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 $\geq 400 \text{ m/k/d oral}$ resulting in forestomach hyperplasia.
- Exposures $\geq 100 \text{ m/k/d oral}$ during pregnancy:
  - Maternal decreases weight gain (>10%)
  - Decreased food consumption
- Exposures $\geq 100 \text{ m/k/d SC}$ 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 $\leq 80 \text{ m/k/d}$
  - 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)

<table>
<thead>
<tr>
<th>Species</th>
<th>NOAEL (mg/kg/day)</th>
<th>Safety Margin*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>&lt;2</td>
<td>&lt;1X</td>
</tr>
<tr>
<td>Rabbit</td>
<td>5</td>
<td>5X</td>
</tr>
<tr>
<td>Mouse</td>
<td>8</td>
<td>2X</td>
</tr>
</tbody>
</table>

* 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 2nd – 3rd trimester
- Developmental delays in prior postnatal studies
- 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