



Memorandum

Date: February 3, 2005
To: Oncologic Drugs Advisory Committee Members and Guests
From: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products, CDER, FDA
Subject: FDA Background Package for morning of March 4, 2005

This memo outlines the purpose of the March 4, 2005 session of the ODAC meeting and describes the content of this briefing package.

The March 4, 2005 session will provide the Committee with updates on approved oncology drugs, specifically Iressa® (gefitinib), and two bisphosphonate drugs, Zometa® (zoledronic acid) and Aredia® (pamidronate disodium for injection). This session will include presentations from the respective pharmaceutical companies. ODAC discussions will center on FDA written questions.

During the Iressa portion of this meeting, you will hear the company's presentation of the results of a phase 4 trial in lung cancer patients. Iressa was approved under the accelerated approval regulations in May 2003 and this trial was a phase 4 commitment intended to verify that Iressa provides clinical benefit to lung cancer patients. Because the final data have not yet been submitted for FDA review, there will be no FDA presentation for this session, nor is there an FDA briefing document.

The discussion of Zometa and Aredia will focus on safety, specifically, osteonecrosis of the jaw (ONJ) occurring in cancer patients using these bisphosphonates. After consultation with the FDA, the company updated the product labels to include this associated toxicity.

In addition to the presentation by the pharmaceutical company, there will also be presentations by FDA on the regulatory history of the bisphosphonates in oncology and on procedures for evaluating post-marketing drug safety, and a presentation by Dr. Brian Durie on his web-based study of osteonecrosis.

The documents in this background package include:

TAB 1 General background document for Aredia and Zometa

FDA/CDER Office of Drug Safety (ODS) Postmarketing Memorandum/Review

TAB 2 November 21, 2003 Memorandum

TAB 3 August 25, 2004 Review

Documents from Brian Durie, MD

TAB 4 Durie, BGM, et.al. Osteonecrosis of the jaws in myeloma: Analysis of risk factors including time dependency of AREDIA® and ZOMETA® use, steroid use and underlying dental problems.

TAB 5 ONJ: Survey Methodology

TAB 6 Durie, BGM, et.al. Magnitude of Response With Myeloma Frontline Therapy Does Not Predict Outcome: Importance of Time to Progression in Southwest Oncology Group Chemotherapy Trials. *J Clin Oncol* 22: 1857-1863, 2004.

TAB 7 Durie, BGM, et.al. Myeloma management guidelines: a consensus report from the Scientific Advisors of the International Myeloma Foundation. *Hem J* 4: 379-398, 2003.

Other References

TAB 8 Migliorati, CA. Letter to the Editor: Bisphosphonates and Oral Cavity Avascular Bone Necrosis. *J Clin Onc* 21: 4253-4254, 2003.

TAB 9 Marx, RE. Letter to the editor: Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 61: 1115-1117, 2003.

TAB 10 Ruggiero, SL, et.al. Osteonecrosis of the Jaws Associated With the Use of Bisphosphonates: A Review of 63 Cases. *J Oral Maxillofac Surg* 62:527-534, 2004.

TAB 11 Estilo, CL. Osteonecrosis of the maxilla and mandible in patients treated with bisphosphonates: A retrospective study. *J Clin Onc* 22: 8008, 2004.

TAB 12 Assael, LA. New Foundations in Understanding Osteonecrosis of the Jaws. *J Oral Maxillofac Surg* 62:125-126, 2004.

TAB 13 Selected Meeting Abstracts from the 2004 47th Annual Meeting of the American Society of Hematology (ASH)

- TAB 13-1: **Abstract 3151**: Post-Marketing Assessments of Serious Adverse Drug Reactions Reported by the Manufacturer to the FDA Differ Markedly with Those from an Independent Pharmacovigilance Program: Empirical Findings Based on Bisphosphonate-Associated Osteonecrosis Descriptions by the Research on Adverse Events and Reports Project and the Product Manufacturer
- TAB 13-2: **Abstract 4905**: Oral Cavity Avascular Bone Necrosis - a Newly Recognized Complication of Intravenous (IV) Bisphosphonate Therapy in Cancer Patients
- TAB 13-3: **Abstract 4908**: Osteonecrosis of the Jaw Associated with Pamidronate Therapy
- TAB 13-4: **Abstract 4925**: Bisphosphonate Therapy Associated with an Increased Incidence of Mandibular/Maxillary Osteomyelitis in Multiple Myeloma Patients
- TAB 13-5: **Abstract 4933**: Osteonecrosis of the Jaw in Myeloma Patients Receiving Pamidronate or Zoledronate
- TAB 13-6: **Abstract 756**: Osteonecrosis of the Jaws in Myeloma: Time Dependent Correlation with Aredia® and Zometa® Use