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***APPLICATION NUMBER:***

# 213801Orig1s000

# NON-CLINICAL REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
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# PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

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| Application number: | 213801 |
| Supporting document/s: | eCTD 0001 |
| Applicant's letter date: | 28 September 2020 |
| CDER stamp date: | 28 September 2020 |
| Product: | MYRBETRIQ® (b) (4) Granules (mirabegron) |
| Indication: | Neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 years and older |
| Applicant: | Astellas Pharma Global Development Inc. |
| Review Division: | Division of Urology, Obstetrics and Gynecology |
| Reviewer: | Laurie McLeod-Flynn, Ph.D., D.A.B.T. |
| Supervisor/Team Leader: | Kimberly Hatfield, Ph.D. |
| Division Director: | Christine Nguyen, M.D. |
| Project Manager: | Nenita Crisostomo, |

*Template Version: September 1, 2010*

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# 1 Executive Summary

## 1.1 Introduction

MYRBETRIQ® (b) (4) Granules (mirabegron) is a beta-3 adrenergic agonist indicated for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 years and older. MYRBETRIQ (mirabegron) 25 mg and 50 mg tablets were approved on 28 June 2012 under NDA 202611, for the treatment of overactive bladder (OAB) in adult patients.

## 1.2 Brief Discussion of Nonclinical Findings

In a juvenile rat study, mirabegron was administered at 0, 3, 10, and 30 mg/kg/day for 13 weeks (beginning at 10 days of age), followed by a 4-week recovery period. At 10 mg/kg/day and above (about twice the exposure in children at the MRHD of 50 mg/day), a reversible decrease in lipid droplets in white and brown adipose tissue (accompanied by decreases in body weight at 30 mg/kg/day, primarily in male rats), an expected effect of increased lipid metabolism in rats following beta-3-adrenergic agonism, was observed. The no effect level for this effect was 3 mg/kg/day. Similar results were observed in adult rats following 13 weeks of exposure. No adverse effects on development, behavior, sensory function, reproductive performance, or fertility were observed even at the high dose of 30 mg/kg/day (greater than 12 times). Liver was identified as a target organ at high doses in adult rats.

No general toxicity specific to the juvenile period of development was identified under the conditions of this study.

## 1.3 Recommendations

### 1.3.1 Approvability

Pharmacology/Toxicology recommends approval of this application.

### 1.3.3 Labeling

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 Drug Information

## 2.1 Drug

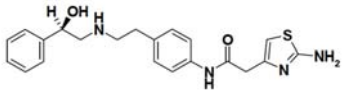
Generic Name: mirabegron

Code Name: YM178

Chemical Name: 2-(2-amino-1,3-thiazol-4-yl)-*N*-[4-(2-{[(2*R*)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl] acetamide

Molecular Formula/Molecular Weight: $C_{21}H_{24}N_4O_2S$ / 396.5 g/mol

Structure or Biochemical Description



Pharmacologic Class: beta-3-adrenergic agonist

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 202611, IND 69416

## 2.3 Drug Formulation

MYRBETRIQ® (b) (4) Granules (Mirabegron granules for oral suspension): The granules in a (b) (4) bottle are mixed with 100 mL of water in the same (b) (4) bottle to prepare 8 mg/mL of oral suspension including the total volume of the granules.

**Composition of Mirabegron Granules for Oral Suspension**

| Component | Function | Reference to Standard | Quantity (mg) | Quantity (mg/bottle) |
|---|---|---|---|---|
| Mirabegron | Active ingredient | in house | 100 | 830 |
| Sodium polystyrene sulfonate | (b) (4) | USP, Ph. Eur. | | (b) (4) |
| Diluted hydrochloric acid | | NF, Ph. Eur. | | |
| Xanthan gum | | NF, Ph. Eur. | | |
| Mannitol | | USP, Ph. Eur. | | |
| Acesulfame potassium | | NF, Ph. Eur. | | |
| Methylparaben | | NF, Ph. Eur. | | |
| Ethylparaben | | NF, Ph. Eur. | | |
| Simethicone | | USP, Ph. Eur. | | |
| Hypromellose | | USP, Ph. Eur. | | |
| Magnesium stearate | | NF, Ph. Eur. | | |
| Silicon dioxide | | NF, Ph. Eur. | | |
| Total | | - | 1000 | 8300‡ |

USP: United States Pharmacopeia, NF: National Formulary, Ph. Eur.: European Pharmacopoeia

(b) (4)

Sponsor's table

MYRBETRIQ ER tablets (approved in 2012): Each MYRBETRIQ extended-release tablet for oral administration contains either 25 mg or 50 mg of mirabegron and the following inactive ingredients: polyethylene oxide, polyethylene glycol, hydroxypropyl cellulose, butylated hydroxytoluene, magnesium stearate, hypromellose, yellow ferric oxide, and red ferric oxide (25 mg tablet only).

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