OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	20-560 (supplemental); S-038
Submission Dates	January 31, 2003; April 24, 2003
Brand Name	FOSAMAX®
Generic Name	alendronate sodium
Reviewer	S.W. Johnny Lau
Team Leader	Hae-Young Ahn
OCPB Division	DPE II (HFD-870)
ORM division	Metabolic and Endocrine (HFD-510)
Sponsor	Merck Research Laboratories
Relevant IND(s)	(b)4
Submission Type; Code	pediatric study report for exclusivity; priority
Formulation; Strength(s)	5, 10, 35, and 70 mg oral tablets, 2.5 mg/mL IV solution
Indication	to treat osteogenesis imperfecta

1 Executive Summary

Alendronate sodium, a bisphosphonate, is approved to treat and prevent osteoporosis in postmenopausal women, treat osteoporosis in men, treat glucocorticoid-induced osteoporosis, and treat Padget's disease. The sponsor submitted supplemental NDA 20-560 in response to the Food and Drug Administration's October 27, 2000 pediatric study Written Request and its March 8, 2002 amendment to seek the following for alendronate sodium:

- pediatric 6-month exclusivity
- indication to treat osteogenesis imperfecta (OI) pediatric patients with one 5 mg oral tablet once daily (<40 kg body weight) and one 10 mg oral tablet once daily (≥ 40 kg body weight)
- orphan drug designation for 7-year exclusivity (since 30,000 – 60,000 patients with osteogenesis imperfecta in the US)
- Waxman-Hatch 3-year exclusivity

The sponsor conducted 2 clinical studies to satisfy the pediatric study Written Request and submitted the results in supplemental NDA 20-560. Briefly, the 2 studies are:

1. an efficacy and safety study (P135) to compare the effects of alendronate (5 or 10 mg daily) versus placebo, on pediatric patients aged 4 through 18 years with severe OI for: (1) change in mean lumbar spine (L1 to L4) bone mineral density at Month 12 and (2) safety and tolerability.
2. an absolute oral bioavailability study (P172) for the 35 and 70 mg alendronate oral tablets as compare to an 125 μg alendronate intravenous injection (2.5 mg/mL) in OI pediatric patients.

Per Study P172, the mean alendronate oral bioavailability (95% CI) with respect to a 125 μg intravenous dose was 0.43% (0.28%, 0.64%) for OI pediatric patients weighing < 40 kg who received 35 mg oral dose and was 0.56% (0.36%, 0.87%) for OI pediatric patients weighing ≥ 40 kg who received 70 mg oral dose. The alendronate oral bioavailability is similar between OI patients and adults (historical data).

See medical officer's review for Study P135.

1.1. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the Human Pharmacokinetics and Bioavailability section for supplemental NDA 20-560 and finds it acceptable. The sponsor should receive the labeling comments below (addition is underscored and deletion appears as strikethrough):

CLINICAL PHARMACOLOGY

Special Populations

Pediatric: Relative to an IV ~~reference~~ 125 µg dose, the mean oral bioavailability of 35 mg alendronate in pediatric patients (4 to ~~16~~ 14 years of age) with osteogenesis imperfecta was 0.43% (0.28%, 0.64%; 95% CI) for patients weighing <40 kg ~~(35 mg dose)~~ and the mean oral bioavailability of 70 mg alendronate in pediatric patients (11 to 16 years of age) with osteogenesis imperfecta was 0.56% (0.36%, 0.87%; 95% CI) for patients weighing ≥40 kg ~~(70 mg dose)~~. When alendronate was administered after an overnight fast and two hours before a standardized meal, oral bioavailability in pediatric patients was similar to that observed in adults.

_____

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

An Optional Intra-Division Clinical Pharmacology and Biopharmaceutics Briefing for supplemental NDA 20-560 was conducted on June 26, 2003; participants included H. Malinowski, J. Hunt, H. Ahn, and J. Lau.

FT signed by Hae-Young Ahn, Ph.D., Team Leader 6/ /03

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Hae-Young Ahn
7/1/03 12:08:56 PM