

**Errata to FDA Briefing Document
September 8, 2008 meeting of the
Advisory Committee for Reproductive Health Drugs**

The committee will discuss efficacy and safety considerations for lasofoxifene for the treatment of osteoporosis in postmenopausal women. Ten items are modified to provide updated information and clarification. Information that has been deleted is identified by “strike through” and new information is identified by “underline.”

Item 1, Page 13, after Table 4

Current:

- "In Phase 2 Study 218-102, ~~0.025~~ mg/d and 1.0 mg/d doses of lasofoxifene were investigated (see Table 5)."

Replaced with:

- "In Phase 2 Study 218-102, 0.25 mg/d and 1.0 mg/d doses of lasofoxifene were investigated (see Table 5)."

Item 2, Page 19

Current:

- "To meet the protocol-defined criteria for a fracture, a presumptive fracture identified by the semiquantitative procedure required confirmation by (1) an independent review (assessed as the presence or absence of a fracture) ~~and~~ (2) quantitative morphometric analysis."

Replaced with:

- "To meet the protocol-defined criteria for a fracture, a presumptive fracture identified by the semiquantitative procedure required confirmation by (1) an independent review (assessed as the presence or absence of a fracture) or (2) quantitative morphometric analysis. "

Item 3, Pages 35-36

Current:

- "The Applicant included only 3-year safety with the original submission of NDA 22-242. During the ongoing review of the NDA, the Applicant submitted preliminary 5-year safety data that included data relating to all-cause mortality in Study A2181002. As noted in the following 2 mortality tables (Table 24 showing 3-year data and Table 25 showing 5-year data), the hazard ratio for “all-cause mortality” in subjects treated with lasofoxifene 0.25 mg/d, compared to that in subjects treated with placebo, has increased from 1.20 to 1.38, ~~and the hazard ratio of 1.38 is statistically significant (p-value = 0.0489) when considering the 5-year data.~~"

Replaced with:

- "The Applicant included only 3-year safety with the original submission of NDA 22-242. During the ongoing review of the NDA, the Applicant submitted preliminary 5-year safety data that included data relating to all-cause mortality in Study A2181002. As noted in the following 2 mortality tables (Table 24 showing 3-year data and Table 25 showing 5-year data), the hazard ratio for “all-cause mortality” in subjects treated

with lasofoxifene 0.25 mg/d, compared to that in subjects treated with placebo, has increased from 1.20 to 1.38 (p-value = 0.0489).”

Item 4, Page 40 (third bullet)

Current:

- **"In summary**, there were numerically more deaths in the lasofoxifene-treated subjects compared to the placebo treated subjects, particularly through Year 5. The excess deaths are primarily in the cancer and non-coronary vascular categories. The number of deaths in the 0.25 mg lasofoxifene group exceeds those in the 0.5 mg group (90 vs. 73). ~~The higher proportion of deaths in the 0.25 mg/d lasofoxifene group was statistically significant (p = 0.0489) compared to that in the placebo group, based on 5-year data from Study A2181002.~~ The excess number of cancer-related deaths in the lasofoxifene-treated subjects does not appear to be focused on any specific organ system. Slightly more deaths were reported for brain, lung, and gastrointestinal systems in lasofoxifene-treated subjects."

Replaced with:

- **"In summary**, there were numerically more deaths in the lasofoxifene-treated subjects compared to the placebo treated subjects, particularly through Year 5. The excess deaths are primarily in the cancer and non-coronary vascular categories. The number of deaths in the 0.25 mg lasofoxifene group exceeds those in the 0.5 mg group (90 vs. 73, p = 0.5109) and the placebo group (90 vs. 65, p = 0.0489). The excess number of cancer-related deaths in the lasofoxifene-treated subjects does not appear to be focused on any specific organ system. Slightly more deaths were reported for brain, lung, and gastrointestinal systems in lasofoxifene-treated subjects."

Item 5, Page 42, under Division Comment

Current:

- "Although the Applicant divides adverse events (AEs) into “all-causality” and “treatment-related,” the Division has historically focused on all AEs, without limitation to those the Applicant considers treatment-related. In a properly randomized trial, confounding factors that might affect the frequency of AEs unrelated to treatment should be balanced across treatment groups.”

Replaced with:

- "Although the Applicant divides adverse events (AEs) into “all-causality” and “treatment-related,” the Division has historically focused on all AEs, without limitation to those the Investigator considers treatment-related. In a properly randomized trial, confounding factors that might affect the frequency of AEs unrelated to treatment should be balanced across treatment groups.”

Item 6, Page 54*Current:*

- "The Applicant also provided curves of the cumulative incidence of first on-study VTE versus time on study in each of the treatment groups ~~in Study A2181002 (3-year interim data)~~; see Figure 4."

Replaced with:

- "The Applicant also provided curves of the cumulative incidence of first on-study VTE versus time on study in each of the treatment groups in the Phase 2/3 program, which includes 3-year interim data from Study A2181002; see Figure 4."

Item 7, Pages 56 and 57, footer for Tables 42 and 43*Current:*

- "* Pooled lasofoxifene includes ~~0.017 mg, 0.025 mg, 0.05 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 10 mg~~ lasofoxifene dose groups."

Replaced with:

- "* Pooled lasofoxifene includes 0.25 mg and 0.5 mg lasofoxifene dose groups."

Item 8, Page 68, first bullet under Division Comments*Current:*

- "In the preceding table it appears that the highest percentage of subjects with an endometrial thickness ≥ 8 mm was noted ~~at~~ Month 36 in Study A2181002."

Replaced with:

- "In the preceding table it appears that the highest cumulative percentage of subjects with an endometrial thickness ≥ 8 mm was noted by Month 36 in Study A2181002."

Item 9, Page 73, last paragraph*Current:*

- "There was a statistically significant increase in the percentage of lasofoxifene-treated subjects reporting vaginal bleeding compared to placebo-treated subjects. In subjects monitored by yearly transvaginal ultrasonography, 18-19% of subjects treated with lasofoxifene were found to have an endometrial thickness of ≥ 8 mm ~~at~~ Year 3."

Replaced with:

- "There was a statistically significant increase in the percentage of lasofoxifene-treated subjects reporting vaginal bleeding compared to placebo-treated subjects. In subjects monitored by yearly transvaginal ultrasonography, 18-19% (cumulative percent) of subjects treated with lasofoxifene were found to have an endometrial thickness of ≥ 8 mm by Year 3."

Item 10, Page 69, footer for Table 56*Current:*

- "* Pooled includes lasofoxifene doses ~~0.017 mg, 0.025 mg, 0.05 mg, 0.15 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, 10 mg.~~"

Replaced with:

- "* Pooled includes lasofoxifene doses 0.25 mg and 0.5 mg."