One Year Post Exclusivity Adverse Event Review: Alendronate

Pediatric Advisory Committee Meeting
September 15, 2004

Hari Cheryl Sachs, MD, FAAP
Medical Officer
Division of Pediatric Drug Development
Center for Drug Evaluation and Research
Food and Drug Administration

Background Drug Information

- **Moiety:** Fosamax® (alendronate)
- **Therapeutic Category:** Bisphosphonate
- **Sponsor:** Merck & Co., Inc
- **Original Market Approval:** September 29, 1995
- **Pediatric Exclusivity Granted:** April 28, 2003
- **Mechanism of action:** inhibits osteoclast-mediated bone resorption activity

Background Drug Information

- **Adult Indications:**
  - Treatment and prevention of osteoporosis in post-menopausal women
  - To increase bone mass in men with osteoporosis
  - Treatment of glucocorticoid-induced osteoporosis
  - Treatment of Paget's Disease
- **Adult Dosage:** Varies based on indication
- **Pediatric Indications**: None

Drug Use Trends in Outpatient Settings: Alendronate

- Fosamax is the most commonly dispensed bisphosphonate in the US (2001-2004)[1]
- Total US prescriptions have increased from 18.6 million (May 2001- April 2002) to 22 million (May 2003-April 2004)[1]
- Pediatric patients (ages 1-16) account for < 1 % (approximately 10,000) prescriptions[1,2*]

[1]IMS Health, National Prescription Audit *Plus*? , On-Line, May 2001 - Apr 2004, Data Extracted May 2004

[2]AdvancePCS? Dimension Rx, On-Line, May 2001 - Apr 2004, Data Extracted May 2004

*Calculation based on application of proportions of pediatric alendronate prescriptions in AdvancePCS? to IMS Health, National Prescription Audit *Plus*? to estimate number of alendronate prescriptions dispensed nationwide to pediatric population

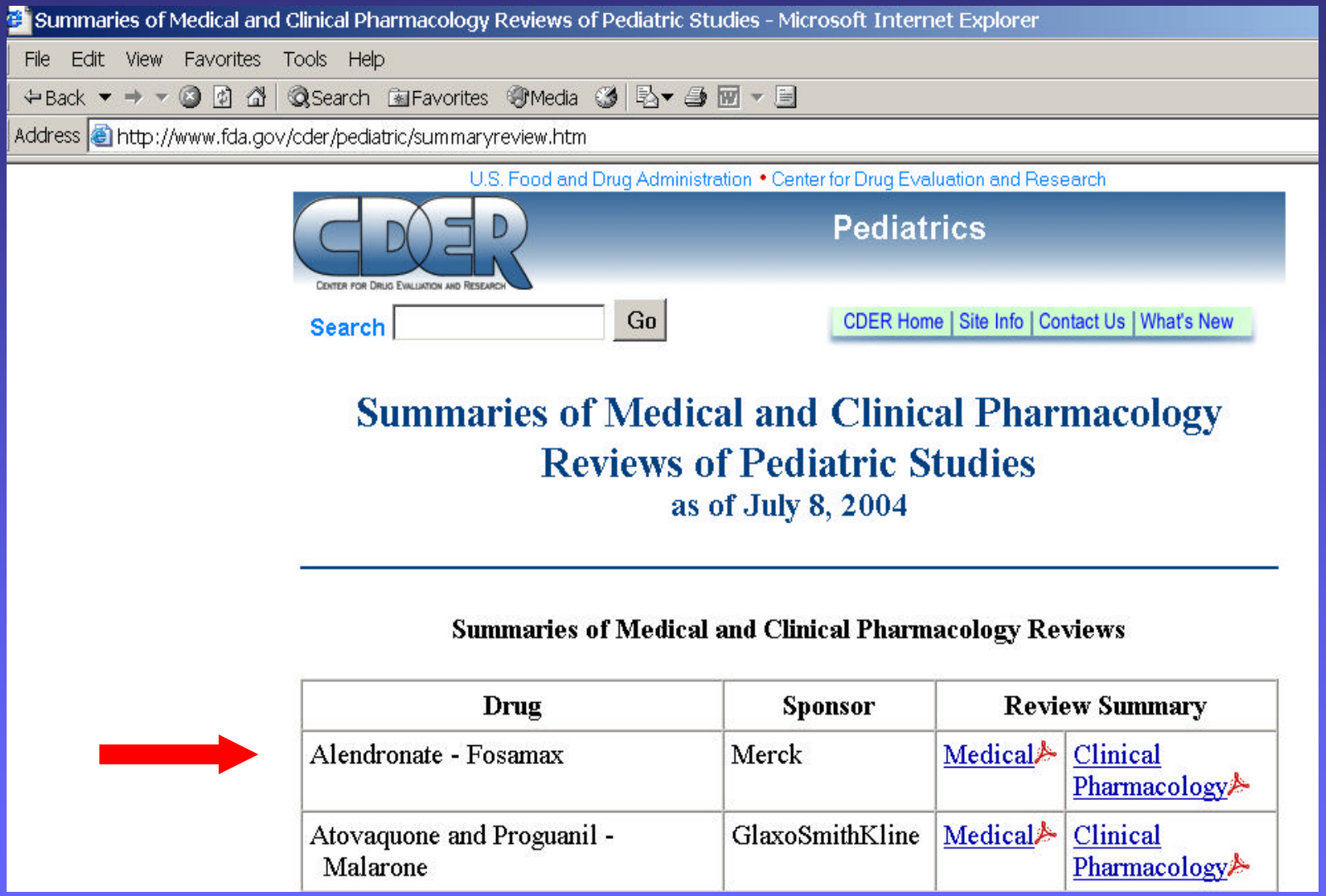
Drug Use Trends in Outpatient Settings: Alendronate

- Prescribers (May 2001- April 2004)[1]
  - Internists, family practitioners and obstetric/gynecology specialists primary prescribers (70 % of prescriptions written).
  - Pediatricians only wrote 0.3 %

- Diagnosis
  - Adults: osteoporosis and osteopenia
  - Pediatrics (off-label):
    - Osteoporosis or osteopenia (renal or connective tissue diseases, glucocorticoid tx), fibrous dysplasia, osteogenesis imperfecta

[1]IMS Health, National Prescription Audit *Plus*? , On-Line, May 2001 - Apr 2004, Data Extracted May 2004

http://www.fda.gov/cder/pediatric/Summaryreview.htm



Pediatric Exclusivity Studies: Alendronate

Indication: Treatment of severe Osteogenesis Imperfecta (OI) in patients 4-18 years

Studies performed:

- Oral bioavailability (tablets vs injection)
- 24 month efficacy and safety study

Pediatric Exclusivity Studies: Alendronate Pharmacokinetics

- Oral bioavailability of alendronate similar between OI patients and adults
- Relative to 125 ug IV dose
  - 35 mg oral dose in pediatric patients 4-14 years and < 40 kg, mean bioavailability is about 0.43 %
  - 70 mg dose in pediatric patients 11-16 years and > 40 kg, mean bioavailability is about 0.56 %

Pediatric Exclusivity Studies: Alendronate Safety and Efficacy

- Placebo Controlled Trial of 139 patients with OI ages 4-18 years (12 month results)
- 5 or 10 mg alendronate significantly increased lumbar spine Bone Mineral Density (primary endpoint)
- No treatment group differences for fractures (key secondary efficacy endpoint)
- Safety review-AEs appear comparable to adults (12 months)

Relevant Safety Labeling

- Pregnancy Category C
- Contraindications:
  - Delayed esophageal emptying or risk of aspiration
  - Inability to stand upright
  - Hypocalcemia
  - Allergy/hypersensitivity
- Warning:
  - GI irritation, esophageal perforation/ulcers/erosions

Relevant Safety Labeling

- Precautions
  - Monitor calcium, Vitamin D status
- Adverse Reactions:
  - Gastrointestinal symptoms (abdominal pain, nausea, dyspepsia, constipation, etc.)
  - Musculoskeletal pain
  - Headache, dizziness
  - Taste perversion
- Postmarketing
  - Stevens-Johnsons/Toxic Epidermal Necrolysis

Adverse Event Reports Since Market Approval: Alendronate

September 1995 – May 2004

- Total number of reports, all ages:
  - 18,712 reports (14,068 US)
    - serious- 4,265 (2,353 US)
    - deaths- 390 (128 US)
- Pediatric reports:
  - 17 reports (11 US)
    - 15 serious (9 US)
    - 0 deaths

Raw counts (US reports are in parenthesis)- includes duplicates

Adverse Event Reports during the One-Year Post-Exclusivity Period: Alendronate

April 2003 – May 2004

- Total number of reports, all ages:
  - 879 reports (413 US)
    - 850 serious (393 US)
    - 67 deaths (18 US)

- Pediatric reports:
  - 4 reports (0 US)
    - 4 serious (0 US)
    - 0 deaths

Adverse Event Reports: Alendronate

April 2003 – May 2004

(n=4)

- Hepatocellular injury (2)
- Drug-drug interaction (1)
- Neonatal Hypocalcemia & Prematurity (1)

Hepatotoxicity (n=2)

- 12 y/o F with JRA (prednisone, ibuprofen, mizoribine, glycyrrhizin, s/p MTX). Liver dysfunction (jaundice and markedly elevated liver enzymes) developed 2 weeks after initiating alendronate for glucocorticoid-induced osteoporosis. Liver biopsy confirmed severe hepatitis, viral studies negative. Resolved after steroid pulse therapy and discontinuation of alendronate
- 5 y/o M with juvenile idiopathic arthritis and hepatic dysfunction, interstitial pneumonia, and drug-induced agranulocytosis (dexamethasone). Liver dysfunction occurred 1 week after initiation of alendronate for glucocorticoid-induced osteoporosis. Liver enzymes improved after discontinuation of alendronate, treatment with cyclosporine, plasma exchange, G-CSF, and pulse steroids. Biopsy or viral studies not performed.

Drug Interaction (n=1)

- 7 y/o male JRA and steroid-induced cataracts (cyclosporine, prednisolone and ibuprofen). Previously stable cyclosporine levels decreased 1 month after starting alendronate with relapse of arthritis after 5 months. Cyclosporine levels increased once alendronate discontinued.

Neonatal Hypocalemia (n=1)

- 2.7 kg 34 week-premature male with hypocalcemia, hypocortisolism, transient tachypnea and port-wine stain born to 31 y/o with asthma, gestational diabetes, hepatitis C, psychosis endometriosis, and polycystic ovarian disease (dexamethasone, montelukast, albuterol, ipratropium, fluticasone, formoterol, theophylline, terbutaline, *furosemide, torsemide, immune globulin, *interferon, ribavirin, insulin and first trimester alendronate)

*drugs known to be associated with hypocalcemia

Summary

- Events confounded, insufficient information to ascribe causality
- This completes the one-year post-exclusivity adverse event monitoring as mandated by BPCA.
- FDA will continue its routine monitoring of adverse events for this drug.