April 27, 2012

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Food and Drug Administration
Department of Health and Human Services
WO51/Room 6133
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Dear Dr. Woodcock and Dr. Monroe:

These comments from Public Citizen’s Health Research Group are being sent in response to New Drug Application (NDA) #202611 — submitted by Astellas Pharma Global Development and considered by the Food and Drug Administration’s (FDA’s) Advisory Committee for Reproductive Health Drugs (ACRHD) on April 5, 2012 — for mirabegron for the treatment of overactive bladder (OAB) with symptoms of urge incontinence, urgency, and urinary frequency.

We strongly oppose FDA approval of the NDA for mirabegron because (1) the drug is not a major breakthrough treatment, has no unique advantages over current treatment options, and offers only marginal symptomatic benefits for OAB, a disorder that is not life-threatening; and (2) there are serious safety signals indicating risk of potentially life-threatening harm to patients.

I. Background

Mirabegron is a new chemical entity and first-in-class compound, a selective agonist for human beta-3 adrenoceptors, with the proposed indication for treatment of OAB. Binding of the drug to beta-3 adrenoceptors in the urinary bladder causes relaxation of the detrusor smooth muscle, the major muscle within the bladder wall. The drug is to be given orally as a tablet at a dose of 50
milligrams (mg) once daily (or 25 mg daily in patients with severe renal impairment or moderate hepatic impairment).¹

II. The benefits of mirabegron are marginal

The FDA’s efficacy assessment of mirabegron was based on an analysis of three randomized, placebo-controlled, phase 3 pivotal clinical trials (178-CL-046, 178-CL-047, and 178-CL-074). One trial, 178-CL-046, included an active comparator control group that received tolterodine, an antimuscarinic drug approved by the FDA for the treatment of OAB. The subjects of these studies were all adults with OAB, predominantly female (approximately 72%) and white (approximately 94%), with a mean age of 59 years (range 18-95 years). Approximately 38% of the subjects were ≥ 65 years of age and approximately 12% of the subjects were ≥ 75 years of age across the treatment groups.²

Three doses of mirabegron (25 mg, 50 mg, and 100 mg) were evaluated across the three pivotal studies. However, because the sponsor is seeking approval only for the 25- and 50-mg doses, the FDA reviewers focused on these two doses in assessing efficacy.³

At baseline, subjects had on average at least eight micturitions (voids) per day, and the mean number of micturitions per 24 hours was 11.6 for all subjects in the three pivotal trials.⁴ The mean number of incontinence episodes per 24 hours was 2.7 in the subset of patients who had incontinence symptoms at baseline.⁵

For all three pivotal phase 3 studies, the co-primary endpoints were the change from baseline to final visit in the following:

(1) The mean number of incontinence episodes per 24 hours as compared to placebo; and
(2) The mean number of micturitions per 24 hours as compared to placebo.⁶

The results of the pooled primary efficacy analysis comparing subjects receiving mirabegron 50 mg to subjects receiving placebo are summarized in Tables 1 and 2.

Table 1: Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 Hours, Pooled Primary Studies in Subjects with Incontinence at Baseline²

<table>
<thead>
<tr>
<th></th>
<th>Mirabegron 50 mg (N=862)</th>
<th>Placebo (N=878)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (SE)</td>
<td>2.7 (0.09)</td>
<td>2.7 (0.09)</td>
</tr>
<tr>
<td>Final visit (SE)</td>
<td>1.2 (0.08)</td>
<td>1.6 (0.09)</td>
</tr>
<tr>
<td>Change from baseline (SE)</td>
<td>-1.5 (0.08)</td>
<td>-1.1 (0.09)</td>
</tr>
<tr>
<td>LSM difference vs. placebo (SE)</td>
<td>-0.40 (0.09)</td>
<td></td>
</tr>
<tr>
<td>95% 2-sided CI</td>
<td>(-0.58, -0.21)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

SE=standard error, LSM=least squares mean, CI=confidence interval
Table 2: Change from Baseline to Final Visit in Mean Number of Micturitions per 24 Hours, Pooled Primary Studies in All Subjects

<table>
<thead>
<tr>
<th></th>
<th>Mirabegron 50 mg (N=862)</th>
<th>Placebo (N=878)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (SE)</td>
<td>11.7 (0.09)</td>
<td>11.6 (0.09)</td>
</tr>
<tr>
<td>Final visit (SE)</td>
<td>9.9 (0.09)</td>
<td>10.4 (0.09)</td>
</tr>
<tr>
<td>Change from baseline (SE)</td>
<td>-1.8 (0.08)</td>
<td>-1.2 (0.08)</td>
</tr>
<tr>
<td>LSM difference vs. placebo (SE)</td>
<td>-0.55 (0.10)</td>
<td></td>
</tr>
<tr>
<td>95% 2-sided CI</td>
<td>(-0.75, -0.36)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
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As compared to placebo, treatment with mirabegron 50 mg resulted in a reduction of incontinence episodes per 24 hours of -0.40 in the subset of patients with baseline incontinence symptoms (p<0.001 corrected for multiplicity). Again, as compared to placebo, treatment with mirabegron 50 mg resulted in a reduction of micturitions per 24 hours of -0.55 (p<0.001 corrected for multiplicity).

One of the key secondary endpoints of the pivotal studies was the change in volume voided per micturition from baseline to final visit. Table 3 summarizes the pooled results for this secondary endpoint comparing subjects receiving mirabegron 50 mg to subjects receiving placebo.

Table 3: Change from Baseline to Final Visit in Mean Volume Voided per Micturition (in Milliliters), Pooled Primary Studies in All Subjects

<table>
<thead>
<tr>
<th></th>
<th>Mirabegron 50 mg (N=1,324)</th>
<th>Placebo (N=1,328)</th>
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</thead>
<tbody>
<tr>
<td>Baseline (SE)</td>
<td>159.0 (1.6)</td>
<td>159.0 (1.5)</td>
</tr>
<tr>
<td>Final visit (SE)</td>
<td>180.2 (2.0)</td>
<td>168.6 (1.9)</td>
</tr>
<tr>
<td>Change from baseline (SE)</td>
<td>21.2 (1.3)</td>
<td>9.4 (1.3)</td>
</tr>
<tr>
<td>LSM difference vs. placebo (SE)</td>
<td>11.9 (1.8)</td>
<td></td>
</tr>
<tr>
<td>95% 2-sided CI</td>
<td>(8.3, 15.5)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td></td>
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</table>

For this endpoint, treatment with mirabegron 50 mg resulted in an 11.9-milliliter increase from baseline to final visit in the mean adjusted volume voided as compared to placebo (p<0.001 corrected for multiplicity).

While mirabegron showed statistically significant reductions in the number of incontinence episodes and micturitions per day and statistically significant increases in mean volume voided per micturition in comparison to placebo, the differences were extremely small and represent marginal clinical improvement in symptoms.
Several members of the ACRHD also apparently considered the benefits of mirabegron to be marginal. For example, one member, Dr. Stuart Howards, an urologist at the University of Virginia, said, “I voted yes, but I had substantial reservations. Although this is statistically significant, it’s a pretty marginal clinical benefit over placebo.”10 Confirming this, four committee members voted no in response to the question, “Do the data provide substantial evidence of benefit for mirabegron in the treatment of overactive bladder?”

III. Serious safety signals identified with mirabegron

Given that OAB is not a life-threatening disorder and mirabegron has been shown to offer meager clinical benefits for OAB patients, approval of this drug would only be justified if there were no serious safety signals identified during the clinical development of the drug. However, this is not the case: The FDA’s safety review of mirabegron revealed several serious safety signals, including adverse changes in cardiovascular parameters, neoplasms, hepatotoxicity, hypersensitivity reactions, and urinary tract adverse events.

A. Adverse cardiovascular effects

Phase 1 studies in healthy individuals revealed that mirabegron markedly increased heart rate in a dose-dependent manner. The maximum mean difference from placebo after adjusting for baseline (90% confidence interval) was 6.7 (5.3, 8.1), 11 (9.4, 12.6), and 17 (15.3, 18.7) beats per minute (bpm) for 50-mg, 100-mg, and 200-mg doses of mirabegron, respectively.11 This increase in heart rate occurred between five and six hours post-dose.

Similarly, mirabegron caused substantial, dose-dependent increases from baseline in systolic and diastolic blood pressure in healthy subjects at three to six hours post-dose. In the phase 1 study 178-CL-077, mirabegron at doses of 50 mg, 100 mg, and 200 mg was associated with mean increases in systolic and diastolic blood pressure of 4.0, 7.7, and 11.6 and 3.7, 4.1, and 7.7 millimeters of mercury (mm Hg), respectively, over baseline in comparison to placebo.12

In the pivotal phase 3 studies, mirabegron 50 mg once daily was associated with an approximately 1 bpm increase in adjusted mean change from baseline pulse compared to placebo, as well as an approximately 1 mm Hg increase from baseline in systolic and diastolic blood pressure compared to placebo.13

The FDA review noted the following as possible explanations for the observed differences in the post-exposure effects of mirabegron on heart rate and blood pressure between the phase 1 studies in health controls and the phase 3 studies in OAB subjects:14

(1) Different populations: Healthy subjects from phase 1 studies were young and had relatively low blood pressure at baseline.

(2) Different blood pressure measurements: Self-measurements of sitting blood pressure were used in phase 3 studies, whereas clinic measurements of supine blood pressure occurred in phase 1 studies.

(3) Different timing of the blood pressure sampling: In phase 1 studies, relatively more measurements within the inter-dosing interval allowed for assessment of drug effect at
peak and trough. In the phase 3 studies, vital signs were collected by the subject during
the morning (after waking up in the morning before the morning dose) and afternoon to
early evening (between 2 PM and 6 PM) in a five-day vital sign diary using a self-
measurement device. This sampling scheme did not allow for the assessment of the peak
effects, which generally occurred around 3–4.5 hours coinciding with the peak
mirabegron concentrations post-dose.

In commenting on the effects of mirabegron on heart rate and blood pressure seen in the phase 3
studies, a consultation review by the Division of Cardiovascular and Renal Products stated the
following:15

We do not agree with the sponsor’s assertion that small incremental increases in vital
signs (such as 1 mm Hg elevation in systolic or diastolic blood pressure) have not been
found to be associated with an increased cardiovascular risk. Increasing risks for
cardiovascular events with 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), and the increase in relative risk per mm Hg of [blood pressure] increase is
the same regardless of baseline [blood pressure]. Consequently, the absolute risk of
increasing [systolic blood pressure] from 169 to 170 is much worse than increasing
[systolic blood pressure] from 119 to 120. Superimposed on this phenomenon are the
effects of other risk modifiers such as smoking status and diabetes.

A cardiovascular risk assessment conducted by the Division of Clinical Pharmacology 1
reporting the following:16

The small increases in [systolic blood pressure] for the pooled twelve-week phase III
trials [for mirabegron] translate into a small increase in the 10-year general
[cardiovascular disease (CVD)] risk [defined as a composite of coronary heart disease
(coronary death, myocardial infarction, coronary insufficiency, and angina),
cerebrovascular events (including ischemic stroke, hemorrhagic stroke, and transient
ischemic attack), peripheral arterial disease (intermittent claudication), and heart failure] … The absolute increase in the mean 10-year CVD risk [with mirabegron 50 mg] on an
average is 0.19% (or 0.19 CVD events per 1000 patient-years) and fails to achieve
statistical significance.

The prevalence of OAB is estimated to be 34 million in the United States. When this
increase in the CVD risk of 0.19 events/1000 patient-years is extended to an OAB
population (with risk characteristics similar to those in the phase III studies) of a million
patients on treatment with mirabegron 50 mg QD for 1 year, 187 additional CVD events
projected ...

This increase in the CVD risk is magnified in patients with a higher baseline risk
(patients in the upper 25th percentile of baseline CVD risk) … These patients in general
tend to demonstrate more advanced age (median: 70 years), higher baseline AM [systolic
blood pressure] (median: 141 mmHg), a greater proportion of diabetes (22 – 23%), more
treatment for hypertension (67 – 68%) and higher baseline 10-year CVD risk (median:
30.6%). Accordingly, in these higher risk patients on treatment with mirabegron 50 mg [daily] for 1 year, an additional 556 CVD events are projected per million patients (still not statistically significant, p-value derived based on 25% of the total sample size in the Phase III trials).

Although these adverse increases in heart rate and blood pressure and projected trends in adverse cardiovascular events did not reach statistical significance, they nevertheless raise significant concern that, if approved, mirabegron will cause hundreds of serious adverse cardiovascular events each year in the intended target population.

B. Neoplasms

In the pivotal phase 3 studies, there was a higher incidence of the total number of neoplasm adverse events reported in the mirabegron subjects than in placebo subjects. A variety of different tumors were reported, with most instances of a particular tumor type reported by one subject. In addition, a higher incidence of serious adverse events reported as “neoplasms” was observed in the mirabegron 100 mg group (1.3%) compared to the mirabegron 50 mg group (0.1%) and to the tolterodine active control group (0.5%) in the one-year long-term follow-up study.17

There is no known common mechanistic explanation to implicate mirabegron as related to any cancer or growth of existing tumor. Nevertheless, these unexplained signals remain a concern.

C. Hepatotoxicity

Table 4 summarizes hepatotoxicity adverse events for the phase 3 studies of mirabegron.

Table 4: Pooled Hepatotoxicity Data on Adverse Events (AE) for the Pivotal Phase 3 Studies18

<table>
<thead>
<tr>
<th>Hepatotoxicity Category</th>
<th>Placebo (N=1,380)</th>
<th>Mirabegron, all doses (N=2,736)</th>
<th>Tolterodine (N=495)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment emergent AE</td>
<td>17 (1.2%)</td>
<td>41 (1.5%)</td>
<td>10 (2%)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>1 (0.7%)</td>
<td>2 (0.7%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>1 (0.1%)</td>
<td>6 (0.2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

The FDA review noted the following regarding hepatotoxicity seen with mirabegron:19

In regard to liver function test abnormalities, infrequent reports of significantly increased liver function tests were observed in subjects taking mirabegron [emphasis in original]. While some of these cases were confounded by co-morbid conditions (e.g., viral hepatitis) or concomitant hepatotoxic drugs, some cases were not confounded. In 2
mirabegron subjects, liver enzyme elevations were observed in association with hypersensitivity reactions. In one case, a liver biopsy showed drug-induced liver injury versus autoimmune hepatitis (although the subject was on possibly confounding drugs). Two subjects met Hy’s Law (one with an associated hypersensitivity reaction and one with hepatitis A, B, C). Two mirabegron 50 mg subjects had serum ALT and AST elevations to 10 times ULN that returned to baseline while on drug. These isolated cases appear to reflect a rare potential for mirabegron to adversely affect liver function.

D. Hypersensitivity reactions

The following comments from the FDA review of mirabegron indicate that the drug has a significant risk of potentially life-threatening 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 subjects, one in a placebo subject, and three in tolterodine subjects. 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 of them were severe (2 cases of erythema multiforme [post marketing-Japan], (1) Stevens Johnson Syndrome, 2 cases of leukocytoclastic vasculitis, (1) hemolytic anemia and (1) possible autoimmune hepatitis).

E. Urinary tract adverse events

A review of the safety data revealed a consistent treatment difference in the proportion of subjects having urinary tract infections (UTIs) in the mirabegron and tolterodine groups compared with the placebo group subjects. In the phase 3 study populations, one or more UTIs were reported in 99/2,736 (3.6%) mirabegron subjects, 15/495 (3.0%) tolterodine subjects, and 34/1,380 (2.5%) placebo subjects. The FDA reviewers concluded that there appeared to be a modestly increased incidence of UTI in mirabegron subjects as compared to placebo subjects.

There also appeared to be an increased incidence of reported nephrolithiasis (kidney stones) in mirabegron subjects. In the phase 3 study population, one or more urolithiasis treatment emergent adverse events were reported in 8/4,414 (0.2%) mirabegron subjects and 1/2,142 (<0.1%) placebo subjects.

IV. Summary and conclusions

Taken together, the multiple safety signals identified for mirabegron demonstrate that the risks of this drug do not outweigh the marginal clinical benefits found in the phase 3 pivotal trials. Mirabegron is not a breakthrough treatment for OAB, and it offers minimal symptomatic benefits in comparison to placebo. Given the large target OAB population for mirabegron — with likely expansion of use to other patients who have minor bladder symptoms that overlap with those of
Public Citizen                         April 27, 2012 Letter to the FDA

OAB but do not meet the diagnostic criteria for this disorder — approval of this drug will almost certainly lead to hundreds of preventable serious adverse events, some of which will result in death.

We note that four of the 11 ACRHD members agree with our position and voted against approval of the drug.

In conclusion, we strongly oppose FDA approval of the NDA for mirabegron for treatment of OAB with symptoms of urge incontinence, urgency, and urinary frequency because (1) the drug is not a major breakthrough treatment, has no unique advantages over current treatment options, and offers only marginal symptomatic benefits for OAB, a disorder that is not life-threatening; and (2) there are serious safety signals indicating risk of potentially life-threatening harm to patients, including risk of adverse cardiovascular events, liver toxicity, neoplasms, hypersensitivity reactions, UTIs, and kidney stones.

Thank you for considering our comments on this very important matter.

Sincerely,

Michael A. Carome, M.D.
Deputy Director
Public Citizen’s Health Research Group

Sidney M. Wolfe, M.D.
Director
Public Citizen’s Health Research Group


4 Food and Drug Administration. Background materials for the April 5, 2012 meeting of the Advisory Committee for Reproductive Health Drugs. Web page 70. Available at


