

DRAFT SUMMARY OF REPRO-TOX STUDIES

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

Summary of repro toxicity studies on NDA 21-213

Conclusions: Lovastatin, at higher doses of 400-800 mg/kg/day (50-100 times the maximal human dose of 80 mg/day), when given during pregnancy in rats produces maternal toxicity (deaths, decreased body weights and food consumption), post implantation losses in animals and skeletal malformations. In rats, lower doses (100 mg/kg/day, or 12 times the maximal human dose based on body surface area) decrease the fetal body weights and produce skeletal incomplete ossification in fetuses. In mice fetus (at 5-50 times the maximal human dose), it decreases the fetal body weights and produces skeletal/visceral malformations. In rabbit fetus (at 0.3-1.2 times the maximal human dose), it produces skeletal incomplete ossification. The lowest doses used in rat and rabbit segment II studies produced the above fetal toxicity. These effects were seen in the number of following studies.

In study A in rats (segment II teratogenicity study, doses 0, 100, 200, 400, 800 mg/kg/day): 400-800 mg/kg/day (50-100 times the human dose of 80 mg/day, based on body surface area), given from day 6-20 of gestation caused maternal toxicity (deaths, decreased weight gains by up to 28%, food consumption by up to 41%, and gross lesions in non-glandular mucosa with histopathology of acanthosis and hyperkeratosis), increased post implantation losses (11-14% vs 6% in controls), decreased fetal body weights (5-17%) and produced skeletal malformations. Lower dose of 100 mg/kg/day (12 times the human dose) decreased the fetal body weight gains (by 5%, $p < 0.05$), increased incomplete ossification (in liters by 2 fold, in fetuses by 5-fold, sternebra defects increased by 3-fold). Thus higher oral doses in rats supposedly produce local maternal GI toxicity (animals eat less and loose weight), which may have caused the fetal toxicity, **but note that the lowest dose produced fetal toxicity independent of maternal toxicity**

In study B in rats (segment II teratogenicity study, doses 0, 100, 200, 400, 800 mg/kg/day): This study was designed to see if the forestomach toxicity of the drug is reversible with continued dosing prior to mating in females. 400-800 mg/kg/day (50-100 times the human dose, based on body surface area), given for 14 days prior to mating, and through gestation day 20, caused maternal toxicity (deaths, decreased weight gains/food consumption by up to 35-41% during premating, and decreased BW by up to 11% during gestation, and gastric changes in non-glandular mucosa), increased post implantation losses (3.8% vs 2.4% in controls), and decreased fetal body weights (up to 5%, $p < 0.05$). Lower

dose of 100 mg/kg/day (12 times the human dose) decreased the fetal body weight (by 1%, $p < 0.05$), increased incomplete ossification (in litters by 3-fold, in fetuses by 4-fold, sternebra defects increased by 3-fold). Thus higher doses produced maternal toxicity, **but again note that the lowest dose produced fetal toxicity independent of maternal toxicity**

In study C in rats (segment II teratogenicity study, oral doses 0, 400 mg/kg/day, subcutaneous doses 0, 12.5, 25 mg/kg/day): Since forestomach toxicity is due to high local conc of the drug after oral administration, and may not be seen after SC dosing, the comparative oral and SC study was conducted here in rats. 400 mg/kg/day of oral drug (50 times the human dose, based on body surface area), given from day 6-20 of gestation caused maternal toxicity (deaths, decreased BW by 25%, food consumption by 36%, caused GI changes), increased post implantation losses (23% vs 5% in controls), decreased fetal body weights (16-18%) and produced skeletal malformations (in litters by 32% vs 13% in controls). Subcutaneous doses of 25 mg/kg/day also produced similar maternal (BW decreased by 15%) and fetal toxicity, but of lesser severity. However SC doses of 12.5 mg/kg/day, which did not produce local GI effects and no maternal toxicity, still produced decreases in the fetal body weights (by 4-6%, $p < 0.05$), increased fetal skeletal malformations (in litters 17% vs 12% in controls), and increased incomplete ossification (in litters 71% vs 2% in controls, in fetuses 56% vs 2% in controls). **Again note that the lowest SC dose, which did not produce maternal toxicity, caused fetal toxicity. These findings were independent of increased systemic maternal or fetal exposures of the drug** (on gestation day 20, oral 400 mg/kg/day produced maternal exposures of 4.6-9.2 $\mu\text{g}\cdot\text{h}/\text{ml}$, with SC 12.5-25 mg/kg/day maternal exposures were 3.8-7.0 $\mu\text{g}\cdot\text{h}/\text{ml}$. The fetal exposures at oral and SC doses were also not that different (oral 1.2-2.1, SC 1.4-2.9 $\mu\text{g}\cdot\text{h}/\text{ml}$). The higher maternal or fetal inhibition of mevalonic acid (effect of HMG-CoA inhibition) also had nothing to do with maternal or fetal toxicity, because mevalonic acid inhibition was similar at all doses.

In study D in mice (segment II teratogenicity study, doses 0, 8, 80, 800 mg/kg/day): 80-800 mg/kg/day (5-50 times the human dose, based on body surface area), given from day 6-15 of gestation, reduced fetal body weights (by 4% and 9%, $p < 0.05$) and produced skeletal (6-8/24 vs 4/24 controls) and visceral (at a high dose 3/24 vs 1/24) malformations/variations in litters.

In study E in rabbits (two segment II teratogenicity studies were conducted, in the first study doses of 0, 1, 5, 25 mg/kg/day were used, in the second study doses of 0, and 15 mg/kg/day): 15 mg/kg/day (4 times the human dose, based on body surface area), given from day 6-18 of gestation, produced maternal toxicity (decreased BW and food consumption) and fetal toxicity (visceral variations 4/17 vs 1/14 in controls). Lower doses of 1 and 5 mg/kg/day (0.3-1.2 times the human dose) produced incomplete ossification in fetuses (56-66% vs 44% in controls), without maternal toxicity.

In study F in rats (segment III perinatal/postnatal study, doses 0, 2, 20, 200 mg/kg/day): 200 mg/kg/day (25 times the human dose), given from day 15 of gestation through day 21 of lactation, caused maternal toxicity (2 animals died, decreased the body weights during gestation, food consumption during lactation). In pups the drug at 20-200 mg/kg/day increased the deaths on day 0 (5-7% vs 2% in controls), all doses (on days 0-21) increased the deaths (by 6-79% vs 1% in controls) and a high dose decreased pre and post-weaning body weights. All doses of the drug affected the behavior of F1 rats, and a high dose produced developmental delays in F1 pups. Thus, lovastatin (at 0.25-25 times the human dose based on body surface area) produced perinatal and postnatal effects in rats.

Overall Summary:

The sponsor claims that all fetal toxicity (skeletal malformations, decreased body weights) seen in rats is due to the maternal toxicity. I agree with the sponsor, that it may be true for higher doses in rats/rabbits, but at lower doses the drug produces rat/rabbit fetal toxicity (decreased body weights and/or incomplete ossification) independent of the maternal toxicity. In mice, this fetal toxicity (reduced body weights, skeletal/visceral malformations) is also seen in the absence of maternal toxicity. Since this is not an incidental finding, and seen in number of studies, it should not be ignored. The increased systemic maternal or fetal exposure of the drug (during pregnancy) does not seem to be responsible for increased maternal or fetal toxicity. Nor the higher plasma maternal or fetal inhibition of mevalonic acid (effect of HMG-CoA inhibition) seems to play a role in this maternal/fetal toxicity. It is possible that the local exposure or sensitivity of the drug in tissues or skeletons of fetus plays a role in this toxicity.

Clinical concerns:

1. Although lovastatin OTC is targeted for postmenopausal women and men who are 40 years of age or older, women who may not have high cholesterol (200 mg/dl) and may not be postmenopausal, but think they need to lower cholesterol, would now have the OTC drug available. 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 does becomes pregnant, by the time she finds out her pregnancy status, it may be already too late, as the development begins as early as gestation day 18.
2. The sponsor has data from the post-marketing experience with lovastatin in pregnant women (during the first 3-months of gestation) and state 'that rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors', however the numbers are small, and 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.

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.

Also note that the lowest tested dose in rats (100 mg/kg/day, 12 time the maximal human dose of 80 mg/day, based on body surface area), and rabbits (1 time the maximal human dose) produced fetal findings, while in mice these findings were seen at mid dose (or at 5-times the maximal human dose). The OTC dose is 10 mg/day in humans, but we do not know if the lower doses in rats/rabbits would not have produced these defects.