

## Raloxifene and Its Salts

Raloxifene (Evista®) is a selective estrogen receptor modulator (SERM). Raloxifene is used for the management of osteoporosis in post-menopausal women, and to reduce the risk of primary breast cancer or its recurrence.

Raloxifene passed the animal data screen, underwent a preliminary toxicological evaluation, and is being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

### Epidemiological data

- Population-based case-control study of endometrial cancer: DeMichele *et al.* (2008)
  - *Significantly lower risk in raloxifene users compared to SERM non-users*
  - *Significantly lower risk in raloxifene users compared to tamoxifen users*

### Animal carcinogenicity data

- Long-term feeding studies
  - 21-month studies in male and female CD-1 mice: as reviewed in FDA (1997a)
    - *Increases in malignant ovarian tumors and liver adenomas in females (by trend)*
    - *Increases in prostate leiomyoblastoma, prostate adenoma and sarcoma (combined), malignant testicular interstitial cell tumor, benign and malignant (combined) testicular interstitial cell tumor and liver malignant interstitial cell tumor (by trend) in males*
  - 24-month studies in male and female F344 rats: as reviewed in FDA (1997a)
    - *Increases in benign ovarian tumors in females (by trend)*
    - *Increase in kidney renal cell carcinoma in males (by trend)*

### Other relevant data

- Genotoxicity
  - As reviewed in FDA (1997b)
    - Reverse mutation assays in *Salmonella typhimurium* and *E. coli* (*negative*)
    - Unscheduled DNA synthesis in adult rat hepatocytes (*negative*)

- Forward mutation assay in mouse lymphoma TK<sup>+/-</sup> assay (*negative*)
  - Chromosome aberration assay in Chinese hamster ovary cells (*negative*)
  - *In vivo* sister chromatid exchange assay in Chinese hamster bone marrow (*negative*)
  - *In vivo* micronucleus assay in mouse bone marrow (*negative*)
- Structure activity considerations with other SERMs
  - The SERM tamoxifen is a Proposition 65 and IARC Group 1 carcinogen. Tamoxifen increases the risk of endometrial cancer in women, and induces liver tumors in rats exposed as adults, uterine and vaginal cervical tumors in rats exposed as neonates, and uterine tumors in mice exposed as neonates.
  - The SERM clomiphene has been reported to increase the risk of ovarian, breast, and uterine cancers in epidemiology studies, and to induce ovarian and uterine tumors in rats.

## References<sup>1</sup>

Food and Drug Administration (FDA, 1997a). Statistical Review and Evaluation (Carcinogenicity Review), Raloxifene hydrochloride (Evista®), Center for Drug Evaluation and Research Application Number 020815. Statistical Review(s).

Food and Drug Administration (FDA, 1997b). Pharmacology/toxicology review of NDA submission. Raloxifene hydrochloride (Evista®), Center for Drug Evaluation and Research Application Number 020815. Pharmacology Review(s). p. 87.

DeMichele A, Troxel AB, Berlin JA, Weber AL, Bunin GR, Turzo E, Schinnar R, Burgh D, Berlin M, Rubin SC, Rebbeck TR, Strom BL (2008). Impact of raloxifene or tamoxifen use on endometrial cancer risk: a population based case-control study. *J Clin Oncol* **26**:4151-4159.

---

<sup>1</sup> Excerpts or the complete publication (presenting epidemiology or toxicology information) have been provided to members of the Carcinogen Identification Committee, in the order in which they are discussed in this document.