DRAFT SUMMARY OF REPRO-TOX STUDIES

Pregnancy category labeling on pravastatin is currently X. The animal reproductive toxicology results are being re-evaluated in conjucntion with the OTC submission.

Summary of repro toxicity studies on NDA 21-198

No new pre-clinical pharmacology/toxicity studies have been submitted in the current NDA 21-198. However, sponsor would like to change the pregnancy category label 'X' to pregnancy category 'B". Therefore, the sponsor has submitted a labeling supplement on 12/10/99 (NDA 19-898, # 038), which provides additional arguments and interpretations of these old repro toxicity studies to justify the change. Following is the summary of repro toxicity studies reviewed from the labeling supplement (NDA 19-898).

Conclusions: Pravastatin when given during pregnancy produces splitting of cervical ribs in rat fetuses, and increases stillbirths/neonatal deaths (at 1-24 times the maximal human dose based on body surface area). These effects were seen in all three following rat studies.

In study A in rats (segment II teratogenicity study, doses 0, 4, 20, 100 mg/kg/day): 100 mg/kg/day (24 times the human dose of 40 mg/day, based on body surface area), given from day 4-17 of gestation increased the splitting of cervical ribs in fetuses (6.7% vs 2.7% in controls, p value was not significant at 0.01, but unknown if it would have been significant at 0.05). At a mid dose of 20 mg/kg/day, this increase was slight (3.7% vs 2.7% in controls) in fetuses. Pravastatin also increased the number of stillborn (1-2% vs 0% in controls) at all tested doses of 4-100 mg/kg/day (1-24 times the human dose).

In study B in rats (segment II teratogenicity study, doses 0, 500, 1000 mg/kg/day): 500-1000 mg/kg/day (120-240 times the human dose), given from day 7-17 of gestation increased the splitting of cervical ribs (1.5-3.3% vs 0% in controls, p=ns at 0.01) in fetuses. Pravastatin at 1000 mg/kg/day (240 times human dose) increased the number of neonates that died on day 4 postpartum (17% vs 8% in controls, p=ns at 0.01). Pre-implantation losses were slightly higher at the high dose (46% vs 34% in controls, p = ns at 0.01). Note that in study A when the drug was given little early in gestation (from day 4, instead of day 7), the skeletal defects and newborn/stillborn deaths occurred at one tenth the dose in the current study

In study C in rats (segment III perinatal/postnatal study, doses 0, 10, 100, 1000 mg/kg/day): 1000 mg/kg/day (240 times the human dose), given from day 17 of gestation through day 21 of lactation increased the body weights after delivery in rats (during days 4-8 by 6-8%, P=0.01). 100-1000 mg/kg produced neonatal deaths (0.5-2.1% vs 0% in controls), decreased body weights in the

offspring's (at 1000 mg/kg/day by 7-11%, p=0.01) during 8-week growth period. All doses of the drug produced functional deficits in fetuses, and a high dose produced effects on postnatal differentiation. Thus, pravastatin (at 24 times the human dose based on body surface area) decreased body weights in offspring's increased neonatal deaths, and all doses (including 2 times the human dose) produced functional deficits in offspring's.

The drug did not produce any effects on fertility in rats up to doses of 500 mg/kg/day (120 times the maximal human), and did not cause any embryo/fetotoxicy or teratogenicity in rabbits up to doses of 50 mg/kg/day (or 20 times the maximal human dose).

Deficiencies in these studies:

1. All repro toxicity studies were conducted in animals (rats and rabbits); not using maximally tolerated doses (MTD), except for the segment III study in rats. Therefore despite the fact that doses used in above studies were not high enough by usual dose selection criteria (though they appear high), the drug caused skeletal abnormalities and deaths in newborns.
2. All above studies were conducted in Japan between 1982-1986 by Japanese GLP standards, and the statistical significance of data was reported at p of 0.01 (instead of 0.05). Therefore, some of the data, which show slight differences, may actually have had statistical significance, but is unknown now.

Clinical concerns:

The pregnancy category of the drug is a concern for OTC approval. **The OTC drug is targeted for subjects 18 years or older.** In humans, (somewhat similar to rats), comparable developmental events occur between day 18 (beginning of neurulation) and day 22 (placental vascularization and initial circulation) of gestation (Pansky, B. Review of medical Embryology. Macmillan Publishing Co., New York, 44-66, 1982). If the woman becomes pregnant, by the time she finds out her pregnancy status, it may be already too late, as the development begins as early as day 18. The approval of the OTC application is at the discretion of the medical reviewer. The pharmacologist recommends changing the pregnancy category label from X to C. The post-marketing information on teratogenic effects of pravastatin in humans is currently in the label, however these studies do not have enough power to be meaningful. This information may have been included in the label, because at that time it was category X. The post-marketing information should be removed from the label if category is changed to C.

Also note that the lowest tested dose (4 mg/kg/day, 1 time the maximal human dose of 40 mg/day, based on body surface area) in one study (A) increased the number of stillborn, and in another study (10 mg/kg/day, 2 time the human dose) produced postnatal functional deficits in animals. The OTC dose is 10 mg/day in humans, but we do not know if the lower doses in animals would not have produced these defects.