Non-Prescription Mevacor® 20 mg Joint Advisory Committee Meeting NDA 21-213

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Outline:

- Regulatory history of Rx-to-OTC switch for lipid-lowering drugs
- Overview of previously submitted applications for nonprescription lipid-lowering drugs
- Initial Mevacor OTC proposal
- Overview of current Mevacor application
- Areas for consideration of the current program

HISTORICAL OVERVIEW

- **Mid-1990s**
  - **bile acid resin binders proposed for OTC use**
- **1997 Guidance on OTC Tx of Hypercholesterolemia**
  - **chronic, asymptomatic condition requiring accurate diagnosis and clinical testing under directed care of HCP**
  - **recommendation that drug treatments for such condition not be sold OTC**

HISTORICAL OVERVIEW

- 1999 two applications for statin Rx to OTC switch submitted to the FDA
- July 2000
  - 2 separate AC mtgs for lovastatin and pravastatin OTC

July 2000 Advisory Committee for Mevacor®

- 10 mg dose proposed

- Target population
  - males > 40 yrs and postmenopausal females
  - no CVD, DM or significant HTN
  - not on prescription lipid-lowering drug
  - TC 200-240 mg/dL
  - LDL-C ≥ 130 mg/dL

July 2000 Advisory Committee for Mevacor® 10 mg

- Efficacy Concerns
  - NCEP guidelines for initiation of tx and treatment goals not incorporated
  - clinical benefit could not be extrapolated from clinical outcomes data for proposed dose and target population
  - consumer comprehension of complexities of treatment not demonstrated

July 2000 Advisory Committee for Mevacor® 10 mg

- Safety Concerns
  - muscle
    - potential for drug-drug interactions
  - hepatic
    - recommendations for hepatic laboratory monitoring
    - safety in patients w/ undiagnosed liver disease
  - pregnancy category X

2000-2005

- 1997 FDA Guidance to Industry withdrawn in 2001
- NCEP ATP III Guidelines published 2001
  - new risk categories
  - new goals of treatment
  - subsequent update July 2004

NCEP - ATP III Guidelines

National Cholesterol Education Progam - Adult Treatment Panel

- Risk Categories (10-yr risk of developing CV event)
  - CHD or CHD risk equivalent (10-yr risk > 20%)
  - 2+ risk factors (10-yr risk ≤ 20%)
  - 0-1 risk factor (10-yr risk < 10%)
- DM, PAD, other clinical presentations of atherosclerosis ~ CHD risk equivalent
- Initiation of drug therapy depends on risk category of individual but on background of lifestyle changes/modifications

CURRENT PROPOSAL FOR MEVACOR® OTC

- Target Population
  - "A primary prevention population with ≤ 20 % 10-yr risk of CHD w/o underlying chronic conditions that complicate consumer self-management"
  - males 45 yrs or older/females 55 yrs or older
  - LDL between 130 and 170 mg/dL
  - have at least one of (smoking, HDL 1-39, FH+, HTN)
- Proposed Dose - fixed daily dose of 20 mg

CURRENT PROPOSAL FOR MEVACOR® OTC

- Treatment goal for target population is LDL < 130 mg/dL (NCEP: if Tg > 200 then nonHDL < 160)
- Consumers need to know cholesterol values before and while on therapy
- Consumers need to know baseline risks and changes in health status that might alter risk/benefit of lovastatin 20 mg

EFFICACY

- Lovastatin 20 mg LDL-lowering
  - EXCEL and AFCAPS/TexCAPS clinical trials
  - Consumer Use study
  - mean LDL reduction ~ 24%
- Clinical benefits of lovastatin 20 mg
  - extrapolation from AFCAPS/TexCAPS, 5 yr pbo controlled outcomes study evaluating lovastatin 20 to 40 mg daily (primary endpt: unstable angina, nonfatal MI, CHD death)

SAFETY

- Re-evaluation of clinical trial database for EXCEL and AFCAPS/TexCAPS
  - 6,582 patients exposed to lovastatin 20-80 mg daily in a 48 wk study (EXCEL)
  - 3,304 patients exposed to lovastatin 20 to 40 mg daily in a 5 yr study (AFCAPS)
- Evaluation of global postmarketing safety database from marketing until present (~17 yrs of postmarketing use; ~27 million patient-yrs exposure

SAFETY

- Conclusion for muscle and liver safety concerns:
  - risk of myopathy/rhabdomyolysis is extremely low that the 20 mg dose, if labeled adequately and understood by the consumer, is an acceptable dose for OTC use
  - there is little to no hepatic risk in patients with normal hepatic function
  - concerns of safety of lovastatin in patients with asymptomatic liver disease including viral hepatitis not addressed in prospective studies; however, abstract of a study in ~40 patients and a retrospective study to be presented by sponsor

SAFETY

- Pregnancy safety concerns:
  - preclinical studies conducted and reviewed under prescription NDA
  - FDA concludes pregnancy category X should be retained based on:
    - findings of preclinical studies
    - agreement b/w sponsor and FDA that risk exceeds benefit during pregnancy - retain contraindication in pregnancy
  - inadvertent exposure in first-trimester of pregnancy and adequacy of labeling/consumer comprehension

Areas for Consideration: Efficacy

- Caveats of extrapolation from AFCAPS/TexCAPS
  - post-hoc analysis
  - nonrandomized comparisons
  - none of the subgroups selected by the sponsor fully reflects the OTC population as AFCAPS included patients who were titrated to 40 mg and were treated to a lower LDL-C goal
  - longterm benefit observed w/ AFCAPS assumes adherence to therapy in the OTC setting
- changes in health status may dictate need for more aggressive tx

Areas for Consideration: Safety

- Current program proposes safety issues addressed through labeling
  - effectiveness of labeling evaluated in CUSTOM
- Impact of changes in health status and interacting meds on safety, particularly long-term