

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202611Orig1s000**

**OFFICE DIRECTOR MEMO**

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

DATE: June 30, 2012  
TO: NDA 202611  
Mirabegron  
Astellas Pharma Global Development, INC.

FROM: Victoria Kusiak, M.D.  
Deputy Director, Office of Drug Evaluation III

SUBJECT: Approval Action

Mirabegron, a new molecular entity (NME), is a beta-3 adrenergic receptor ( $\beta$ 3-AR) agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency. Its mechanism of action relaxes the detrusor smooth muscle during the urinary bladder fill-void cycle by activation of  $\beta$ 3-AR without interfering with voiding contraction. Studies in OAB animal models have shown that mirabegron increases bladder capacity. Non-clinical and clinical studies suggest that mirabegron also has some  $\beta$ 1-AR agonist activity. Animal studies and cardiac impedance evaluations in humans have shown that  $\beta$ 1-AR stimulation occurs at high mirabegron exposures even though mirabegron showed very low intrinsic activity for cloned human  $\beta$ 1-AR and  $\beta$ 2-AR.

The recommended starting dose of mirabegron is 25 mg taken orally once daily. If further efficacy is required, the dose may be increased to 50 mg orally once daily after 8 weeks of therapy.

Mirabegron has been marketed in Japan under the tradename Betanis® since July of 2011 for a similar indication at a maximum oral dose of 50 mg once daily.

This memorandum documents my concurrence with the Division of Reproductive and Urologic Product's (DRUP'S) approval recommendation for mirabegron 25 mg and 50 mg once daily for the treatment of OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency.

#### **REGULATORY HISTORY**

Prior to submission of the IND, on August 26, 2004, advice in the form of two non-clinical Special Protocol Assessments (SPAs) was requested and received by the applicant.

A pre-IND telecom was held on December 21, 2005 and the IND was filed on May 10, 2006.

On October 15, 2007 an End of Phase 2 (EOP2) meeting was held with the applicant and the Division during which agreement was reached on appropriate study efficacy populations and size; efficacy endpoints; and size and duration of exposure of the safety population. Additionally, adequate safety monitoring measures for both hypertension and liver function tests (LFTs) were identified as the potential safety issues of increase in blood pressure (BP) and increase in LFTs had been identified in phase 2 trials.

On December 21, 2007, DRUP agreed to two clinical SPAs for the conduct of phase 3 trials.

A pre-NDA meeting was held on June 15, 2011 during which agreements were reached between DRUP and the applicant concerning NDA format and electronic presentation.

The NDA was submitted on August 29, 2011.

## **CHEMISTRY MANUFACTURING and CONTROLS**

There are no outstanding CMC issues. The proposed testing and acceptance criteria for both the drug substance and drug product are considered adequate to assure identity, strength, purity, and quality for the requested dosage strengths of mirabegron.

## **CLINICAL MICROBIOLOGY**

Clinical microbiology review found the applicants proposal to perform (b) (4) for Microbial Limits to be unacceptable due to non-compliance with 21 CFR 211.165 (a) and (b). As an alternative to (b) (4), the applicant will omit finished product microbial testing for batch release and perform the microbial limits testing at the initial time point on stability samples. With this alternative microbial limits testing, the application is approved from the microbiology standpoint

## **NONCLINICAL PHARMACOLOGY/TOXICOLOGY**

Non-Clinical Pharmacology:

In non-clinical pharmacology studies, mirabegron was shown to increase bladder capacity and reduce bladder contractions. It is readily absorbed following oral administration and distributed widely in animals. Mirabegron and its metabolites are eliminated in urine and feces in rats, monkeys and humans. Enterohepatic circulation was confirmed in rats.

Findings in animals at exposures similar to the maximum recommended human dose (MRHD) were characteristic for a mixed beta adrenergic agonist and included decreased

frequency of urination, slight decrease in BP, slight increase in heart rate (HR) and increases in lacrimation and salivation.

#### Non-Clinical Toxicology:

Elevation in HR was observed in rats after IV dosing at exposures < 2x MRHD and after oral exposure in dogs at exposures  $\geq 0.1$ x MRHD, rabbits at  $\geq 9$ x MRHD and monkeys at 12x MRHD. Mirabegron also promoted ventricular tachycardia in dogs and monkeys at  $\geq 29$ -37 times the MRHD. Mirabegron-induced increases in HR were at least partially reversible with treatment with metoprolol, a  $\beta$ 1-AR antagonist, suggesting that the increase in HR seen with mirabegron may be at least partially due to  $\beta$ 1-AR agonism.

In both rats and monkeys the liver was the tissue with the greatest exposure, and elevated liver enzymes < 2 fold compared to non-treated animals were noted in rats and dogs at high doses which returned to baseline after drug withdrawal. Adverse liver histology included eosinophilic pigment deposition at exposures 12-17 the MRHD, while hepatocyte swelling and fibrosis were seen at lethal exposures  $\geq 130$ x the MRHD. Hepatotoxicity was observed in rodents and dogs, but not in monkeys. The hepatotoxicity was reversible and occurred only at or near the lethal dose with large multiples of clinical exposure. The potential for hepatotoxicity at the dose proposed for humans is considered to be low.

Mirabegron had no effect on development in rats at doses up to 6x the MRHD or in rabbits at clinically relevant doses. Rat fetuses exposed to mirabegron in utero at maternal exposures of  $\geq 22$  times the MRHD displayed wavy ribs and decreased ossification. At a dose that was lethal to the mother (96x MRHD), decreased fetal weight and bone malformations were seen. At doses  $\geq 14$  x MRHD in rabbits, reduced fetal weights were seen; exposures 36x the MRHD in rabbits caused cardiomegaly, dilated aortas and impaired ossification in the fetuses.

Mirabegron was transferred to rat fetuses through the placenta and through lactation, resulting in a slight increase in death in the first few days after birth along with decreased body weight at exposures of 22x the MRHD.

In a standard battery of *in vitro* and *in vivo* studies mirabegron was not genotoxic; in addition 2 year carcinogenicity studies at doses 25-45 the MRHD suggest that mirabegron is not carcinogenic.

Mirabegron will be labeled a pregnancy category C and the fetal risk statement will note that mirabegron is predicted to have a low probability of increasing the risk of adverse developmental effects above the background risk.

## CLINICAL PHARMACOLOGY

#### Pharmacokinetics:

With oral administration, mirabegron reaches peak plasma concentrations (C<sub>max</sub>) between 3 and 4 hours. The absolute bioavailability increases from 29% at the 25 mg dose to 35% at the 50 mg dose. Mean C<sub>max</sub> and AUC increase more than dose proportionally over the dose range. In the overall population of males and females, a 2 fold increase in dose from 50 to 100 mg increased C<sub>max</sub> and AUC by 2.9 and 2.6 fold respectively, whereas a 4 fold increase from 50 to 200 mg increased C<sub>max</sub> and AUC by 8.4 and 6.5 fold. Steady state is achieved in 7 days of once daily dosing with mirabegron.

Co-administration of mirabegron with a high fat meal reduced C<sub>max</sub> and AUC by 45% and 17% respectively, while co-administration with a low fat meal decreased C<sub>max</sub> and AUC by 75% and 51% respectively. Phase 3 trials were conducted and demonstrated efficacy and safety without regard to food; therefore, mirabegron may be taken with or without food.

Mirabegron is extensively distributed at steady state, is 71% bound to plasma proteins and shows moderate affinity for albumin and alpha-1 acid glycoprotein. It also distributes to erythrocytes.

Mirabegron is metabolized via multiple pathways including dealkylation, oxidation, direct glucuronidation and amide hydrolysis. Two major inactive metabolites were observed in humans representing 14% and 11% of exposure respectively. *In vivo* studies suggest that CYP2D6 and CYP3A4 isoenzymes play a limited role in the oxidative metabolism of mirabegron.

The terminal half-life of mirabegron is 50 hours. 55% of a dose of mirabegron was recovered in the urine and 34% in the feces. Renal clearance of mirabegron is primarily through active tubular secretion along with glomerular filtration.

#### Drug/Drug Interactions:

As mirabegron is transported and metabolized through multiple mechanisms, clinically relevant drug interactions between mirabegron and drugs that inhibit or are a substrate for one of the cytochrome P450 (CYP) isoenzymes or transporters are not expected. A moderate inhibitory effect of mirabegron on the metabolism of CYP2D6 substrates, was demonstrated in *in vitro* studies.

Studies of mirabegron using human liver microsomes and recombinant human CYP enzymes showed that mirabegron is a moderate and time-dependant inhibitor of CYP2D6 and a weak inhibitor of CYP3A. Mirabegron is unlikely to inhibit the metabolism of co-administered drugs metabolized by the following cytochrome P450 enzymes: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2E1 as it did not inhibit the activity of these enzymes at clinically relevant concentrations. Additionally mirabegron did not induce CYP1A2 or CYP3A.

Mirabegron at doses of 100-160 mg was evaluated in single and multiple dose clinical pharmacology trials when co-administered with the following agents: ketoconazole,

rifampin, solifenacin, tamsulosin (all given once daily) and metformin (given twice daily). No dose adjustment was found to be required with any of these agents. Likewise, no dose adjustment was required with co-administration of ethinylestradiol, levonorgestrel or warfarin.

The inhibitory potency of mirabegron with respect to CYP2D6 is moderate and the CYP2D6 activity recovers within 15 days of discontinuation of mirabegron. Never the less, caution is advised when giving mirabegron with agents that have a narrow therapeutic index that are metabolized by the CYP2D6 system such as thioridazine, flecainide and propafenone. A starting dose adjustment of digoxin to the lowest dose is advised with monitoring of digoxin levels.

#### Special Populations:

**Geriatric:** Geriatric use has been well evaluated. Pharmacokinetic studies showed that the pharmacokinetics of mirabegron are not significantly effected by age, and the C<sub>max</sub> and AUC of mirabegron and its metabolites following multiple oral doses were similar in the elderly ( $\geq 65$  years) and the young ( $< 65$  years of age). Of 5648 patients who received mirabegron in phase 3 trials, approximately 36% (2029) were 65 years of age or older and approximately 10% (557) were 75 years of age or older. No differences in safety or effectiveness were observed between patients younger than 65 years of age as compared to those older than 65 years of age in these studies.

**Gender:** The C<sub>max</sub> and AUC of mirabegron were approximately 40-50% higher in females than in males. Gender differences are attributed to differences in body weight and bioavailability. In general, this difference is not clinically relevant.

**Renally Impaired:** Following single dose administration of 100 mg of mirabegron to subjects with mild renal impairment (eGFR 60 to 89 mL/min/1.73 m<sup>2</sup>) mean mirabegron C<sub>max</sub> and AUC were increased by 6% and 31% as compared to subjects with normal renal function. In subjects with moderate renal failure (eGFR 30-59 mL/min/1.73 m<sup>2</sup>) C<sub>max</sub> and AUC were increased by 23% and 66% respectively. In patients with severe renal failure (eGFR 15-29 mL/min/1.73 m<sup>2</sup>) mean C<sub>max</sub> and AUC were 92% and 118% higher. Mirabegron was not studied in patients with end stage renal failure. Based upon these values for C<sub>max</sub> and AUC, no dose adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment, the dose is 25 mg daily.

**Hepatically Impaired:** Following single dose administration of 100 mg mirabegron to patients with mild hepatic impairment (Child-Pugh Class A), mean mirabegron C<sub>max</sub> and AUC were increased by 9% and 19% relative to subjects with normal hepatic function. In patients with moderate hepatic impairment (Child-Pugh Class B), mean C<sub>max</sub> and AUC values were increased by 175% and 65%. Patients with severe hepatic impairment (Child-Pugh Class C) were not studied. No dose adjustment is necessary in patients with mild hepatic impairment. The dose in patients with moderate hepatic is 25 mg daily.

## Pharmacodynamics:

**Urodynamics:** The effect of mirabegron on parameters of urodynamics was evaluated. Mirabegron at doses of 50 and 100 mg once daily in men with lower urinary tract symptoms and bladder outlet obstruction showed no effect on cystometry parameters and was well tolerated. Administration of mirabegron at doses of 50 and 100 mg once daily for 12 weeks did not adversely affect the maximum flow rate or the detrusor pressure at maximum flow rate.

**QT Study:** A through QT study (n= 164 healthy men and 153 healthy women) evaluated the effect of repeat oral dosing of mirabegron at the clinically relevant dose of 50 mg once daily as well as two supra-therapeutic doses of 100 and 200mg once daily on the QT interval individually corrected for HR. The study found no clinically relevant effect of mirabegron at the doses studied on corrected QT interval. Mirabegron did elevate HR in a dose dependant manner across the 50-200 mg dose range. The maximum mean difference in HR from placebo ranged from 6.7 bpm with mirabegron 50 mg to 17.3 bpm with mirabegron 200 mg. Increases in SBP were seen at 3 or 6 hours post dosing of 4.0, 7.7 and 11.6 for the 50, 100 and 200 mg doses respectively and increases in DBP of 3.7, 4.1 and 7.7 mmHg respectively.

**Effects of mirabegron on HR:** In the 12 week EU/ NA phase 3 trials (n= 2736), the mean adjusted difference in HR vs. placebo for change from baseline for patients receiving mirabegron 25 mg, 50 mg, and 100 mg was 0.9, 1.0 and 1.9 respectively for AM measurements and for mirabegron 25 mg, 50 and 100 mg the differences were 0.6, 1.0, and 2.3 bpm respectively for PM measurements, which was similar to the tolterodine positive control (1.0 AM and 2.1 PM).

**Effects of mirabegron on BP:** In the 12 week EU/NA phase 3 trials (n=2736), with respect to BP the adjusted mean difference vs. placebo for change from baseline SBP for mirabegron 25 mg, 50 mg and 100 mg was -0.5, 0.6 and 0.4 respectively for AM measurements and 1.0, 0.5, 0.9 for PM measurements. Tolterodine (positive control) was -0.1 for the AM measurement and 0.0 for the PM measurement. The change in diastolic BP was -0.1, 0.4, and 0.2 respectively for mirabegron 25 mg, 50 mg and 100 mg in the AM and -0.3, 0.4, and 0.5 respectively for the PM measurement. Over-all, at the 50 mg dose, an increase of approximately 1 bpm in HR and an increase of 1 mm Hg or less in both systolic and diastolic blood pressure was seen as compared to placebo. Changes in HR and BP were reversible upon discontinuation of treatment.

**Effect of mirabegron on intraocular pressure:** Mirabegron 100 mg once daily did not increase intraocular pressure (IOP) after 56 days of treatment in healthy subjects. In a phase 1 trial(n=310) assessing the effect of mirabegron on IOP using Goldman applanation tonometry, a dose of 100 mg mirabegron was non-inferior to placebo in mean change from baseline to day 56 in subject-average IOP (upper bound of the two-sided 95% confidence interval of the treatment difference between mirabegron 100 mg and placebo was 0.3mm Hg).

## **EFFICACY:**

Mirabegron was evaluated for efficacy in 3 twelve week phase 3 double blind, randomized, placebo controlled, parallel group, multicenter trials for the treatment of OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency. Entry criteria required that patients have symptoms of OAB for at least 3 months with at least 8 micturitions per day and at least 3 episodes of urgency [Patient Perception of Intensity of Urgency Scale (PPIUS) grade 3 or 4] with or without incontinence during a 3 day diary period at randomization. 48% of the study population was naïve to antimuscarinic agents and 52% had been previously treated with antimuscarinic therapy. Overall the population studied was reflective of the expected OAB population. Patients were predominantly female (72%) and white (94%) with a mean age of 59 years (range 18-95 years). Approximately 38% of patients were  $\geq 65$  years of age and approximately 12% of patients were  $\geq 75$  years of age across treatment groups.

At baseline the mean number of micturitions per 24 hours was 11.6 and the mean number of incontinence episodes per 24 hours was 1.8. The three types of OAB were represented (urgency incontinence only, mixed stress/urgency incontinence with urge as a predominant factor and frequency/urgency without incontinence). Mean duration of OAB symptoms was similar across treatment groups, ranging from 85.2 to 88.3 months. The proportion of patients with urological surgery for incontinence was relatively comparable across groups (8.3% to 9.5 %). Demographics and OAB characteristics of the population enrolled were generally similar across the 3 primary phase 3 trials.

Efficacy was based on two co-primary efficacy endpoints: 1) the change from baseline to endpoint in the mean number of incontinence episodes per 24 hours as compared to placebo at week 12 and 2) the mean change from baseline to endpoint in the mean number of micturitions per 24 hours as compared to placebo at week 12. Efficacy endpoints were also measured at weeks 4 and 8.

The efficacy analyses included individual study and pooled data from three pivotal phase 3 trials: 178-CL-046, 178-CL-047 and 178-CL-074. Study 178-CL-046 randomized 1987 patients to either mirabegron 50 mg, mirabegron 100 mg, tolterodine extended release 4 mg (positive control) or placebo (1: 1 randomization, approximately 497 patients per arm); Study 178-CL-047 randomized 1329 patients to either mirabegron 50 mg, mirabegron 100 mg or placebo (1:1 randomization, approximately 440 per arm) and Study 178-CL-074 randomized 1306 patients to either mirabegron 25mg, mirabegron 50 mg or placebo (1:1 randomization, approximately 435 per arm). In the combined 3 trials, 1380 patients received placebo, 432 patients received mirabegron 25 mg, 1375 patients received mirabegron 50 mg, 929 patients received mirabegron 100 mg and 495 patients received active control (oral antimuscarinic) once daily.

In the pooled efficacy analysis for the 25 and 50 mg mirabegron dose, the primary efficacy analysis demonstrated the following:

- At week 12, treatment with mirabegron 25 mg resulted in a statistically significant reduction of incontinence episodes of -0.40 episodes per 24 hours ( $p=0.005$  adjusted for multiplicity); treatment with mirabegron 50 mg resulted in a statistically significant reduction of incontinence episodes per 24 hours as compared to placebo of -0.40 ( $p<0.001$  corrected for multiplicity).
- At week 12, treatment with mirabegron 25 mg resulted in a statistically significant reduction of micturitions in 24 hours as compared to placebo of -0.47 ( $p=0.007$ , adjusted for multiplicity) while treatment with mirabegron 50 mg resulted in a statistically significant reduction of micturitions per 24 hours as compared to placebo of -0.75 ( $p<0.001$  corrected for multiplicity).

Secondary efficacy endpoints were evaluated including:

- Change from baseline to week 12 in mean voided volume per 24 hours in the pooled pivotal studies. This secondary endpoint was expressed as adjusted difference versus placebo. For mirabegron 50 mg, the change from baseline in mean voided volume was statistically significant at 11.9 cc ( $p<0.001$  adjusted for multiplicity). Mirabegron 25 mg resulted in a mean change from placebo of 4.6 cc which was not statistically significant ( $p=0.15$ ).
- Week 4 efficacy analyses; at week 4, a statistically significant decrease in the number of incontinence episodes for 24 hours was reported for mirabegron 50 mg (-0.45,  $p=0.001$ ) as compared to placebo as well as a statistically significant decrease in the number of micturitions for 24 hours (-0.45,  $p=0.001$ ) as compared to placebo. Mirabegron 25 mg did not show statistically significant separation from placebo for either endpoint (incontinence episodes or micturitions for 24 hours) at 4 weeks (-0.34,  $p=0.39$  and -0.34,  $p=0.39$  respectively).
- Week 8 efficacy analyses; at week 8, a statistically significant decrease in the number of episodes of incontinence and of micturitions for 24 hours was seen with both mirabegron 25 mg (-1.38,  $p=0.036$ ; and -1.53,  $p=0.017$ ) and mirabegron 50 mg (-0.40,  $p=0.016$ ; and -0.05,  $p=0.006$ ) as compared to placebo.

The results for each of the three trials (178-CL-046, 178-CL-047 and 178-CL-074) showed similar results when analyzed individually.

In the 1 year active controlled safety study (049), mirabegron 50 mg maintained efficacy over the course of the study period as assessed by the co-primary endpoints. The 25 mg dose was not included in this study.

Subpopulation efficacy analyses of clinical interest included:

- Gender: Mirabegron 25 mg and 50 mg were effective in reducing the mean number of incontinence episodes and micturitions per 24 hours from baseline to final visit for both male and female subjects. A larger reduction versus placebo in mean number of incontinence episodes was observed in female subjects compared to male subjects.
- Age: Mirabegron 50 mg reduced the mean number of incontinence episodes per 24 hours (adjusted mean versus placebo) from baseline to final visit less in the <65 years of age group (-0.22) as compared to the ≥65 years of age group (-0.66). There was a similar finding for mirabegron 25 mg, with the values being -0.29 for under < 65 years and -0.59 for ≥65 years of age. With respect to mean number of micturitions per 24 hours, efficacy is also greater in the over 65 year age group, compared to under 65 years group, but this difference did not reach statistical significance.

Both mirabegron 25 mg and 50 mg showed statistically significant reductions in the number of incontinence episodes per 24 hours as compared to placebo and also in the number of micturitions per 24 hours as compared to placebo at the 12 week primary efficacy timepoint. The 100 mg dose also showed efficacy at this time point, but is not under consideration for marketing approval.

## **SAFETY**

The safety data from this NDA submission raise concerns related to the effect of mirabegron on heart rate and blood pressure secondary to its β agonist mechanism of action. Additionally, specific adverse reactions documented during clinical trials have raised potential concerns involving effects on neoplasia, liver function, urinary tract-related adverse reactions (urinary tract infection [UTI] and renal colic), and hypersensitivity reactions.

The overview in this section is intended as a brief summary of the safety information contained in the NDA.

Safety Data Base:

The trials conducted provide adequate patient exposure to assess the safety of mirabegron used once a day for the treatment of OAB. In the pivotal and additional analysis sets supporting the safety of the OAB indication:

- There were a total of 8752 subjects in phase 2/3 trials and 1800 subjects in phase 1 trials. 7325 subjects received at least 1 dose of mirabegron.
- The phase 2/3 population receiving the to-be-marketed formulation formed the primary safety database. This database included a total of 4414 subjects: 811 mirabegron 25 mg patients, 2131 mirabegron 50 mg patients, 1305 mirabegron 100 mg patients, 167 mirabegron 200 mg patients, and 2142 placebo patients. There were also 958 patients who received tolterodine extended release 4 mg in active comparator arms.
- The long-term positive controlled safety trial (Study 178-CL-049), included 812 patients exposed to mirabegron 50 mg, 820 patients exposed to mirabegron 100 mg (of the total 1632, 901 patients were re-exposures) and 812 patients exposed to tolterodine ER 4 mg active comparator.
- There were other trials included in the safety database as follows:
  - Phase 2 trials of either short duration (2-4 weeks) or special purpose (a 12-week study in BPH subjects). Within these trials, there were 170 placebo patients, 70 mirabegron 50 mg patients, 65 mirabegron 100 mg patients, 145 mirabegron 200 mg patients, and 65 mirabegron 300 mg patients.
  - A Japanese long-term uncontrolled trial in which 153 patients received mirabegron 50 mg and 50 patients received mirabegron 100 mg as the highest dose in this titration study.
- The global phase 2/3 population (n=5863) had the following continuous mirabegron exposure:  $\geq 84$  days (n=4191);  $\geq 182$  days (n=1572);  $\geq 365$  days (n=622).

Demographics: Subjects in the primary phase 3 trials were predominantly female (approximately 72%) and White (approximately 94%) with a mean age of 59 years (range 18-95 years). Approximately 38% of subjects were  $\geq 65$  years of age and approximately 12% of subjects were  $\geq 75$  years of age across the treatment groups.

Safety Profile:

Adverse Reactions:

In the pivotal Phase 3 trials (n=3187), the overall treatment emergent adverse events (TEAEs) reported by  $\geq 1.0\%$  of patients and at an incidence  $>$  placebo were: **hypertension** 49/432 (11.3%) for mirabegron 25 mg versus 103/1375 (7.5%) for mirabegron 50 mg versus 105/1380 (7.6) for placebo; **nasopharyngitis** 15/432 (3.5%) for mirabegron 25mg versus 54/1375 (2.9%) for mirabegron 50 mg versus 35/1380 (2.5%) for placebo; **urinary tract infections** 18/432 (4.2%) for mirabegron 25 mg versus 40/1375 (2.9%) for mirabegron 50 mg versus 25/1380 (1.8%) for placebo; **constipation** 7/432 (1.6%) for mirabegron 25 mg versus 22/1375 (1.6%) for mirabegron 50 mg versus 20/1380 (1.4%) for placebo; **fatigue** 6/432 (1.4%) for mirabegron 25 mg versus 17/1375 (1.2%) for mirabegron 50 mg versus 14/1380 (1.0%) for placebo; **tachycardia** 7/432 (1.6%) for mirabegron 25 mg versus 17/1375 (1.2%) for mirabegron 50 mg versus

8/1380 (0.6%) for placebo and **abdominal pain** 6/432 (1.4%) for mirabegron 25 mg versus 8/1375 (0.6%) for mirabegron 50 mg versus 10/1380 (0.7%) for placebo. Patients on mirabegron who reported hypertension were reviewed and the majority of subjects had hypertensive blood pressures noted prior to exposure to mirabegron.

Serious adverse events (SAEs):

In the OAB 12-week Phase 3 population (n=4611), one or more SAEs was reported for 62/2736 (2.3%) mirabegron, 29/1380 (2.1%) placebo, and 11/495 (2.2%) tolterodine subjects, with no apparent mirabegron dose response.

In the total mirabegron global safety database, the most common SAEs were atrial fibrillation (mirabegron: 5/2736 [0.2%]; placebo: 1/1380 [0.1%]; tolterodine: 0/495), chest pain (mirabegron: 4/2736 [0.1%]; placebo: 2/1380 [0.1%]; tolterodine: 0/495.)and pneumonia: 6/2736 [0.2%]; placebo: 2/1380 [0.1%]; tolterodine: 1/495 [0.2%]).

Deaths:

In the entire mirabegron development program, there were 11 deaths, none of which appear directly related to treatment with mirabegron. There were 2 deaths in ongoing Study 178- CL-090 (one sudden death on blinded treatment and one death that occurred prior to randomization; a chemical poisoning). Nine deaths occurred in subjects participating in completed trials (5 subjects treated with mirabegron, one treated with placebo and 3 treated with tolterodine). Of the five deaths occurring in subjects treated with mirabegron: one subject died due to metastatic colon cancer, one due to pneumonia that progressed to sepsis, respiratory failure, multi-organ failure and renal vein thrombosis, one due to cardiac failure, one due to suicide, and one due to aortic dissection. All of these deaths had confounding conditions making attribution to mirabegron problematic.

Key potential safety issues identified for mirabegron include: cardiovascular safety (effects on blood pressure, heart rate, and cardiovascular AEs), neoplasms, hepatic safety, urinary tract related AEs, and hypersensitivity reactions. These are outlined as follows:

Cardiovascular Safety:

- Blood pressure:

A mirabegron-related elevation in blood pressure of approximately 1 mm Hg was observed in Phase 3 trials. Mirabegron-related elevations in blood pressure of approximately 3-4 mm Hg were observed in the Phase 1 trials.

Phase 3 Trials:

Mirabegron 50 mg once daily was associated with an approximate 1 mm Hg increase from baseline in systolic and diastolic blood pressures (SBP/DBP) as compared with placebo. Categorical increases from baseline in SBP and DBP for the EU/NA OAB 12-Week Phase 3 and the EU/NA Long-term Controlled Study 178-CL-049 populations were generally comparable across all treatment groups.

#### Phase 1 Trials:

In a phase 1 thorough QT study (178-CL-077) mirabegron at doses of 50 mg, 100 mg and 200 mg, was associated with mean increases in SBP of 4.0, 7.7, and 11.6 mm Hg respectively and mean increases in DBP of 3.7, 4.1, 7.7 mm Hg respectively as compared to placebo at hours 3 or 6 post dose .

In Study 178-CL-031 in healthy subjects given mirabegron 50 mg daily, at 8 hours post-dose the maximum increases from baseline in SBP and DBP on Day 14 were 6.3 and 4.8 mmHg, respectively as compared to changes of 2.4 and 2.3 mm Hg respectively for the placebo treated group in same time period post dose.

- Heart rate:

#### Phase 3 Trials:

Mirabegron 50 mg once daily was associated with an approximate 1 bpm increase in adjusted mean change from baseline pulse compared to placebo. Categorical increases from baseline ( $\geq 2$ ,  $\geq 5$ ,  $\geq 10$  or  $\geq 15$ bpm) in pulse rate in the 12 week pivotal studies were noted more frequently at various cut points with mirabegron than with placebo.

#### Phase 1 Trials:

In the Phase 1 through QT study, at doses of 50 mg, 100 mg and 200 mg mirabegron was associated with maximal mean increases in HR of 4.0, - 4.1, and 10.3 respectively. In Study 178-CL-031, mirabegron 50 mg was associated with an 11.8 bpm increase in HR, at one or more time points.

#### Potential Increase in Risk of CV Events as a Function of Increase in BP:

A consultation from the Cardiovascular and Renal (CR) Division was obtained on 20 Jan 2012. The CR consultant confirmed that the increase in blood pressure with 50 mg mirabegron in the Phase 3 clinical trials (1bpm) and phase 1 trials (3 bpm) were small; however, increasing risks for cardiovascular events as a function of increasing levels of blood pressure are a continuum, i.e., these risk curves do not demonstrate risk thresholds as a function blood pressure, but increase continuously (e.g., the absolute risk associated with increasing SBP from 169 to 170 mmHg is much worse than increasing SBP from 119 to 120 mmHg).

At FDA's request, the sponsor provided data from a Framingham risk model to predict the likely impact of small mirabegron-related BP changes on CV event rates in the post-marketing milieu. Both the Sponsor and the FDA conducted the data analysis using the Framingham model for both the small BP change noted in phase 3 trials (1 mmHg), and for the larger BP change noted in phase 1 trials (3 mmHg).

In the phase 3 trials, the SBP increased 0.5 mmHg at 4 weeks and 1.0 mmHg at 12 weeks. Based on the FDA calculations, and using the Framingham risk model for predictions, the potential for increase in major cardiovascular disease (CVD) events in all patients as stated in CVD events/million patients/year was 1026 for placebo subjects and 1213 for mirabegron 50 mg subjects (an increase of 187 events per million patients treated for a year). In high-risk patients, the CVD events were estimated to be 1412 for placebo patients and 1968 for mirabegron 50 mg patients (an increase of 556 events per million patients treated for a year).

In the Phase 1 studies, where an approximate 3 mmHg increase was noted in blood pressure in mirabegron 50 mg subjects, the predicted risk of mirabegron on CVD events was greater. The predicted number of CVD events/million patients/year was 117 for placebo subjects and 956 for mirabegron 50 mg subjects (an increase of 839 events per million patients treated for a year). In high risk patients the CVD events were estimated to be 244 for placebo patients and 1580 for mirabegron 50 mg patients (an increase of 1446 events per million patients treated for a year).

- Cardiovascular Adverse Events:

In the Global OAB safety database, the relative risk of major adverse cardiovascular events (MACE) was 0.24 (95%CI: 0.02, 1.69) for subjects receiving mirabegron compared with placebo. The TEAEs and SAEs related to hypertension were similar for mirabegron, placebo and tolterodine in the long term study.

#### Neoplasms:

An increased incidence of adverse event reports for a variety of solid malignancies and non-melanoma skin malignancies was reported for mirabegron in both short-term studies and in the mirabegron 100 mg group in the 1-year active controlled safety trial (178-CL-049). Most, but not all of the new malignancies that were reported occurred during the 1 year, active-controlled Study 049, with an apparent excess in the mirabegron 100 mg arm compared to both the mirabegron 50 mg arm and the tolterodine arm.

In the short-term studies (6 trials in the Phase 2/3 OAB population each of which was 12 weeks duration), the number of serious adverse events in the category of neoplasms benign, malignant and unspecified (including cysts and polyps), were higher in the total mirabegron group (n=4414) compared with placebo group (n=2142). 10 new neoplastic events were reported in 9 mirabegron subjects as compared to 2 in the placebo

population. The reported neoplasm SAEs were heterogeneous and represented benign as well as malignant events, generally reflecting the most prevalent malignancies in the US and Europe.

In the long-term safety trial (178-CL-049), there were three treatment arms: mirabegron 50 mg (n=812), mirabegron 100 mg (n=820) and tolterodine ER 4 mg (n=812). The incidence of adverse events of neoplasia in each arm was 1 (0.1%) in the mirabegron 50 mg arm, 11 (1.3%) in the mirabegron 100 mg arm and 5 (0.7%) in the tolterodine arm. The incidence of new malignant adverse events in each arm was 3 (0.37%) in the mirabegron 50 mg arm, 9 (1.1%) in the mirabegron 100 mg arm and 4 (0.5%) in the tolterodine arm. The relative risk of new malignant events for the total mirabegron group compared with the total tolterodine group was 1.50 (95% CI: 0.45, 6.38). A total of 21 events were reported in 16 subjects across 7 tumors organs of origin, with 2 reports each for breast, prostate, endometrial and lung cancers.

There is no mechanistic explanation to implicate mirabegron as causing cancer or promoting growth of existing tumors. Based upon review of individual cases, some of the neoplasia events could have preexisted treatment with mirabegron. The reported increased incidence of neoplasms, while of concern, occurred in the 100 mg mirabegron dose group and not in the to-be-marketed 25 and 50 mg dose group.

#### Urinary Tract Related AEs:

In the pivotal Phase 3 studies, the frequency of UTI was higher in mirabegron subjects compared with placebo subjects in the 12-week studies, and was similar to tolterodine subjects. Three urolithiasis SAEs (renal colic) were reported in the mirabegron group versus none in placebo in the EU/NA 12-Week, Phase 3 Population. Although acute urinary retention (AUR) was reported in Japan post-marketing data, the available clinical trial data do not reveal the occurrence of acute urinary retention or clinically significant adverse increases in post void residual) volume.

#### Hepatotoxicity:

In the 12-Week Phase 3 Population, one mirabegron 25 mg, one mirabegron 50 mg subject and one tolterodine subject developed elevated liver enzymes. In the overall mirabegron development program, there were three cases of severe hepatotoxicity in association with hypersensitivity reactions in subjects taking mirabegron. One of these severe cases had a liver biopsy interpreted as drug-induced liver injury (DILI) versus autoimmune hepatitis. In addition, two subjects in the long-term safety trial (178-CI-049) had rises of ALT and AST to 10 times ULN with return to normal or baseline levels while continuing mirabegron 50 mg.

#### Hypersensitivity reactions:

While there were no cases of anaphylaxis or angioedema reported, the incidence of plausible and related hypersensitivity events was higher in mirabegron subjects than it was in placebo subjects. In the non-immediate hypersensitivity category, there were 29 reports in mirabegron treated patients, one in a placebo patient, and three in tolterodine treated patients. There was one case of immediate hypersensitivity reaction in a 100 mg mirabegron subject (pruritis). Mirabegron was associated with the occurrence of significant hypersensitivity reactions: 7 hypersensitivity reactions were severe (2 cases of erythema multiforme [post marketing-Japan], 1 case of Stevens Johnson Syndrome, 2 cases of leukocytoclastic vasculitis, 1 case of hemolytic anemia and 1 case of possible autoimmune hepatitis).

### **ADVISORY COMMITTEE:**

Because mirabegron is an NME, an Advisory Committee Meeting was held for the purpose of evaluating the benefits and risks associated with treatment with mirabegron for the proposed indication of treatment of OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency. The Advisory Committee for Reproductive Health Drugs (ACRHD) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on April 5, 2012. The benefit/risk discussion was focused on the adequacy of the demonstration of efficacy and safety in the treatment of OAB.

With regard to efficacy, the committee voted “yes” in answer to the question “Do the data provide substantial evidence of benefit for mirabegron in the treatment of overactive bladder?” (Yes-8, No-4, Abstain-0)

The committee members agreed that the pivotal phase 3 clinical trials met their predefined primary efficacy endpoints by demonstrating a statistically significant decrease in the number of incontinence episodes and micturitions in a 24 hour period compared to baseline. These effects were not seen as ‘robust’ and the clinical benefit of mirabegron was seen as potentially limited. The committee members noted however, that the efficacy results seen with mirabegron are similar to those seen with available medications on the market for the treatment of overactive bladder, and further, that mirabegron offers a unique mechanism of action for those patients who do not tolerate the currently available agents (antimuscarinics). There were recommendations from some panel members to consider the 25 mg dose as a starting dose because it appeared to represent the lowest effective dose, and also to consider ongoing research of the clinical benefit and of the potential effects on quality of life for users of mirabegron.

With regard to safety, the Committee voted “yes” in answer to the question “Has adequate safety been demonstrated for mirabegron in the treatment of overactive bladder?” (Yes-9, No-3 , Abstain-0).

The majority of Committee members agreed that side effects had been examined thoroughly and that mirabegron was generally safe. Nonetheless, panel members voiced concerns regarding the effects of mirabegron on blood pressure, and the potential for

effects on neoplasia, as well as regarding the hepatic and hypersensitivity signals reported in the clinical trials. They recommended continued collection of long term data on cardiovascular, neoplastic, hepatic, and hypersensitivity adverse reactions.

In terms of risk/benefit, the Committee voted “yes” in answer to the question “Considering all the available data, including information from the briefing documents and today’s discussion, does the overall benefit-risk assessment support approval of mirabegron for the treatment of overactive bladder?” (Yes-7, No- 4, Abstain-1).

The majority of Committee members agreed that the overall benefit-risk assessment supported approval because the predefined primary efficacy objectives had been achieved and the product appeared generally safe. Several members discussed consideration of the lower 25 mg dose as a starting dose. Several members concurred with the testimony of the speaker during the open public comment period, that is, the clinical benefit of this medication may be limited. Based upon reservations concerning the potential for mirabegron to affect BP, potentially affect neoplasia, and upon the hepatic and hypersensitivity signals generated in the safety database, panel members strongly recommended that the applicant conduct directed post-marketing surveillance and conduct post-marketing studies to further define the risk associated with use of mirabegron in OAB.

#### **RISK/ BENEFIT ASSESSMENT:**

The only currently available approved therapies for the treatment of OAB are the antimuscarinic agents. These agents have modest efficacy, having shown an approximate 8-9% increase in the number of patients experiencing either a modest decrease in the number of micturitions/ 24 hours (0.8) or a decrease in the number of incontinence episodes/24 hours (0.7) as compared to placebo. The side effects associated with antimuscarinic agents are well described and include dry mouth, constipation, blurred vision, dry eyes and urinary retention. These side effects limit use of these agents in some patients.

Mirabegron is an NME with a unique mechanism of action as compared to that of currently available therapies for OAB:  $\beta_3$  agonism with partial  $\beta_1$  agonism. The efficacy of mirabegron has been well established in 3 randomized, placebo controlled phase 3 trials of adequate size (Mirabegron 25 mg [n=433], Mirebegron 50 mg [n=1379], mirabegron 100 mg [n=931], placebo [n=1384] and tolterodine [n=495]. The efficacy seen in these pooled trials (178-CL-046, 178-CL-047, and 178-CL-074) is similar to that seen with the antimuscarinics. Mirabegron 50 mg decreased the number of micturitions per 24 hours by approximately 0.55 and the number of incontinence episodes per 24 hours by 0.4 as compared to placebo. Both classes of drug (the antimuscarinics and mirabegron with  $\beta_3$ -AR agonism) decrease the endpoint measures of either incontinence or micturition by less than 1 episode per day. The placebo subtracted percentage of

patients who responded to therapy with mirabegron is similar to that seen with antimuscarinics at approximately 9%.

As would be predicted by its mechanism of action, mirabegron produced dose related increases in HR and BP in phase 1 and phase 3 trials. The effects on HR are not clinically relevant at the 25 or 50 mg doses (4 bpm). The effects seen on BP are small increases, on the order of 3 mmHg in phase 1 trials and 1 mmHg in phase 3 trials at the 50 mg dose. Changes in BP were seen to be dose related over the 50 mg, 100mg and 200mg doses. No effect on BP was seen at the 25 mg dose; however, the amount of data available on BP at that dose is insufficient to allow for conclusions as to the effect.

Evaluation of the potential for these small increases in BP seen at the 50 mg dose to increase the risk of CV events was modeled by both FDA and the applicant using a Framingham model which specified definitions for events and levels of risk. The results showed that at the 1 mmHg increase seen in phase 3 trials, the increase in CV events/million patient years was 187 events. In patients at high risk for CV events, the increase was predicted to be 556 events. For the 3 mmHg increase in BP seen in the phase 1 study, the increase in CV events/million patient years was predicted to be 839. For high risk patients it was 1336. Both the epidemiologists working with the model and the Advisory Committee members cautioned against drawing any firm conclusions from this model.

With regard to neoplasia, the increase was seen only at the 100 mg dose. In the long term safety trial (178-CL-049) the incidence of adverse events of new malignancy was 0.37% in the mirabegron group (n= 812), 1.1% in the mirabegron 100 mg group (n=820), and 0.5% in the tolterodine group (n=812). Review of the individual cases indicated that some of the malignancies could have predated treatment. There is no known mechanistic explanation to implicate mirabegron as related to any cancer or as promoting tumor growth. Additionally, animal studies showed no carcinogenic potential.

Three cases of possible hepatic toxicity (one possibly immune related), 7 cases of severe hypersensitivity reactions and one case of immediate hypersensitivity reaction were noted during clinical trials. As well an increase in the number of urinary tract infections was seen in mirabegron treated patients as compared to placebo. The increase was similar to that seen with the positive control.

#### Summary:

A majority of the Advisory Committee members agreed that mirabegron was safe and effective for the treatment of OAB and that the risk benefit assessment supported approval. Although the efficacy effect is modest, it is similar to that seen with the antimuscarinics. Additionally, because it does not have the anticholinergic side effects associated with the antimuscarinics mirabegron may provide an alternative therapy for patients who cannot tolerate the currently available therapy.

Although there is insufficient data on the effect on BP of mirabegron at the 25 mg dose, the available information suggests that the BP elevations are dose related. The mechanism of action would support the evidence of a dose response relationship with regard to the observed increase in BP. The modest increases in BP seen with the 50 mg dose of mirabegron significantly increase the risk of CV events in the Framingham model only for those patients at high risk. This risk can be reduced by excluding patients with severe hypertension from exposure.

Similarly, the increase in adverse events of malignancy occurred at the 100 mg dose. It was not seen at the 50 mg dose.

The recommended dose for mirabegron will be 25 mg with an increase to 50 mg at 8 weeks only for lack of efficacy. The 25 mg dose has not been associated with significant BP increases or with an increase in malignancy in clinical trials.

Post Marketing Requirements (PMRs) under FDAA will require a CV study to assess the potential for mirabegron to increase CV risk. Likewise, a tumor registry will be required to further assess the potential association of mirabegron to the development of tumors of various types.

The issues of potential hepatotoxicity and hypersensitivity reactions will be addressed by enhanced pharmacovigilance surveillance. The incidence of potential urinary tract adverse events will be monitored by standard adverse event surveillance.

Given that there is a segment of the OAB population that cannot be adequately treated with currently available therapy due to side effects; that the safety issues observed during review of this application can be mitigated by dose reduction to 25 mg and labeling; and that the safety issues will be further elucidated by the PMRs and enhanced safety surveillance, this reviewer is in agreement with the Advisory Committee and finds that the risk benefit assessment supports approval.

#### **PEDIATRIC CONSIDERATIONS:**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosage regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the condition for which this product is indicated cannot be reliably diagnosed in children under the age of 5, and because many children in this age group are not yet bladder trained, the necessary studies for this population are not possible or would be highly impractical. Therefore, the pediatric requirement is waived for children age 0- 4

years 11 months. The requirement is deferred for the population >5years of age but ≤17 and 11 months years of age because the product is ready for approval in adults and the pediatric studies have not yet been completed. Pediatric studies in this age range are a post-marketing requirement

#### **POSTMARKETING REQUIREMENTS and COMMITMENTS:**

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic act (FDCA) authorizes the FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes if FDA makes certain findings required by the statute.

FDA has determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to access either a signal of increase in cardiovascular events or an increase in neoplasms with mirabegron use.

Therefore, based on appropriate scientific data, FDA has determined that the following studies/trials be conducted:

- A long term observational study using electronic healthcare databases with appropriate linkages in the United States and Europe to evaluate the incidence of serious cardiovascular outcomes (both individual and composite outcomes) in patients taking mirabegron.
- A long term observational study using electronic healthcare databases with appropriate linkages to prospectively evaluate the incidence of new malignant events (excluding non-melanoma skin cancer) in patients taking mirabegron. If the study using electronic healthcare data is unsuccessful, an interview based prospective cohort study will follow.

#### **TRADENAME REVIEW:**

On April 17<sup>th</sup>, 2012, the Applicant submitted a request to the Agency for an assessment of the proposed proprietary name “Myrbetriq” under NDA 202611. This is the fifth proposed proprietary name submitted for this product:

- The proposed proprietary name (b) (4) (IND069416) was found unacceptable on December 8, 2009 because of potential name confusion with (b) (4)
- The proposed proprietary name (b) (4) was found unacceptable on August 10, 2010 due to potential confusion with (b) (4) and again found unacceptable subsequent to a request for reconsideration on July 15, 2011.
- The proposed proprietary name (b) (4) was found unacceptable on December 16, 2011 due to likelihood of confusion with (b) (4).
- The proposed proprietary name (b) (4) was found unacceptable due to orthographic similarity and shared product characteristics with the marketed product (b) (4) on March 28, 2012.

On June 11, 2012, the proprietary name “Myrbetriq” was approved by the Division of Medication Error Prevention and Analysis of the FDA.

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/s/  
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VICTORIA KUSIAK  
06/28/2012