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APPLICATION NUMBER:

213801Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader (CDTL) Brief Memo

Date	March 24, 2021
From	Mark S. Hirsch, M.D.
Subject	Cross-Discipline Team Leader (CDTL) Brief Memo
NDA/BLA# /Supplement#	NDA 202611 S-017 NDA 213801
Applicant	Astellas Pharma US, Inc.
Date of Submission	September 28, 2020
PDUFA Goal Date	March 26, 2021
Proprietary Name / Established (USAN) names	Myrbetriq (mirabegron extended-release tablets) Myrbetriq Granules (mirabegeron extended-release granules for oral suspensión)
Dosage forms / Strengths	Myrbetriq: Starting dose: 25 mg once daily. May increase to 50 mg once daily after 4 to 8 weeks. Myrbetriq Granules: See table for once daily starting dose. May increase to lowest effective once daily dose after 4 to 8 weeks.
Indication(s)	Myrbetriq: Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 years and older and weighing 35 kilograms or more Myrbetriq Granules: Treatment of NDO in pediatric patients aged 3 years and older
Recommended:	***Approval***

Body Weight	Starting Dose	Maximum Dose
11 kg to less than 22 kg	3 mL (24 mg)	6 mL (48 mg)
22 kg to less than 35 kg	4 mL (32 mg)	8 mL (64 mg)
Greater than or equal to 35 kg	6 mL (48 mg)	10 mL (80 mg)

The purpose of this CDTL Brief Memo Update is:

1) To confirm my agreement with the review teams' recommendations for Approval of these applications,

2) To provide brief summaries of the discipline-specific and consultative reviews, and

3) To confirm my agreement with the final labeling for these NDAs.

1. Confirm CDTL Recommendation for Approval

CDTL Note: For full CDTL conclusions on benefits and risks of Myrbetriq and Myrbetriq Granules for treatment of NDO in pediatric patients, the reader is referred to the final Clinical Review dated March 18, 2021, under the heading "Benefit-Risk Assessment" (Section 1.3). Here, I briefly summarize conclusions on the product's benefits and risks

and confirm my agreement with the teams' regulatory decisions to approve these applications.

Background

Mirabegron is a selective beta-3 adrenergic receptor agonist. Activation of beta-3 adrenergic receptors that reside on bladder smooth muscle causes relaxation of bladder smooth muscle inhibition of involuntary detrusor muscle contractions, and increased bladder capacity. Mirabegron is currently approved as Myrbetriq 25 mg and 50 mg mirabegron extended-release tablets for the treatment of overactive bladder (OAB) in adults. The Sponsor now provides data concerning the safety and efficacy of mirabegron for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 years and older. NDO is defined as detrusor overactivity that occurs as a result of a known neurologic lesion, such as congenital myelomeningocele (spina bifida) or spinal cord injury. The goal of therapy in pediatric NDO is to preserve renal function and to minimize symptoms of detrusor overactivity by increasing bladder capacity. The clinical studies that support these applications investigated the approved Myrbetriq tablets (mirabegron extended-release tablets) and also a new mirabegron formulation, Myrbetriq Granules (mirabegron extended-release granules for oral suspension). Myrbetriq tablets are considered appropriate for children weighing 35 kg or more. Mybretriq Granules, the new oral suspension, facilitates swallowing for younger children and allows more accurate dose titration.

Efficacy

The efficacy of Myrbetriq and Myrbetriq Granules was demonstrated in the phase 3 study 178-CL-206A, an open-label, baseline-controlled, multicenter, dose-titration study in 86 pediatric patients aged 3 to < 18 years with NDO who had been practicing continuous intermittent catheterization (CIC). The study included a 24-week, dose-titration period followed by a 28-week, fixed-dose period. As previously mentioned, two dosage forms were studied: Myrbetriq (in patients ≥ 35 kg), and Myrbetriq Granules (in patients < 35 kg, and patients ≥35g who could not, or who preferred not, to take tablets). The study demonstrated clinically meaningful increases in maximum cystometric capacity, the primary efficacy endpoint, as well as improvements in the secondary efficacy endpoint, that included other urodynamic parameters and e-diary recorded bladder volume and urinary leakage measurements. The magnitude of treatment effect was similar across age groups.

Safety

The safety of Myrbetriq and Myrbetriq Granules was assessed in a total of 86 pediatric patients with NDO. Overall, the safety profile of mirabegron in pediatric patients with NDO was consistent with its safety profile in the treatment of adults with OAB. In the 52-week study 178-CL-206A, there were no deaths and no drug-related SAEs. Discontinuations due to AEs were few (n=3) and none were determined to be study drug related. The most commonly reported adverse reactions were UTI (24.4%, which includes E.coli UTI, UTI bacterial, UTI, and UTI Pseudomonal), nasopharyngitis (5.8%), constipation (4.7%), and headache (3.5%). The high incidence of UTI events was thought to reflect, at least in part, the high incidence of UTI in pediatric NDO patients practicing CIC. AEs of special interest, also determined to be not drug related, included: bradycardia, QT prolongation, neoplasm, and seizure, each reported in a single patient; hypersensitivity reactions (n=5); and fetal disorder after exposure during

pregnancy (n=1), which was erroneously coded. Vital signs assessment showed a mean increase from baseline in blood pressure (BP) of 4.3 mm Hg systolic and 1.7 mm Hg diastolic for patients less than 12 years of age. Larger BP increases were observed in patients less than 8 years of age. The increases in BP did not appear to increase with mirabegron exposure. Finally, postmarketing AE cases were either confounded by comorbid conditions and concomitant medications or lacked key clinical information.

Risk: Benefit
From an overall risk: benefit perspective, mirabegron tablets and oral suspension are efficacious, have an acceptable safety profile consistent with the safety profile in adults, and provide an alternative treatment option for pediatric patients with NDO. Mirabegron tablets and oral suspension are a once-daily dosing regimen, and the data support safety and efficacy for patients as young as 3 years. The benefits compare favorably against the risks, which are similar to, and consistent with, the known risks in adults with OAB. The clinical studies of mirabegron tablets and oral suspension in pediatric patients with NDO identified no safety signals beyond those already known for mirabegron tablets in adults with OAB. Labelling is adequate to address the known risks.

I confirm my agreement with the review team that the applications for Myrbetriq and Myrbetriq Granules for the treatment of NDO in patients 3 years of age and older should be Approved.

2. Brief Summaries of the Discipline-Specific and Consultative FDA Reviews

CDTL Note: For additional details on the discipline-specific and consultative reviews completed through May 18,2020, the reader is referred to the final Clinical Review dated March 18, 2021, under "Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety." The reader is also referred to the final discipline-specific reviews themselves. Here, I summarize the recently completed discipline-specific and consultative reviews.

2.1 Chemistry

In the final Integrated Quality Assessment (IQA), dated March 24, 2021, the ***Chemistry*** (OPQ) team of Sam Bain, Donna Christner, Mark Seggel, Wendy Wilson-Lee, Yong Wu, Yubing Tang, Jason God, Julie Nemecek, Assadollah Noory, Vidula Kolhatkar, and Hong Cai had the following Recommendation and Conclusion:

"Astellas Pharmaceuticals' 505(b)(2) New Drug Application 213801, for MYRBETRIQ Granules (mirabegron for extended-release oral suspension), 8 mg/mL of mirabegron after reconstitution, is recommended for APPROVAL from the OPQ perspective.

Sufficient chemistry, manufacturing and controls information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, and bioavailability of the drug product.

The prescribing information (PI) and patient package insert (PPI) as submitted March 23, 2021 (0036) and March 19, 2021 (0037) are accurate, complete and comply with the requirements under 21 CFR 201.

All drug substance and product-related manufacturing, packaging and testing facilities have acceptable drug CGMP status. An overall manufacturing inspection recommendation of APPROVE was issued on March 17, 2021. The recommendation remains current as of this review.

The claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) is acceptable."

From the Chemistry review, the following is also notable:

- The maximum use-period after Myrbetriq Granules are reconstituted with water is 28 days at room temperature. This information was incorporated into labeling.

- The dissolution rate of mirabegron from Myrbetriq Granules when alcohol is added (alcohol dose-dumping study) is increased. The addition of alcohol (5, 10, 20, and 40%) increased the dissolution rate of mirabegron from Myrbetriq granules at pH 6.8. This information was incorporated into labeling.

2.2 Division of Biometrics III (DB3)

In their final ***Statistical*** review dated March 11, 2021, Jia Guo and Daphne Lin had the following Conclusion:

"*…Based on reviewer's analyses, the submitted study demonstrated clinical benefit for this indication in pediatric patients…The study demonstrated that there is clinical benefit of mirabegron in treatment of NDO in pediatric subjects".*

2.3 Clinical

In our final ***Clinical*** review dated May 18, 2020, Elena Boley and I had the following Conclusion:

"*At this time, the Clinical review team recommends that this NDA and sNDA should be APPROVED".*

In regard to efficacy, safety and risk: benefit analysis, the Clinical team concluded:

- "*From the Clinical perspective, the evidence presented in this NDA and sNDA is adequate to support the effectiveness of this product in the treatment of pediatric patients with NDO."*

- "*The safety profile of mirabegron tablets and oral suspension is consistent with the known risks of mirabegron tablets for the treatment of OAB in adults*".

- "*Mirabegron tablets and oral suspension provide an alternative treatment to the currently approved options, is efficacious, and has a different side effect profile. Additionally, mirabegron tablets and oral suspension offer a convenient once daily dosing regimen and data (was provided) to support safety and efficacy for pediatric patients as young as 3 years old. The benefits compare favorably against the safety profile which reflects the known risks apparent in the premarket and post-market experience with mirabegron tablets to date. The clinical trials of mirabegron tablets and oral suspension provided no safety signals beyond those known for mirabegron tablets in adults with OAB. Labelling is adequate to address the known risks of mirabegron….*"

2.4 Office of Clinical Pharmacology (OCP)

In their final ***Clinical Pharmacology*** review dated March 5, 2021, Peng Zou, Yun Wang, Jingyu (Jerry) Yu, and Yanhui Lu had the following Conclusion:

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

From the Clinical Pharmacology review, the following is also notable:

- In pediatric patients, Myrbetriq and Myrbetriq Granules should be taken with food. This information was incorporated into labeling.

- The weight-based doses of mirabegron in pediatric patients are:
  - Body weight ≥ 35 kg: tablets 25 to 50 mg once daily; granules 48 to 80 mg once daily
  - Body weight ≥ 22 kg and < 35 kg: granules 32 to 64 mg once daily
  - Body weight < 22 kg: granules 24 to 48 mg once daily

  This information was incorporated into labeling.

- The dosing recommendations for specific pediatric populations are:
  - No dose adjustment is needed for pediatric patients with mild to moderate renal impairment or mild hepatic impairment.
  - The daily dose should not exceed the recommended starting dose in pediatric patients with severe renal impairment or moderate hepatic impairment.
  - Myrbetriq and Myrbetriq Granules are not recommended for use in pediatric patients with end-stage renal disease (ESRD) or severe hepatic impairment.

  This information was incorporated into labeling.

2.5 Pharmacology/Toxicology

In their final ***Pharmacology/Toxicology*** review dated February 26, 2021, Laurie McLeod-Flynn and Kim Hatfield had the following Conclusion:

> "*Pharmacology/Toxicology recommends approval of this application.*"

From the Pharmacology/Toxicology review, the following was also notable:

- *"In a juvenile rat study…no general toxicity specific to the juvenile period of development was identified under the conditions of this study*".

- *"No changes to Section 8 (Pregnancy) or Section 13 (Animal Toxicology) of the label are proposed, since adult and pediatric exposures to mirabegron (AUCs) are similar".*

2.6 Division of Medical Policy Program (DMPP)

In their final ***Patient Labeling*** review dated March 4, 2021, Nyedra Booker, Elvy Varghese and LaShawn Griffiths had the following Conclusion:

> "*…The PPI is acceptable with our recommended changes."*

All labeling changes recommended by DMPP were successfully instituted.

2.7 Office of Prescription Drug Promotion (OPDP)

In her final ***OPDP*** review dated March 3, 2021, Elvy Varghese stated:

> *"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…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…"*

All labeling comments made by OPDP were successfully addressed, either through internal discussion or by instituting specific labeling changes.

2.8 Division of Medication Errors Prevention and Analysis (DMEPA)

In their final ***DMEPA*** labeling reviews dated March 17, 2021 and February 22, 2021, Denise Baugh and Celeste Karpow had the following Conclusions:

> In regard to container and carton labeling:
> "*Although the Applicant implemented or considered all of our Myrbetriq Granules container and carton labeling recommendations (Note: the recommendations from DMEPA's February 22, 2021, review), we have additional recommendations…below…*".
>
> "*The revised container and carton labeling submitted for Myrbetriq extended release tablets revised the established name from 'Myrbetriq (mirabegron) extended release*

tablets' to 'Myrbetriq (mirabegron extended release tablets)'…We have no concerns with the revisions to the established name based on the recommendations from OPQ".

In regard to the Prescribing Information (PI):
"*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)*"

On March 24, 2021, the Sponsor returned a final carton label that was found acceptable by DMEPA (via email from Celeste Karpow, March 24, 2021). That final item served to conclude the successful labeling discussions with Sponsor that resolved all carton and container labeling issues. All labeling changes recommended by DMEPA were successfully instituted or resolved.

In their final ***DMEPA*** tradename review dated February 5, 2021, 2020, Beverly Weitzman and Celeste Karpow had the following Conclusion:

"The proposed proprietary name, Myrbetriq Granules, is acceptable.".

2.9 Office of Scientific Investigations (OSI)

In their final ***OSI*** consult dated January 28, 2021, Ling Yang, Min Lu and Kassa Ayalew had following Conclusion:

"*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*".

We conducted a thorough review of the results from study 178-CL-206A and identified no data discrepancies, significant differences between subgroups, nor reasons to request a for-cause inspection. For these reasons, we dispensed with routine clinical site inspections.

2.10 Interdisciplinary Review Team for Cardiac Safety Studies (IRT-CSC)

In their final ***IRT-CSC*** consult dated January 27, 2021, in response to DUOG questions concerning AEs reported as QT prolongation, Lars Johannesen and Christine Garnett had following Conclusions:

"*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. 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."

"*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".*

2.11 Division of Pediatric and Maternal health (DPMH)

In their final ***DPMH*** consult dated February 16, 2021, in response to a DUOG request for consultative advice on vital signs data, Shamir Tuchman, Mona Khurana and John Alexander had the following findings and Conclusions:

- *"In children, the (mean) SBP increased by 4.3 mm Hg and the (mean) DBP by 1.7 mm Hg from baseline after the week 4 in-clinic visit. Within this group, the (mean) SBP increased by 5.9 mm Hg and the (mean) 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 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….*
- *Mirabegron appears to have increased BP disproportionately in children compared with adolescents…. 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 (Note: for normal BP) in Study 178-CL-206A, and HTN (Note: BP at or above the 95th percentile for normal BP) was sustained in approximately 60% of these children.*
- *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… A potential explanation in the preferential increase in SBP relative to DBP with mirabegron use may include off-target beta-1adrenergic 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…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… 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…. 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…Describe (the) BP and HR*

findings from Study 178-CL-206A in Sections 5, 6, and 8.4 of product labeling with pediatric approval for NDO".

All labeling changes recommended by DPMH were instituted in labeling.

2.12 Pediatric Review Committee (PeRC)

In the final March 11, 2021, meeting minutes from the February 23, 2021, PeRC meeting, ***PeRC*** had the following Conclusion:

"*The PeRC agrees that the PREA PMR has been fulfilled and that this product has been fully assessed for pediatric patients 3 years and older and the labeling will be updated accordingly".*

2.13 Pediatric Exclusivity Meeting (PedEx)

In the final March 1, 2021, meeting minutes from the February 10, 2021, PedEx meeting, Niquiche Guity and Mary Thanh Hai of PedEx stated:

"*Pediatric Exclusivity Granted*"

3. Confirm CDTL Agreement with Final Labeling

Labeling discussions were held with the entire FDA review team on February 4, 5, 10, 11, 16 and 18, 2021. The Division's edits to the Myrbetriq/Myrbetriq Granules (combined) PI were conveyed to Sponsor on February 24, 2020.

The Sponsor accepted most of the Division's edits and returned the PI with revisions on March 5, 2021.

The FDA review team met again on March 10, 2021 to discuss the Sponsor's edits to the FDA-edited PI and to complete FDA edits to the Sponsor's Myrbetriq and Myrbetriq Granules combined PPI. The Division's current edits to the PI and PPI were conveyed to Sponsor on March 11, 2021 and March 16, 2021, respectively.

The Sponsor accepted almost all of the Division's edits to the PI and returned that document on March 17, 29021 with a few minor additional Sponsor revisions. The Division accepted the Sponsor's edits to the PI, made one final edit, and conveyed the PI back to Sponsor on March 18, 2021. The Sponsor returned the PI on March 19, 2021 with full agreement.

The Sponsor also returned the PPI on March 19, 2021, accepting all the FDA edits, and adding a few Sponsor edits. FDA had two final edits to the PPI which were conveyed to the Sponsor on March 22, 2021, and the Sponsor agreed to these last two PPI changes and returned the final PPI (along with a final PI) on March 23, 2021.

I confirm that I agree with the final agreed-upon Myrbetriq/Myrbetriq Granules PI and PPI.

In parallel with labelling discussion on the PI and PPI, there have been discussions with Sponsor concerning the container and carton labeling. On March 19, 2021, the Sponsor

submitted revised container/carton labeling meant to comply with all prior DMEPA requests for revision. The final container/carton labels, containing minor Sponsor edits only, were reviewed by DMEPA and found acceptable, except for one minor additional DMEPA recommendation for the carton label, which was conveyed to Sponsor on March 23, 2021 and agreed by Sponsor on March 24, 2021. All issues for carton and container labeling have been resolved.

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/

MARK S HIRSCH
03/24/2021 05:40:00 PM

CHRISTINE P NGUYEN
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