Six Month Oral Toxicity of (E/Z)-Endoxifen In Rats

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ABSTRACT

The Tamoxifen metabolite, endoxifen (N-demethyl-tamoxifen), is being developed for oral and local topical administration for prevention and therapy of breast cancer. As part of the development, the toxicity of oral endoxifen was evaluated in a chronic (six-month) study in rats. Groups of 25 female CD rats each received oral doses of endoxifen at target average plasma levels of 20 mg/L in female rats. Endoxifen-related effects included slightly decreased body weight gain in endoxifen groups; mean relative ovarian weight was increased and mean relative uterine weight was decreased in endoxifen groups. Microscopic findings in the ovaries were identified in both endoxifen groups; mean relative ovarian weight was increased and mean relative uterine weight was decreased (in endoxifen groups). Findings were consistent across all endoxifen dose levels and were likely related to endoxifen’s pharmacologic activity. The most important determinant of endoxifen efficacy against breast cancer: Data from clinical studies demonstrate that (E/Z)-endoxifen is a more potent and selective estrogen receptor modulator than tamoxifen and that this results in a 10-fold or greater reduction in body weight gain that is apparently secondary to pharmacologic activity rather than as clear evidence of its toxicity. On this basis, we interpret the observed suppression of body weight gain by endoxifen in this study as secondary to its pharmacologic activity rather than as clear evidence of its toxicity. In support of this, we concluded that endoxifen at doses of up to 50 mg/kg was well tolerated by female rats. On this basis, we interpret the observed suppression of body weight gain by endoxifen in this study as secondary to its pharmacologic activity rather than as clear evidence of its toxicity. In support of this, we concluded that endoxifen at doses of up to 50 mg/kg was well tolerated by female rats. Six Month Oral Toxicity of (E/Z)-Endoxifen In Rats...