolongation by mirabegron because there were no cases of QTcF prolongation as defined by QTcF > 450 ms. The fluctuations in QTcF are due to normal variability in the QTcF.

2 Internal Comments for the Division

Not applicable.

3 BACKGROUND

Mirabegron, a beta-3-adrenergic agonist, is currently approved under NDA 202611 as Myrbetriq® 25 mg and 50 mg tablets for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.

A Pediatric Written Request was issued on March 18, 2016, for a study in the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients. NDO is a bladder dysfunction associated with a neurologic condition. In pediatric patients the most common neurologic condition associated with NDO is congenital myelomeningocele (spina bifida).

On September 28, 2020, Astellas submitted a new NDA (NDA 213801) that contains the results of their pediatric program, including the development of a new dosage form (granules for oral liquid suspension), for the treatment of NDO in pediatric patients aged 3 years and older. Astellas also submitted a supplement to the original mirabegron NDA 202611 (Supplement 017) that contains the same new pediatric labeling.

The pediatric NDO is based on two, Phase 1, single-dose, PK studies and a single, open-label, uncontrolled, Phase 3, efficacy and safety study in the target population. The total safety population in the NDA comprises < 100 subjects.

This consult pertains to 9 individual cases from this pediatric program in which QT prolongation was reported as a treatment-emergent AE (TEAE) (n=3) or as an ECG abnormality (n=6). We seek IRT-QT input on these 9 cases.

For this consult, we seek IRT-QT interpretation of the 9 individual cases of QT prolongation identified by Sponsor as either a TEAE (n=3) or ECG abnormality (n=6) in the two Phase 1 single dose pediatric studies (studies 178-CL-202 and 178-C-203) and one Phase 3 pediatric study 178-CL-206A.

For the consultants' convenience, we have gathered the QTc data for these 9 cases and collated the data in tables and text shown below. The case numbers are highlighted in blue. The QTc data that led to the report of a TEAE or lab abnormality are highlighted in yellow.

Patient/Gender/ Weight Cohort, Dose	QTcB QTcF	Baseline	Day 1				EoS
			1 h	2 h	4 h	6 h	
Study 178-CL-202							
(b) (6) /F/58 kg Cohort 3, 75 mg 15 yo White female with OAB QTcB increase >30 ms	QTcB	407.8	389	409.3	448.3 (+40.5)	421.3	394.3
	QTcF	403.3	396	416.7	432.7	417.3	392
(b) (6) /F/34kg Cohort 2, 25 mg 9 yo White female with OAB Mean QTcB>450 ms	QTcB	428	424.5	443	452.5	425	431.5
	QTcF	407.8	410	425	427.5	407.5	408

EoS: end of study; QTcB: corrected QT interval using Bazett's method; QTcF: corrected QT interval using Fridericia's method
Baseline was defined as mean of triplicates at screening and at pre-dose
Source: 178-CL-202 CSR, p. 3154 and Appendix 13.2.8.3.2.1 p. 387 and 374.

For Subject (b) (6), ECG showed a mean increase of QTcB > 30 ms compared to baseline at 4 h postdose (448.33 vs 407.83 ms, respectively) which, per Investigator assessment, was considered to be clinically significant and was reported as a TEAE of ECG QT prolonged.

For Subject (b) (6), a 9-year-old female with idiopathic OAB who received 25 mg in Cohort 2, ECG showed a mean QTcB value of 452.5 ms at 4 h postdose (after 2 measurements) that was reported as a TEAE of ECG QT prolonged.

Patient/Gender/ Weight	QT QTcF	Screening Baseline (1) Baseline (2)	Week			
			4	12	24	52
Study **178-CL-206A**						
(b) (6) /M/35 kg 9 yo White male with NDO	QT duration	Screening 342 Baseline (1) 349 Baseline (2) 345.5	359.3	360	344.7	348
	QTcF	Screening 388.3 Baseline (1) 397.7 Baseline (2) 393	402.7	405	407.7	412.3

Source: 178-CL-206A CSR, Appendix 13.2.8.3.2.4, p. 2233, 2393.

For Subject (b) (6), ECG showed a QTcF of 417msec for 1 of the triplicate measurements at Week 24, and a QTcF of 428msec for 1 of the triplicate measurements at Week 52. Both were reported as mild TEAEs by the Investigator. In addition, an ECG obtained on Day 166, showed a QTcB of 461msec, and this event was reported as a mild TEAE.

Patient/Gender/ Weight Cohort, Dose	QTcB QTcF	Baseline	Day 1				EoS
			1 h	2 h	4 h	6 h	
178-CL-202							
(b) (6) **M/25.7kg Cohort 5, 50 mg 8 yo White male with OAB QTcF increase >30 ms**	QTcB	Screening 387.67 Predose mean 412.67 Baseline 400.17	434	437	467	433.67	414.67
	QTcF	Screening 381 Predose mean 406.33 Baseline 393.67	422.33	420.67	431.67 (+38)	402.67	398.67
(b) (6) **M/35 kg Cohort 4, 50 mg 9 yo White male with OAB Mean QTcF>450 ms**	QTcB	Screening 467.33 Predose mean 433.33 Baseline 450.33	430.67	439.67	467.33	464	475.33
	QTcF	Screening 457.33 Predose mean 425 Baseline 441.17	422.67	435.33	446.33	449.67	450.33
178-CL-203							
(b) (6) **F/17 kg 5 yo White female with NDO Mean QTcB>450 ms**	QTcB	Screening 445.33 Predose mean 453 Baseline 449.17	450.67	445.67	NE	NE	453.33
	QTcF	Screening 409.33 Predose mean 416 Baseline 412.67	409.33	412	NE	NE	412.67

NE: not evaluated due to technical problems.
Baseline = (Screening + Pre-dose mean)/2
Source: 178-CL-202 CSR, Appendix 13.2.8.3.2.1, p. 369 and 362; 178-CL-203 CSR, Appendix 13.2.8.3.2.1, p. 123.

Reviewer's comment: *Althought subject (b) (6) has EOS of 450.33 msec, the screening ECG read higher at 457.33 msec. Therefore there is no concern with this observation.*

For Subject (b) (6), ECG showed a mean increase of QTcF > 30 ms compared to baseline at 4 h postdose (431.67 vs 393.67 ms, respectively). This was accompanied by a mean increase of QTcB > 60 ms and a mean increase in HR > 30 bpm.

For Subject (b) (6), ECGs showed two values of QTcF > 450 ms, one at screening and one at End-of-Study (457.33 and 450.33 ms, respectively).

For Subject (b) (6), ECG showed mean QTcB intervals > 450 ms on three occasions, one at predose (453 ms), one at 1 h postdose (450.67 ms), and one at the EoS examination (453.33 ms).

Patient/Gender/ Weight	QTcF	Screening Baseline (1) Baseline (2)	Week			
			4	12	24	52
178-CL-206A						
(b) (6) **F/69.7 kg 10 yo White female with NDO QTcF increase > 30 ms**	QTcF	Screening 387.7 Baseline (1) 384.3 Baseline (2) 386	381.3	387.3	419 (+33)	403.3
(b) (6) **M/20.9 kg 6 yo Asian male with NDO QTcF increase > 30 ms**	QTcF	Screening 371 Baseline (1) 374.3 Baseline (2) 372.7	380.7	385.7	399.3	413.3 (+40.7)
(b) (6) **F/78.5 kg 14 yo White female with NDO QTcF increase > 30 ms**	QTcF	Screening 381 Baseline (1) 382 Baseline (2) 381.5	390.3	388.7	415.7 (+34.2)	377.7

Baseline 2 = (Screening + Baseline 1)/2
Source: 178-CL-206A CSR, Appendix 13.2.8.3.2.6, p. 2371.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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