Overview of Lovastatin Nonclinical Developmental Data

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Introduction

- Overview Pregnancy Category labeling
  - As per Code of Federal Regulations (CFR)

- CDER interpretation of developmental data
  - Extensive data 1980-2004
  - Subject to interpretation
    - Focus CDER's approach to data analysis
      - Definition of maternal toxicity
      - Drug dependent effect on development
        - » Fetal/neonatal mortality
        - » Developmental delays
        - » Skeletal malformations

21 CFR 201.57
Pregnancy Category Labeling

A: Studies in pregnant women/animals show no fetal risk

B: No studies in humans & animals show no fetal risk

OR

Animal studies show fetal risk but studies in pregnant women indicate no fetal risk

C: No human studies & animals show fetal risk

OR

No human/animal studies but risk:benefit acceptable

D: Human fetal risk based on studies or post-marketing but benefit outweighs risk

X: Human/animal fetal risk outweighs clinical benefit

1987 Marketing Approval
Mevacor Pregnancy Category X

- No well controlled studies in pregnant women
- Some post-marketing reports of fetal adverse effect on live births
  - Exposure established 1st trimester
  - Limited data so cause & effect not demonstrated
- Animal studies show fetal/neonatal adverse effects without maternal toxicity evident
  - Findings w/o maternal toxicity are potentially relevant because clinically you don't dose to toxicity
- No benefit to temporarily treating pregnant women
  - CDER/Merck agree with contraindication during pregnancy

Standard Reproductive/Developmental Evaluations

ICH S5A (1994) Guidance to Industry: Detection of Toxicity to Reproduction for Medicinal Products

1. Fertility/Early Embryonic Development- one species, exposure prior to and during mating/to implantation in female
2. Embryo-Fetal Development- two species, exposure during organogenesis
3. Pre- & Postnatal Development- one species, exposure from implantation to end of lactation

Merck: Lovastatin Repro-Developmental Toxicology Data 1980-2004

Merck interpretation:

- Developmental toxicity consists of rat skeletal anomalies at maternally toxic oral doses ≥400 mg/kg/day
  - Fetal nutritional deficits
    - Result of reduced maternal food & body weight
  - Maternal Toxicity
    - Forestomach edema/inflammation resulting in progressive hyperplasia of squamous epithelium
    - HMG CoA reductase up-regulation in forestomach results in rat specific histopathology which is reversible by co-administered mevalonate

Difference in interpretation: Definition of Maternal Toxicity

- According to Merck maternal toxicity occurs at ≥400 m/k/d oral resulting in forestomach hyperplasia

BUT

- Exposures ≥100 m/k/d oral during pregnancy:
  - Maternal decreases weight gain (>10%)
  - Decreased food consumption
- Exposures ≥100 m/k/d SC during pregnancy:
  - Maternal mortality
  - Decreased body weight gain

SUGGESTS

- A maternal NOAEL= 80 m/k/d or 60X exposure at 20 mg clinical dose
- Review of repro/dev data 1980-1999 for fetal/neonatal findings ≤ 80 m/k/d
  - Fetal/neonatal findings are observed in fertility, embryo-fetal thru postnatal developmental study designs
    - See briefing document Tab 4 pg. 4

Fetal/Neonatal Findings At Clinically Relevant Exposures

- At ≤ 5X Therapeutic Exposure (20 mg):
  - Fetal/pup mortality
  - Fetal/pup decreased body weight
- At ≥ 6X Therapeutic Exposure (20 mg):
  - Developmental Delays
    - Righting reflex- (freefall, negative geotaxis)
    - Auditory startle response
    - Swimming, Open field effects
    - Incomplete skeletal ossification
- At > 25X Therapeutic Exposure (20 mg):
  - Skeletal Malformations
    - Increased supernumerary ribs, wavy ribs
    - Incomplete skeletal ossification

Lovastatin Co-administration of Mevalonic Acid/Cholesterol

- Attenuation of more severe fetal malformations
  - Wavy ribs &incomplete ossification still present
  - Evidence of maternal toxicity
- Supports fetal toxicity is related to disruption of cholesterol biosynthesis by lovastatin

CDER: Lovastatin Rat Developmental Data

- Fetal/neonatal toxicity is seen in the absence of maternal toxicity
- Drug related fetal/neonatal toxicity includes
  - Skeletal malformations
  - Mortality
  - Developmental delays
- Some fetal findings occur at exposures similar to clinical exposure (20 mg lovastatin OTC dose)
- Findings are potentially relevant to clinical risk assessment
- Pregnancy Category designation is valid

Cross-species Developmental No Effect Level Established

Exposure Compared to Lovastatin OTC (20 mg)

Species	NOAEL (mg/kg/day)	Safety Margin*
Rat	<2	<1X
Rabbit	5	5X
Mouse	8	2X

* Exposure Compared to Lovastatin 20 mg based on body surface area

2000-2004
New Postnatal Neurodevelopmental Evaluation

- To address data gaps in neurologic development based on limitations in postnatal study design between species
  - e.g. Rat myelination-postnatal weeks 2-4
    Human 2 nd – 3rd trimester
- Developmental delays in prior postnatal studies a
- Requested a detailed neurodevelopmental assessment
  - Direct dosing during the critical period of neuro development
  - Evaluation of: exposure, est. NOEL, detailed brain histology, behavioral/functional developmental assessments

Direct Dosing Neonatal Rat Study

- Dose-range finder- 20 m/k/d shows -5% wt. gain & injection site alopecia/scabbing
- Lovastatin 2.5, 5, 10 m/k/d SC, PND 4-41/51
- Short-term learning retention decrease
  - Passive avoidance test-increase in trials to criterion in 10 m/k/d females
- FOB shows increased CNS activity HD females
- NOAEL= 5 m/k/d exposure 20X a 20 mg dose based on AUC

Assessment of New Neurodevelopmental Data

- **Decreases in short-term learning retention (passive avoidance test) & increased activity in CNS (FOB) in HD females were observed**
  - **Learning/behavioral findings are consistent with prior postnatal evaluations**

Neurologic evaluation was minimal

- Passive avoidance test (short term learning) was the only measure of cognitive function, since various tasks can be assisted by different neural systems a 2nd neurobehavioral test was previously recommended e.g. swimming maze
- Standard toxicology endpoints not performed, histopath in neuro tissues (C, HD), neuroanatomical/biochemical evaluation only if lesions were observed in HD
- Study design to evaluate acute not delayed developmental effects

Overall Summary

- Established statin mechanism of action
- Extensive developmental studies 1980-2004 show consistent findings with lovastatin exposure
  - Fetal mortality
  - Decreased fetal weight
  - Skeletal malformations
  - Behavioral/Learning delays
    - Limited neurodevelopmental neonatal rat study with delayed learning effects consistent with prior postnatal studies
- Some findings occur in animals at exposures similar to therapeutic exposure (20 mg lovastatin OTC dose)
  - Consensus of CDER Reproductive Toxicology experts
- Post-marketing reports of 1st trimester fetal adverse effects
  - Limited data results in failure to show cause & effect
  - Does not allay potential concern

Conclusion

- Based on extensive animal data a potential human fetal risk exists following exposure to Lovastatin during pregnancy in women of CBP
- Contraindication of statins including lovastatin during pregnancy is valid