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APPLICATION NUMBER:

213801Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

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

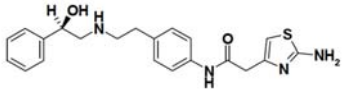
Generic Name: mirabegron

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).

2.6 Proposed Clinical Population and Dosing Regimen

Pediatric patients aged 3 years to < 18 years with neurogenic detrusor overactivity (NDO)

2.7 Regulatory Background

Myrbetriq (mirabegron) 25 mg and 50 mg tablets were approved on 28 Jun 2012 under NDA 202611 for the treatment of OAB in adult patients.

3 Studies Submitted

3.1 Studies Reviewed

A 13-Week Oral Dose Toxicity Study of YM178 in Juvenile Rats with a 4-Week Recovery Period

3.3 Previous Reviews Referenced

Application	Reviewer	Date in DARRTS
IND 69416	Eric Andreasen	5/13/13
NDA 202611	Eric Andreasen	4/11/12

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: A 13-Week Oral Dose Toxicity Study of YM178 in Juvenile Rats with a 4-Week Recovery Period

Study no.:	178-TX-055
Conducting laboratory and location:	(b) (4)
Date of study initiation:	6 February 2012
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	YM178, Lot no. GLP-08020004, 100.7% pure

Key Study Findings

At 10 mg/kg/day and above, a decrease in lipid droplets in white and brown adipose tissue (accompanied by decreases in body weight at 30 mg/kg/day), 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. However, no adverse effects on development, behavior, sensory function, reproductive performance, or fertility were observed even at the high dose of 30 mg/kg/day.

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

Methods

Doses:	0, 3, 10, or 30 mg/kg/day (based on death at 100 mg/kg/day in a dose range-finding study (IND 69416, 178-TX-054, 13 November 2012).
Frequency of dosing:	daily
Route of administration:	Oral, gavage
Dose volume:	10 mL/kg/day
Formulation/Vehicle:	0.5% aqueous methylcellulose
Species/Strain:	Rats (SPF), Crl:CD(SD)
Number/Sex/Group:	16 for general toxicity; 24 for development
Age:	10 days
Weight:	Males 22.0-31.5 g, Females 22.9-32.1 g
Satellite groups:	6/sex/group for toxicokinetics
Study design:	Juvenile rats were initially dosed at 10 days of age. One group was assessed for general toxicity; a second group was used to assess development, behavior, and reproductive function after 13 weeks of dosing and 4 weeks of recovery.

Observations and Results

Mortality

No treatment related mortality was observed. One male each at 3 and 30 mg/kg died from dosing errors, and one female at 30 mg/kg was euthanized 25 days after the last dose (irregular breathing first observed 16 to 18 days after the last dose), with foamy fluid observed in lungs and trachea.

Clinical Signs

Increased salivation was observed at 10 mg/kg/day (approximately 2-fold the MRHD in children, as it was in the 13-week adult rat toxicity study (NDA 202611, Study no. 178-TX-020).

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	3	10	30	0	3	10	30
Number of animals	31	26	26	31	31	26	26	31
Unusual resting position			26	30			24	31
Salivation			2	24				4
Lacrimation				1				

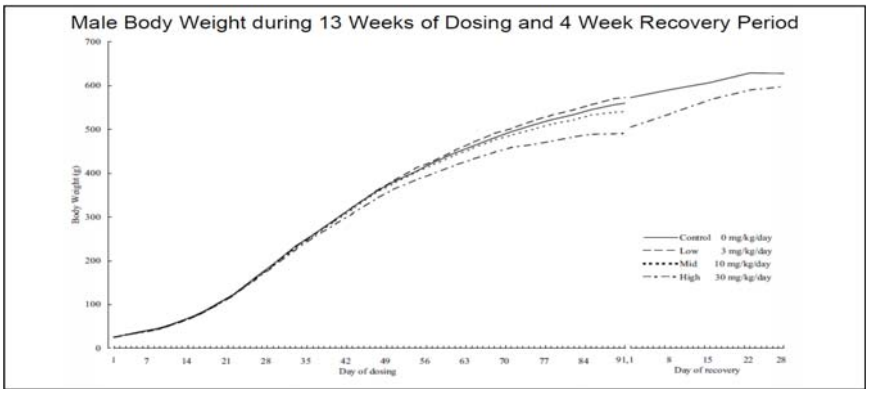
Body Weights

Body weights in males were decreased (7% to 12%) in the general toxicology group (and 6 to 16% in the development group) at 30 mg/kg/day (12-fold) from weeks 10 to 13. Following the recovery period, body weights recovered by about half. Decreased

weight gain is expected pharmacology for beta-3 agonists in rats due to effects on fat metabolism.

Female body weights were transiently reduced weeks 7 to 19 of dosing at 30 mg/kg/day in the general toxicology group but not in the development group. Body weights of dams were not affected during pregnancy.

Decreases in body weight were also observed in the adult rat toxicity studies at 30 and 100 mg/kg/day.



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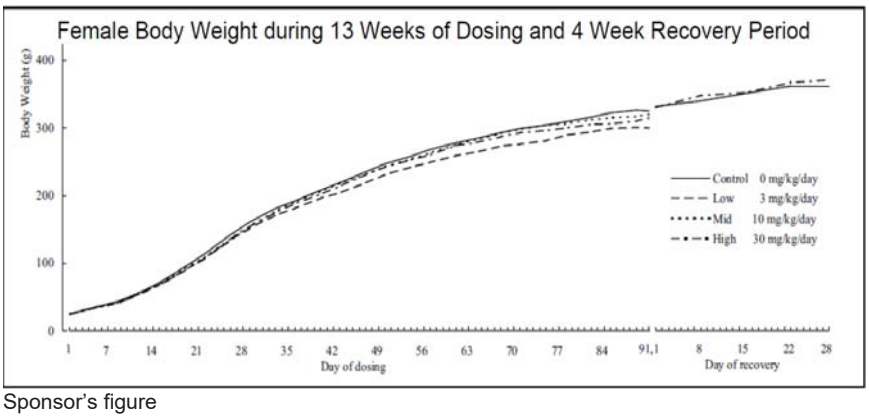

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Feed Consumption

Food consumption was slightly increased during weeks 9 to 10 of dosing in males at 30 mg/kg.

Ophthalmoscopy

No treatment related effects were observed.

Hematology

At 30 mg/kg/day, lymphocytes were slightly increased females, a finding that persisted following recovery. No effects were observed at 10 mg/kg/day. Similar findings were observed in adult rats.

Clinical Chemistry

At 30 mg/kg/day, AST (20 %) and ALT (48%) were increased in both sexes, and triglycerides (58%) and calcium (3%) were decreased in males. All effects were reversed in males following recovery but were incompletely reversed in females.

Similar findings were observed in adult rats at 30 and 100 mg/kg/day in the 26-week study, in the absence of any histopathology (Study no. 178-TX-025).

Urinalysis

At 30 mg/kg, urine output was increased and lighter in color in males (47%) at 6 weeks and in females at 6 (51%) and 13 (52%) weeks. No effect was observed following recovery.

Gross Pathology

No treatment related effects were observed.

Organ Weights

At 30 mg/kg/day, relative heart and lung weights were increased in both sexes (along with decreased body weight gain), relative kidney and submandibular gland weights were increased in males, relative liver weight was increased in females, absolute and relative ovarian weights were increased, and absolute (males and females) and relative thymus weights (males) were decreased, all in the absence of related histopathology. After 4 weeks of recovery, absolute and relative thymus weights, were still depressed (26 to 29%) in males, and absolute and relative ovary weights were increased (30 to 33%). Relative heart and lung weights were also increased in adult males at 100 mg/kg/day in the 13-week rat toxicology study (Study no. 178-TX-020), although increases in ovarian weight were not observed at this dose. At 3 and 10 mg/kg/day, no effects on organ weights were observed.

		Males (mg/kg/day)			Females (mg/kg/day)		
		3	10	30	3	10	30
Heart	Absolute Relative			 +18%*			 +10%**
Lung	Absolute Relative			 +9% *			 +6%*
Liver	Absolute Relative						 +16%**
Kidney	Absolute Relative			 +12%*			
Ovaries	Absolute Relative						+27%** +34%**
Submandibular Gland	Absolute Relative			 +15% *			
Thymus	Absolute Relative			-36%** -25%*			-25%* -18%

Statistically different from control
* $p < 0.05$, ** $p < 0.01$
Relative organ weights are normalized to body weight

Histopathology

At 30 mg/kg/day, a slight to moderate decrease in lipid droplets was observed in the brown and white adipose tissue of male and female rats following treatment but was not observed following 4 weeks of recovery.

At 10 mg/kg/day, a slight decrease in lipid droplets was observed in the brown and white adipose tissue of male and female rats following treatment but was not observed following 4 weeks of recovery.

In the 13-week adult rat toxicity study, similar decreases in lipid droplets were observed at similar doses, and hepatocyte swelling and focal necrosis were observed at 300 mg/kg/day. Mirabegron has been shown to alter lipolysis and lipid metabolism in rats through beta-3 adrenergic receptor agonist activity, an effect that has not been reported in humans.

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	3	10	30	0	3	10	30
Brown Adipose, decreased lipid droplets	0/10	0/10	8/10	10/10	2/10	0/10	4/10	10/10
White Adipose, decreased lipid droplets	0/10	0/10	6/10	9/10	0/10	0/10	4/10	10/10

Effects on Postnatal Development and Behavior

Physical Development

No treatment related effects on hair growth or eruption of incisors on Days 2 and 5 of dosing (11 and 14 days of age) or eye opening on Days 5 and 9 of dosing (14 and 18 days of age) were observed. Additionally, no treatment related effects on genital development (preputial separation on Days 33 and 40 of dosing [42 and 49 weeks of age] and vaginal opening on Days 26 and 33 of dosing [35 and 42 days of age] were observed.

Early Behavior

No treatment related effects on back righting and negative geotaxis on Days 2 and 5 of dosing (11 and 14 days of age) were observed.

Sensory Functions

On Days 19 to 25 of dosing (4 weeks of age), no treatment related effects on visual (visual placing response, pupillary reflex), auditory (Preyer's reflex) or pain responses were observed.

Open Field Test

On Days 26 to 39 of dosing (5 to 6 weeks of age), no treatment related effects on

motility and emotionality (ambulation, grooming, rearing, defecation, and urination) in open field tests were observed.

Conditioned Avoidance Response

On Days 33 to 53 of dosing (6 to 8 weeks of age), no effects on conditioned avoidance response (2 60-minute shuttle box trials) were observed.

Mating Ability

During the 3-week mating period following the recovery period, no treatment related effects on mating, fertility index, embryofetal loss (mean number of corpora lutea, number of implantations, pre-implantation loss, post-implantation loss, or number of live fetuses) were observed. No embryo/fetal malformations were observed.

Toxicokinetics (188 ng·h/mL is the predicted AUC at the MRHD of 50 mg mirabegron)

Cmax and AUC_{0-24} values varied throughout the dosing period. AUC_{0-24} values were 1.7 to 8.9 times on Day 1, 0.3 to 0.5 times on Day 12, and 0.2 to 0.6 times on Day 36 compared to those on Day 91. No apparent sex differences were observed. At 30 mg/kg/day, a minimum of 12-times the AUC at the MRHD of 50 mg was observed on Day 12.

Exposures in juvenile rats on days 12 and 36 of dosing were similar to those in adult rats administered a single dose (Study no.178-TX-020) or after 13 weeks of dosing (Study no.178-TX-042).

		Males (mg/kg/day)			Females (mg/kg/day)		
		3	10	30	3	10	30
Tmax (hr)	Day 1	2	4	4	2	2	4
	Day 12	4	4	4	4	4	4
	Day 36	4	2	2	2	2	2
	Day 91	4	2	2	2	2	2
Cmax (ng/mL)	Day 1	97	577	1,530	92	662	1,822
	Day 12	6	64	336	6	58	412
	Day 36	4	88	699	21	178	845
	Day 91	17	251	1,167	31	261	1,530
AUC_{0-24} (ng•hr/mL)	Day 1	986	4,967	14,756	1,004	4,602	20,730
	Day 12	61	374	2,461	70	372	2,284
	Day 36	19	504	3,006	90	705	3,055
	Day 91	110	1,057	8,574	148	1,159	8,139
Predicted multiple at the MRHD	Day 1	5 X	26 X	78 X	5 X	24 X	110 X
	Day 12	0.3 X	2 X	13 X	0.4 X	2 X	12 X
	Day 36	0.1 X	2.7 X	16 X	0.5 X	3.8 X	16 X
	Day 91	0.6 X	5.6 X	46 X	0.8 X	6.2 X	43 X

11 Integrated Summary and Safety Evaluation

Mirabegron is a beta-3 adrenergic receptor agonist, as demonstrated using cloned human beta-3 adrenergic receptor (AR). Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of beta-3 AR which increases bladder capacity. Although mirabegron showed very low intrinsic activity for cloned human beta-1 AR and beta-2 AR, results in humans indicated that beta-1 AR stimulation occurred at a mirabegron dose of 200 mg. (MYRBETRIQ label)

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. However, 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 the MRHD).

No general toxicity specific to the juvenile period of development was identified under the conditions of this study, although variations in exposure over developmental periods in juvenile animals complicate direct comparison with exposures and effects in the 13-week study in adult rats.

In a 13-week study in adult rats, mirabegron was administered at 0, 10, 30, 100, or 300 mg/kg/day, followed by four weeks of recovery. Lethality was observed at 100 mg/kg/day and above, and dose dependent reductions in body weight and body weight gain were observed in males at 30 mg/kg/day and greater. Decreased lipid droplets in brown and/or white adipose were observed at 10 mg/kg/day and greater. Liver toxicity (hepatocyte swelling) was observed at 300 mg/kg/day. (NDA 202611 Review, Andreasen, 11 April 2012)

Mirabegron was also previously reviewed in studies up to 26 weeks in rats and 52 weeks in dogs under NDA 202611.

In a 26-week study in rats, no mortality was observed up to 100 mg/kg/day (56-59x MRHD in adults) Reduced body weight was observed at 30 mg/kg in males. Relative liver weights increased at ≥ 30 mg/kg/day in both sexes. Effects on fat accumulation were observed at 10 and 30 mg/kg/day, in males and females, respectively. (Andreasen, 2012)

In a 52-week study in monkeys, no drug related deaths occurred at doses up to 30 mg/kg/day (8x MRHD). Increased PR interval was observed at ≥ 30 mg/kg within 2 hours of dosing. A NOAEL was 10 mg/kg/day (2x MRHD in females and 2.5x MRHD in males). (Andreasen, 2012)

Elevated liver enzymes (< 2 fold) compared to non-treated animals, were noted in rats and dogs at high doses which fully or partially returned to pre-exposure levels after drug withdrawal. Adverse hepatic histology observed in rats included eosinophilic pigment deposition at exposures 12-17 times the MRHD, along with hepatocyte swelling and fibrosis at lethal exposures 130 times the MRHD. Hepatocyte hypertrophy, vacuolation and lipid accumulation were noted in dogs at 25 times the MRHD. Since hepatotoxicity was only observed in rodents and dogs but not monkeys, was reversible, and did not cause adverse histopathology except at or near the lethal dose with large multiples of the clinical exposure, the potential for hepatotoxicity at the dose proposed for marketing was judged as low (Andreasen, 2012).

Cardiac effects

Increases in heart rate were observed in rats (i.v., about 2 times the exposure at the MRHD), dogs (oral, about at 0.1 times), and rabbits (i.v., 9 times), and monkeys (oral, 12 times). Ventricular tachycardia was observed in dogs and monkeys at exposures 29 to 37 times the MRHD. The beta-1-adrenergic agonist metoprolol partially reversed the increases in heart rate in these species indicating that increased heart rate in animals may be mediated at least partly through beta-1-adrenergic receptor activity overlap. Risk assessment for cardiovascular effects was conducted in clinical trials in adults and children (Andreasen, 2012).

Reproductive toxicity

Fertility studies in rats showed that mirabegron had no effect on either male or female fertility at non-lethal doses up to 100 mg/kg/day. Systemic exposures (AUC) at 100 mg/kg in female rats was estimated to be 22-fold the MRHD in women and 93-fold the MRHD in men (MYRBETRIQ label).

No embryo-fetal lethality or morphological fetal developmental abnormalities were produced in pregnant rats following daily oral administration of mirabegron during the period of organogenesis (Days 7 to 17 of gestation) at 0, 10, 30, 100, or 300 mg/kg, doses which were associated with systemic exposures (AUC) 0, 1, 6, 22, and 96-fold the MRHD. Skeletal variations (wavy ribs, delayed ossification) were observed in fetuses at doses 22-fold the systemic exposure at the MRHD and were reversible during development. Exposures 96-fold the MRHD were maternally-toxic (mortality, decreased body weight gain) and associated with fetal growth reduction (MYRBETRIQ label).

Mirabegron-related material was present in rat milk and in the stomach of nursing pups following administrations of a single 10 mg/kg oral dose of ^{14}C-labeled mirabegron to lactating rats (MYRBETRIQ label).

Pregnant rabbits were treated with daily oral doses of mirabegron at 0, 3, 10, or 30 mg/kg/day during the period of organogenesis (Days 6 to 20 of gestation), which resulted in plasma exposures that were 0, 1, 14, or 36-fold the MRHD based on AUC.

At 10 mg/kg/day (14-fold the MRHD) and higher, fetal body weights were reduced. At 30 mg/kg/day, maternal toxicity (increased heart rate, mortality, reduced body weight gain, reduced food consumption) occurred, and fetal deaths, fetal cardiomegaly and fetal dilated aortae were observed at systemic exposure levels (AUC) 36-fold the MRHD (MYRBETRIQ label).

In a pre- and postnatal developmental study, rats were treated with daily oral doses of mirabegron at 0, 10, 30, or 100 mg/kg/day (0, 1, 6, or 22-fold the MRHD) from day 7 of gestation until day 20 after birth. Decreased maternal body weight was observed along with decreased pup survival in the first few days after birth (92.7% survival) compared to the control group (98.8% survival), at 100 mg/kg/day (22-fold the MRHD). Pup body weight gain was reduced until postnatal day 7 but not further affected throughout the remainder of the lactation period. *In utero* and lactational exposure did not affect developmental milestones, behavior, or fertility of offspring. No effects were observed at 30 mg/kg/day.

Genotoxicity/Carcinogenicity

Mirabegron was not mutagenic in the Ames bacterial reverse mutation assay, did not induce chromosomal aberrations in human peripheral blood lymphocytes at concentrations that were not cytotoxic, and was not clastogenic in the rat micronucleus assay (MYRBETRIQ label).

Long-term carcinogenicity studies were conducted in rats and mice dosed orally with mirabegron for two years. Male rats were dosed at 0, 12.5, 25, or 50 mg/kg/day and female rats and both sexes of mice were dosed at 0, 25, 50, or 100 mg/kg/day. Mirabegron showed no carcinogenic potential at systemic exposures (AUC) 38 to 45-fold higher than the MRHD in rats and 21 to 38-fold higher than the MRHD in mice than the human systemic exposure at the 50 mg dose (MYRBETRIQ label).

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/s/

LAURIE L MCLEOD FLYNN
02/26/2021 01:35:28 PM

KIMBERLY P HATFIELD
02/26/2021 01:40:01 PM
I concur with the review and recommendations of Dr. McLeod-Flynn.