

Items from the FDA Briefing Document issued for the Advisory Committee meeting held October 17, 2018.

The text for correction is identified by a ~~strike through~~, with correction following in double underline, unless otherwise specified.

1. The following paragraph appears on page 26:

From a mechanistic perspective, the potential for tegaserod to cause CV ischemia is not well understood. Available 5-HT receptor affinity and functional response data for tegaserod indicate that the drug binds to 5-HT<sub>4</sub> receptors with high affinity as an agonist, and binds with moderate to high affinities for 5-HT<sub>1</sub> receptor subtypes, as an agonist. Tegaserod also has antagonistic activity at 5-HT<sub>2</sub> receptor subtypes.

This paragraph is revised to the following:

From a mechanistic perspective, the potential for tegaserod to cause CV ischemia is not well understood. Available 5-HT receptor affinity and functional response data for tegaserod indicate that the drug binds to 5-HT<sub>4</sub> receptors with high affinity as an agonist, and binds with moderate to high affinities for 5-HT<sub>1</sub> and 5-HT<sub>2</sub> receptor subtypes, ~~as an agonist~~. Tegaserod ~~also~~ has antagonistic activity at the 5-HT<sub>1</sub> and 5-HT<sub>2</sub> receptor subtypes that mediate vasoconstriction [24]. Based on the C<sub>max</sub> of tegaserod (10 nM) at the recommended dose, it is likely that tegaserod binding to 5-HT receptors in humans will be mostly limited to the 5-HT<sub>4</sub> and 5-HT<sub>2B</sub> subtypes (see Table 15 below).

2. The following paragraph appears on page 26:

Intravenous administration of 1 mg/kg in rats (1.6 times the recommended oral human dose (6 mg/dose) based on mg/m<sup>2</sup>) produced reductions in systolic and diastolic blood pressure, with no effects observed at 0.1 mg/kg or lower.

This paragraph is revised to the following:

Intravenous administration of 1 mg/kg in rats (approximately 43 times the clinical plasma levels at the recommended human dose), ~~(1.6 times the recommended oral human dose (6 mg/dose) based on mg/m<sup>2</sup>)~~ produced reductions in systolic and diastolic blood pressure, with no effects observed at 0.1 mg/kg or lower.

3. The following paragraph appears on Page 27:

Tegaserod did not induce contractions in isolated coronary artery preparations from pigs, non-human primates, and humans, but produced a small and variable contractile response in canine coronary arteries.

This paragraph is revised to the following:

Tegaserod did not induce contractions in isolated coronary artery preparations from pigs, non-human primates, and humans; Tegaserod did but produced a very small and variable contractile response in 3 of 6 canine coronary arteryies preparations at suprathapeutic concentrations. The vasoconstrictor effects of 5-HT on porcine and canine coronary arteries were inhibited by tegaserod [24].

4. Page 27: Table 15 Selectivity of Tegaserod for 5-HT Receptor Subtypes:

Add footnote to bottom of table as follows: Note: Most of the “Average Binding Affinity” values (pK<sub>i</sub> and K<sub>i</sub>) in this table were generated using only human recombinant 5-HT receptors, with the exception of the mean pK<sub>i</sub> and K<sub>i</sub> for 5-HT<sub>1B</sub>, 5-HT<sub>1D</sub>, and 5-HT<sub>2C</sub> receptors. For 5-HT<sub>1B</sub>, the mean pK<sub>i</sub> and K<sub>i</sub> values (7 and 100 nM, respectively) were calculated from 2 human values and 1 rat value; the mean of the 2 human values alone for pK<sub>i</sub> and K<sub>i</sub> was 7.5 and 32 nM, respectively. The mean pK<sub>i</sub> and K<sub>i</sub> values for 5-HT<sub>1D</sub> (7.6 and 25.1 nM, respectively) were calculated from 2 rat values. The mean pK<sub>i</sub> and K<sub>i</sub> values for 5-HT<sub>2C</sub> (6.9 and 125.9 nM, respectively) were calculated from 3 human values and 1 pig value; the mean of the 3 human values alone for pK<sub>i</sub> and K<sub>i</sub> was 6.8 and 158 nM, respectively.

5. The following paragraph appears on Page 27:

An in vitro study was conducted to assess the effects of HTF 919 on cloned hERG channels expressed in HEK293 cell. The results indicated that HTF 919 inhibited the hERG current, with IC<sub>50</sub> of 13,000nM. In contrast, cisapride produced almost complete inhibition at 2,000nM, with IC<sub>50</sub> of 44nM.

This paragraph is revised to the following:

An in vitro study was conducted to assess the effects of HTF 919 on cloned hERG channels expressed in HEK293 cells. The results indicated that HTF 919 is not a significant inhibitor of hERG channel current ~~inhibited the hERG current~~, with an IC<sub>50</sub> of 13,000nM. In contrast, cisapride produced almost complete inhibition at 2,000nM, with an IC<sub>50</sub> of 44nM.

6. The following paragraph appears on Page 28:

In contrast, cisapride, used as a positive control, increased QT interval by 15% at concentration of 0.1µM. (This study was performed after cisapride was identified to cause cardiac electrophysiologic changes.)

This paragraph is revised to the following:

In contrast, cisapride, used as a positive control, increased QT interval by 15% at a concentration of 0.1µM. ~~(This study was performed after cisapride was identified to cause cardiac electrophysiologic changes.)~~

7. The following paragraph appears on Page 28:

Tegaserod had no contractile activity at concentrations up to 10 or 30 $\mu$ M in isolated coronary artery preparations from pigs, non-human primates, and humans. Tegaserod produced a small and variable contractile response in canine coronary arteries at 3 to 10 $\mu$ M [24].

This paragraph is revised to the following:

Tegaserod had no contractile activity at concentrations up to 10 or 30 $\mu$ M in isolated coronary artery preparations from pigs, non-human primates, and humans. Tegaserod produced a very small and variable contractile response in 3 of 6 canine coronary arteries at 3 to 10 $\mu$ M preparations at supratherapeutic concentrations. The vasoconstrictor effects of 5-HT on porcine and canine coronary arteries were inhibited by tegaserod [24].

8. The following paragraph appears on Page 30:

The in vivo interaction potential between concomitant P-gp inhibitor(s) and tegaserod was not evaluated prior to the original approval [27]. An increase in the systemic exposure of tegaserod by 74% by a concomitant P-gp inhibitor, quinidine, was later reported in the literature [27] and a short summary of the study results (A2422) was submitted in the summary of clinical pharmacology. However, the full study report of A2422 was not available to FDA.

This paragraph is revised to the following:

The in vivo interaction potential between concomitant P-gp inhibitor(s) and tegaserod was not evaluated prior to the original approval [27]. Single and multiple doses of a P-gp inhibitor, quinidine (600 mg QD), increased the systemic exposure of tegaserod by 44% and 63% respectively, and AUC by 50%, and 70% (AUC<sub>0-12h</sub>) respectively. An increase in the systemic exposure of tegaserod by 74% by a concomitant P-gp inhibitor, quinidine, was later reported in the literature [27] and a short summary of the study results (A2422) was submitted in the summary of clinical pharmacology. However, the full study report of A2422 was not available to FDA.

9. Page 60: Table 27- Demographic Characteristics in Db15 by Subgroup and CV Risk Factors

n (%) with CV Risk Factor = 1, in Female IBS-C Patients, on Tegaserod: 1461 (333% 33%)

10. Page 62: Table 29- CVI Events by Various Subgroups

In the column titled “Low CV Risk Females, Db15”:

Drug (N = ~~7815~~ 7756) and Placebo (~~4701~~ 4664)