

APPENDIX F

Chronology of significant regulatory activities between Applicant and FDA during the IND and NDA periods:

IND PERIOD

08/12/93	Submitted original IND Application.
08/19/93	FDA LETTER (93-147) acknowledging receipt of the original IND which is assigned IND No. 43,240.
10/01/93	Submitted IRB approval and Informed Consent covering Protocol 01 for Dr. Siris.
11/03/93	Submitted IRB approval and Informed Consent covering Protocol 01 for Dr. Lyles.
11/17/93	Submitted unpublished preclinical report.
11/24/93	FDA LETTER (93-179) regarding the IND submitted August 12, 1993 and indicating that the study may proceed.
01/24/94	Submitted Amendment 01 to Protocol 1 which allows for enrollment of four completed patients at a higher dose levels of 400 µg of drug.
02/10/94	In response to concerns raised in FDA letter of November 24, 1993 submitted additional chemistry information and copy of the clinical label which complies with the FDA investigational label requirements. Also, in fulfillment of commitments made in the original IND, included the official English translation of documents regarding drug substance and drug product stability report.
03/02/94	Submitted new protocol: Protocol 02 and provided new investigator.

04/13/94 Amendment I to Protocol 02 and IRB approval for various investigators to cover Protocol 02 Amendment I.

04/19/94 Requested review of the protocol for a preclinical study.

05/19/94 Submitted additional chemistry and labeling information in response to FDA letter of November 24, 1993. Also included Stability Report.

06/03/94 Submitted for FDA review and assessment, a draft copy of the protocol for a preclinical study entitled "Effects of 16 months treatment with the bisphosphonate CGP 42446 on bone mineral density, bone mechanics and bone cell function in ovariectomized adult rhesus monkeys".

06/08/94 Provided for various investigators.

06/08/94 Submitted the following investigators for Protocol 02: Drs. Buckler, Davies, Fogelman, Fraser, Reid, Maricic, Moses, Singer and Siris, and Dr. Fazer.

06/10/94 Submitted final copy of the preclinical protocol entitled "Effect of 12 months treatment with the bisphosphonate CGP42446 on bone mineral density, bone mechanical properties and bone histomorphometric parameters in ovariectomized rats".

06/14/94 Submitted unpublished preclinical reports: "Disposition of 14C-labelled CGP 42446 in rats", Wiegand, H.

07/07/94 Submitted new investigators for participation in Protocol 02 and covering Protocol 02, Amendment I for Dr. Fraser.

07/18/94 Submitted Stability Report dated 6/30/94.

07/26/94 Submitted unpublished preclinical reports: C-G (Basle) Chemistry Support Report IL 7/1993, August 13, 1993, "CGP 42446: Synthesis of carbon-14 labelled compound", Laboratory Notebook Mo-57.3/Mo-57.4, Mory, H. and C-G (Basle) Toxicology Test 90-6190, 4/30/93, "CGP 42446B: 6-month oral toxicity study in dogs", Mertz, B. et al.

08/19/94 Provided documentation for Dr. R.D. Altman's (Miami, Florida Protocol 02) additional study site. Provided IRB approval for Amendment I for Dr. P. Selby's (Protocol 02) study site. Also submitted updated Form FDA 1572 to add new subinvestigators to Dr. M. Maricic's and Dr. A.M. Moses's Protocol 02 studies.

08/19/94 Submitted new investigators to Protocol 02.

08/26/94 Provided Amendment I to Protocol 03.

08/26/94 Submitted new protocol: Protocol 03 and provided new investigator.

10/05/94 Submitted unpublished preclinical report: Ciba TRE Report No. 94010, 9/8/94.

10/10/94 Annual Report covering the period of August 1, 1993 to August 1, 1994.

11/09/94 Submitted unpublished preclinical reports: C-G (Basle) Toxicology Test 92-6248, March 2, 1993, "CGP 42446: cytogenic test on Chinese hamster cells in vitro (EC-CONFORM)" and Toxicology Test 92-6297.

11/30/94 Submitted Final Medical Report for Protocol 001.

01/27/95 Submitted for FDA review a draft copy of a preclinical protocol.

01/30/95 Submitted Report No. 936059 advising of adverse teratological findings in rats.

02/15/95 Submitted new protocol, Protocol 003 extension. Also provided for Dr. Lipton who will conduct a study according to Protocol 003 extension. Provided for additional investigators who will conduct studies according to Protocols 02 and 03.

03/03/95 Submitted for FDA review a draft copy of preclinical protocol.

03/10/95 Submitted unpublished preclinical reports: C-G (UK) Preclinical Safety Report 024/93/SL, Test Number 936060, 9/23/94 and provided Final Report Amendment 1; submitted Preclinical Safety Reports 024/93/SL and 003/94/SL.

03/20/95 Provided documentation to support formulations; submitted stability information and an unpublished preclinical report.

03/23/95 Submitted request for review of the final version of the preclinical protocol and Amendments 1 & 2.

04/19/95 Submitted Amendment II to Protocol 03 and investigator documentation for Protocol 03.

04/19/95 Submitted Amendment I to Protocol 03 Extension and investigator documentation.

05/02/95 Submitted unpublished preclinical report: T/P Report 95004, (MIN 944073), Test No. 94-6024, 2/10/95.

05/09/95 FDA FAX (95-112) providing review comments of the Executive Committee for the Carcinogenicity Assessment Committee's recommendations for the doses in the rat carcinogenicity study. Also confirmed agreement on the doses used in the mouse carcinogenicity study (Amendments 024 & 025).

07/21/95 Provided background/reference material for August 14, 1995 meeting with FDA and submitted draft Protocol 017 which included preclinical and technical information.

08/16/95 Submitted IRB approval for Dr. James Berenson to cover Protocol 003, Amendment II.

08/25/95 Submitted CMC information and provided Stability Report dated 5/10/95.

08/31/95 As requested, provided a copy of the 8/14/95 meeting minutes and overheads used to discuss issues associated with the development of CGP 42446 in a transdermal formulation to treat patients with bone and postmenopausal osteoporosis.

10/27/95 Annual Report covering the period of August 1, 1994 to July 1, 1995.

12/04/95 Submitted unpublished preclinical report.

01/31/96 Requested FDA review and response to outlined concerns related to the clinical development of CGP 42446 for malignant indications.

02/05/96 Submitted new investigator to Protocol 03X: Dr. Berenson.

02/15/96 Submitted new Protocol 4244603007 in response to Mr. Hedin's (FDA) 2/13/96 request.

02/26/96 Submitted Amendment III to Protocol 003. Also IRB approval and patient consent form to cover the protocol amendment for Dr. Lipton, principal investigator.

03/22/96 Provided updated CMC information and Stability Reports.

03/28/96 Submitted Final Medical Report for Protocol 02.

05/22/96 Submitted unpublished preclinical report C-G Limited (Basle) Test No.: 93-6230, 1/12/96, "CGP 42446: 6/12-month subcutaneous toxicity study in rats," Meister, L., et al.

06/20/96 Advised the agency of improprieties discovered during a routine review of the study records at Dr. Berenson's site where he is conducting a study according to Protocol 003.

06/25/96 Amendment III to Protocol 03 which provides for the addition of two more dosing groups (4 mg and 8 mg dose).

07/09/96 Letter addressed to Dr. Williams advising him that as requested by the Division of Metabolism and Endocrine Drug Products, Ciba is providing him with a copy of all submissions relating to oncology indications of zoledronate and also a copy of Amendment 049 dated July 9, 1996.

07/09/96 Submitted new protocol – Protocol 4244603007 and provided new investigator: Dr. Morley.

07/17/96 Submitted toxicology reports and Toxicology/Pathology Test No. 926259, 2/3/95; Preclinical Safety Test No. 936063, 9/23/94; and unpublished preclinical reports: Ciba (Basle) Genetic Toxicology Report Test No. 926249, 7/7/93, CGP 42446: Gene Mutation Test with Chinese Hamster Cells V79 In Vitro, Galeick, D.

08/01/96 Submitted new investigators to Protocol 4244603007.

09/05/96 Submitted a new investigator to Protocol 03 Extension.

09/05/96 Submitted Amendment II to Protocol 03 Extension which allows for the monthly infusion of two additional dose groups (4000 µg and 8000 µg groups).

09/10/96 Submitted unpublished preclinical reports: C-G Limited, Basle, Preclinical Safety Report Test No. 936282, 10/24/94, CGP 42446: Local intravenous irritation study in rabbits, Nogues, V. and C-G Limited, Summit, NJ, U.S., Manuscript No. 96-0059, 4/15/96.

09/12/96 Submitted new investigators and a new subinvestigator to Dr. R. Dreicer's study.

10/21/96 Annual Report covering the period of July 1, 1995 to July 1, 1996.

11/14/96 Submitted an updated drug substance control document and a method validation.

11/22/96 Submitted IRB approval for Protocol 007, Amendment I and revised informed consent for Drs. Kuross, Dreicer, Morley and IRB approval for a revised informed consent for Dr. George.

11/22/96 Submitted documentation for investigators who will conduct a study according to Protocol 4244603007: Also included IRB approval for Amendment 1, revised informed consent and revised FDA 1572 to reflect the addition of two subinvestigators for Dr. Kardinal.

11/25/96 Sent letter addressed to Dr. Williams (FDA) indicating that as requested, Ciba is providing him a copy of amendment 057 to IND 43,240 dated November 22, 1996.

01/30/97 Provided investigators for Protocol 42446 03 007 and included IRB approval for revised consent for Drs. Kardinal and Morley; revised FDA 1572 to add two subinvestigators for Dr. Campbell and IRB approval for revised consent; also submitted IRB approval for Protocol 007, Amendment 1 and revised informed consent for Drs. Coleman and Young; Amendment 1 IRB approval for Drs. Keiser and Porter and an address change for the latter.

02/12/97 Submitted letter from Ciba transferring ownership of IND 43,240 to Novartis effective January 1, 1997 and letter from Novartis accepting ownership of the IND file from Ciba and identifying the new monitor of the IND.

02/24/97 Submitted preclinical report.

02/28/97 Submitted two investigators who will conduct a study in accordance with Protocol 007; noted that commercial Aredia (pamidronate disodium for injection) 90 mg sterile lyophilized vials manufactured by Ciba Pharmaceuticals, Summit, NJ will be used (H-3980); and included investigator signed Amendment 1 for Protocol 007 for Drs. Howell, Parker and Clarke..

03/24/97 Submitted documentation for drug substance manufactured by Synthesis D and the 4 mg powder for injection in vials, and provided a Stability Report.

03/28/97 Submitted new Protocol 035 and extension thereof and provided for Dr. Berenson who will conduct Protocol 035.

04/24/97 Submitted Protocol 007 Extension and a Form FDA 1572 for Dr. Morley.

04/25/97 TELEPHONE REPORT: Discussion with D. Spillman regarding the need for an additional IND for Zoledronate for the Oncology division.

05/05/97 Received FDA LETTER (97-105) regarding the 2/24/97 submission which provided the 26/52 week intravenous toxicity study. The study may continue but additional information is requested as outlined.

08/05/97 Submitted new investigators to Protocols 007, 007E and 07; subinvestigators to Protocol 03E study and new study site submitted.

08/06/97 TELEPHONE REPORT: Discussion with R. Hedin (M/E Division) regarding Zoledronate INDs and new IND in the Oncology Division.

09/19/97 Submitted response to FDA letter dated May 5, 1997 which requested response to comments regarding the 26/52 week intravenous toxicity study submitted on February 24, 1997.

09/24/97 Submitted investigators for Protocol 007 extension and new subinvestigators for Drs. Gibbons and Webb.

09/26/97 Submitted record of agreements reached during the September 17, 1997 telephone conference between FDA and Novartis to discuss the development plans for CGP 42446 for TIH.

10/01/97 Resubmitted serial no. 066, dated 8/5/97, in its entirety to the Division of Metabolic and Endocrine Drug Products. The contents of the submission was inadvertently sent to the Division of Oncology Drug Products.

10/02/97 Submitted new investigators to Protocol 007E: Drs. Fine and Rosen.

11/18/97 Submitted Annual Report covering period of July 1, 1996 through July 1, 1997 and Stability Report.

12/15/97 Submitted new investigators to Protocol 07E and 035E as well as new subinvestigators to Drs. Theriauet and Berenson's Protocol 007 study.

12/16/97 TELECON FROM FDA requesting that the BPK(CH) 1996/067 report be submitted for review.

12/18/97 Submitted new protocol: Protocol 4244604037 and submitted new investigators.

01/14/98 Submitted unpublished preclinical report: BPK (CH) 1996/067, 5/6/97, Plasma Concentrations of CGP 42446 During a 3-Month Intravenous Toxicity Study in Dogs.

01/20/98 Submitted new investigator to Protocol 007E and new investigators to Protocol 037.

01/26/98 TELECON FROM FDA: Approval of the compassionate use of zoledronate as requested by Novartis on January 26, 1998.

01/29/98 Formal request for compassionate use of zoledronate in the treatment of a single patient.

02/26/98 Added new investigators to Protocol 037.

04/01/98 Informed the agency that an updated investigator alert letter was issued.

04/02/98 Submitted new investigators for Protocol 037.

04/07/98 Request for compassionate use of zoledronate for the treatment of a single patient.

04/30/98 Provided for new investigators for Protocol 4244604037.

05/11/98 Response to FDA facsimile dated August 21, 1997 and response to FDA 12/8/97 telephone request for information concerning GI irritation.

06/11/98 Amendment 1 to Protocol 037.

06/17/98 Submitted new investigators to Protocol 4244604037.

07/02/98 Submitted draft Protocol 4244601005 and draft Extension Protocol.

07/22/98 Provided documentation for Dr. Levin participating in Protocol 037.

07/29/98 Submitted documentation for drug substance manufactured by Modified Synthesis D and documentation to support the addition of a new manufacturing site.

08/06/98 Provided table which includes the anticipated extent of zoledronate exposure data that will be available for the planned Paget's disease NDA filing based on the successful completion of Protocol 005 in response to FDA request of July 30, 1998.

08/14/98 FDA fax providing comments regarding the draft zoledronate Protocol 005 submitted July 2, 1998.

08/20/98 TELECON FROM FDA chemistry reviewer inquiring what phase Novartis has reached with the development of zoledronate. FDA suggested requesting a pre-NDA meeting especially with regard to the stability protocol.

08/26/98 Submitted new investigators to Protocol 42446037.

11/19/98 Submitted new investigators to Protocol 037.

11/23/98 Submitted new investigator to Protocol 037.

01/21/99 Requested a pre-NDA meeting to present an overview of Novartis' planned NDA submission.

02/11/99 Submitted new investigator to Protocol 037: Dr. Durie.

03/15/99 Submitted copies of a briefing documentation that includes a list of attendees, background information, and specific proposals for consideration for the meeting scheduled with the FDA on 4/15/99.

03/19/99 Submitted new investigators to Protocol 037.

03/25/99 Submitted general correspondence notifying the agency of the suspension of approval for Protocol 011 by the Local Ethics Committee in Great Britain.

04/09/99 Requested a pre-NDA meeting to discuss the CMC section of the NDA which Novartis anticipates to submit at the end of 1999 for treatment of patients with TIH.

04/15/99 Received minutes of the pre-NDA meeting dated April 15, 1999.

04/27/99 Submitted Annual Report for period August 31, 1997 through August 30, 1998.

05/04/99 Submission in response to an FDA request for information dated April 21, 1999 on the occurrence of lung cancer in randomized, placebo-controlled, trials in Paget's Disease, osteoporosis treatment, and osteoporosis prevention.

05/26/99 Submitted draft protocol for the proposed 2-week intravenous toxicity study in Sprague-Dawley rats.

05/27/99 Submitted briefing documentation in preparation for a meeting scheduled for June 22, 1999 to discuss the CMC section of a new NDA for zoledronate for treatment of patients with TIH.

06/02/99 Submitted new investigators to Protocol 037.

06/07/99 Received FDA FAX which includes pharmacology review comments regarding the May 26, 1999 submission, two week intravenous toxicity study in Sprague-Dawley rats.

06/22/99 FDA minutes of a pre-NDA meeting held on June 22, 1999 to discuss Novartis' proposals regarding the content and format of the CMC section of the NDA.

06/24/99 Submitted draft protocol for drug metabolism and pharmacokinetics study in rats. Also included response to FDA comments included in the June 7, 1999 facsimile regarding the 2 week i.v. toxicity study in rats, 5/26/99.

06/24/99 Submitted general correspondence in reference to the 4/15/99 pre-NDA meeting.

07/7/99 Submitted new investigators for Study No. 037.

07/15/99 Request for pre-clearance of proposed tradename, Zometa[®]/Zabel, in preparation for commercialization of this product. Background information on this product is provided to support the review.

07/19/99 Sent E-mail to FDA asking to communicate issues via e-mail concerning the NDA submission. Feedback was requested on previous issues (CMC and Clinical) as well as new issues (Statistical and General).

07/21/99 Submitted a draft study report (Study No. 997049), in response to a June 7, 1999 request.

07/22/99 TELECON from FDA indicating that the proposals detailed in our June 24, 1999 submission are acceptable. The statistician requests SAS efficacy programs as transport files with the NDA.

08/04/99 Submitted new investigator to Study 037: Dr. Hutchins.

08/17/99 Sent E-MAIL to FDA requesting a proposal to submit CRFs as previously defined but to limit NDA submission to those for the pivotal TIH trials (036 and 037) and the supportive study (CJ/HC1).

08/18/99 Received E-MAIL from FDA agreeing to CRFs proposal submitted in E-mail dated August 17, 1999.

09/21/99 Submission containing five serious adverse event reports that were submitted to IND 55,831 but inadvertently omitted from this IND.

09/23/99 Submitted request for an orphan drug designation for zoledronate in the treatment of TIH.

10/19/99 Sent E-MAIL to FDA containing several questions concerning the upcoming NDA.

10/26/99 Annual Report covering the period July 1, 1998 through July 1, 1999.

10/29/99 Resubmitted the September 23, 1999 request for orphan drug designation.

11/18/99 Received FDA LETTER acknowledging the submission for orphan designation and assigned reference number 99-1308.

12/06/99 Sent FAX to FDA containing 2 safety reports.

12/09/99 Sent FAX to FDA containing follow-up (#6.8) information.

12/15/99 Submitted investigator report.

12/21/99 Submitted investigator follow-up #3.4.

12/22/99 Letter to FDA authorizing FDA to refer to this IND in support of IND to be filed by Dr. S.E. Bulun.

12/29/99 Submitted investigator follow-up #2.3.

01/03/00 Submitted investigator follow-up #1.2.

01/04/00 Sent correspondence informing the Office of Orphan Products Development that an NDA was submitted to the FDA on December 21, 1999.

01/07/00 Submitted Amendment No. 1 to the Investigator's Brochure dated December 23, 1999.

02/08/00

Submitted safety reports containing 9, 15-day reports previously submitted to this IND with respect to the issue of 'acute renal failure'. The contents of the investigator alert for this case is included and contains what actions Novartis has taken and will take.

02/15/00

Submitted a Proposed Pediatric Study Request for FDA's review and issuance of a Written Request for pediatric exclusivity for zoledronic acid for children with osteogenesis imperfecta (OA).

NDA PERIOD

12/21/99 An original NDA was submitted for Zometa[®] for the treatment of TIH. A request for priority review was made as well as a request for a 90-day post-submission conference regarding the general status of the review.

12/27/99 FDA LETTER acknowledging receipt of the original NDA.

01/07/00 Submitted amendment to the pending NDA containing the statistical analysis output tables and figures for the Clinical Study Report 037 (Appendix 5, Section 5.1.2).

01/20/00 FAX to FDA containing references to support pamidronate as the current treatment of choice for TIH and a copy of the Aredia package insert providing comparative data of pamidronate versus etidronate.

01/31/00 TELECON with FDA regarding verification of the testing sites listed in the summary table.

02/02/00 Submitted amendment containing clarifications to the manufacturing, packaging and control sites for the drug product.

02/02/00 E-Mail to FDA confirming that the therapeutic classification is IP (priority review) and that the Division does not anticipate an advisory committee hearing on this application.

02/04/00 FDA LETTER requesting information on the Clinical Pharmacology and Biopharmaceutics section of the original NDA.

02/11/00 In response to the FDA letter dated February 4, 2000, submitted 2 reports, which were originally included in Section 5 of the NDA, Section 6: DMPK (US) R98-106 and DMPK (CH) 1997/530.

02/16/00 FAX from FDA containing a preliminary draft of information requested from the Statistical Reviewer concerning the NDA.

02/18/00 Submitted to the Office of Medical Policy, DSI, the names and addresses of the investigators in Protocol 37 and 36, listed by center number.

02/22/00 FAX from FDA of the second draft of an information request from the Statistical Reviewer concerning the NDA.

02/25/00 FDA LETTER agreeing that the waiver submitted in the NDA dated December 21, 1999, is justified for pediatric studies.

02/28/00 Submitted amendment containing a complete response for additional information pertaining to the statistical section of the NDA.

03/07/00 E-MAIL to FDA providing the NONMEN command and control file requested.

03/08/00 TELECON from FDA statistical reviewer requesting additional data analyses from the NDA.

03/16/00 E-mail to FDA on a proposal to limit the CRFs and narratives to be submitted in the 120-day Safety Update due April 21.

03/17/00 E-mail to FDA requesting a teleconference to discuss the submission of an NDA amendment to include a correction for the variables BUN and BUN/Creatinine Ratio that are reported in Protocol 036, ISE and the ISS.

03/21/00 Submitted amendment containing updated stability reports for both the drug substance and drug product in accordance with an agreement reached with the Agency at the June 22, 1999 pre-NDA CMC meeting.

04/04/00 E-mail to FDA regarding the preferred format for the submission of the revised Bun/Creatinine ratio variable and to inquire about the acceptability of the proposed tradename and proposed carton and vial labels in preparation for launch.

04/07/00 Submitted an amendment in reference to an e-mail to FDA dated March 17, 2000 to include a correction to the NDA for the summaries of BUN and BUN/Creatinine Ratio data reported in the pooled analysis (ISE, Appendix 1) and the ISS.

04/13/00 Submitted amendment provides additional statistical analysis and data presentation as requested on March 8 and March 31, 2000.

04/13/00 Submitted request for approval to import the subject bulk product Zometa[®], 4 mg vials, in anticipation of FDA approval.

04/14/00 Submitted amendment providing for a revision to the font size for the strength on the Zometa[®] vial label.

04/14/00 Submitted electronic version of January 7, 2000 amendment which provides for Appendix 5, Section 5.1.2 for Protocol 037 Clinical Study Report.

04/19/00 Submitted amendment providing for the 120-Day Safety Update.

04/20/00 Submitted amendment containing the final stability update report for the drug substance, Synthesis E.

04/27/00 Submitted response to an April 12, 2000 request, for electronic data sets for the tumor data in Reports 951021 and 951159.

04/28/00 Submitted amendment in response to FDA's request dated March 31, 2000, for additional statistical analyses and data presentations.

04/28/00 E-mail from FDA containing questions generated from the NDA review of Studies 036 and 037 including some other clinical reports.

05/02/00 FAX from FDA containing a pharm/tox request to the Precautions section of the package insert.

05/05/00 Submitted letter is in response to an FDA facsimile dated May 2, 2000 requesting additional information and revisions to the Precautions section of the proposed package insert.

05/05/00 FAX from FDA containing comments on the review of the microbiology section of the NDA.

05/08/00 FAX from FDA requesting individual historical tumor incidence control data from the rat and mouse.

05/10/00 Submitted CMC amendment requested by FDA on May 3, 2000.

05/11/00 Submitted a complete response to a May 8, 2000, facsimile request from FDA for historical control incidence information.

05/12/00 Submitted complete response to an April 28, 2000, FDA e-mail containing questions and comments from the statistical reviewer.

05/12/00 Submitted electronic data sets for carcinogenicity studies in response to a request from the Biostatistics reviewer on May 4, 2000.

05/12/00 E-mail to FDA attaching revised SAS transport files containing data from the two carcinogenicity studies as requested on May 4, 2000.

05/15/00 E-mail to FDA containing MSWord documents for appendices 1-12 in response to the May 12 response review comments/questions.

05/16/00 TELECON from FDA Biopharmaceutics Reviewer requesting information on Studies J001 and 503.

05/17/00 Submitted complete response to all Microbiological/Sterile Validation comments received on May 5, 2000.

05/18/00 E-mail to FDA regarding preliminary feedback from the Data Monitoring Board (DMB) on potential concerns relating to renal safety in the ongoing Zometa® studies in patients with bone metastases.

05/18/00 E-mail to FDA of PDF versions of the carton and vial labels if needed for review.

05/18/00 Submitted response to review questions of May 16, 2000.

05/22/00 TELECON to FDA Medical Reviewer in response to his review comments.

05/23/00 TELECON with FDA Biopharmaceutics reviewer concerning the location of data from each study that supports a statement in the proposed package insert.

05/23/00 E-mail from/to FDA concerning the location of exclusivity for Zometa®.

05/26/00 Submitted specificity of the zoledronic acid radioimmunoassay, in response to a May 24, 2000 voice mail from FDA.

05/31/00 Submitted response to a May 31, 2000 e-mail requesting narratives for patients who died in Studies 036 and 037.

05/31/00 TELECON and E-mail to FDA on DSMB concerns regarding renal adverse events and narratives for patients who died in Studies 036 and 037.

05/31/00 E-mails from/to FDA regarding unequal distribution of patients in Studies 036 and 037.

06/01/00 Submitted request for a teleconference to discuss an anticipated amendment concerning potential concerns relating to renal safety in the ongoing Zometa® studies in patients with bone metastases.

06/01/00 E-mail to FDA regarding correspondence to pending NDA (renal function deterioration) and to request a telcon.

06/02/00 Submitted a complete response to all CMC questions received on May 25, 2000.

06/07/00 FAX and E-mail to FDA containing information in preparation for the June 7, 2000, teleconference regarding potential concerns relating to renal safety.

06/08/00 FDA's minutes of the June 8, 2000, teleconference to discuss the unblinded data package on renal safety and it's effect on the review of the NDA.

06/09/00 Submitted analyses of unblinded data in reference to the assessment made by the Data Safety Monitoring Board and the Renal Advisory Board from three ongoing bone metastases clinical trials.

06/21/00 TELECON with FDA Project Manager to discuss unblinded data, tradename review and OI protocols.

06/27/00 TELECON from FDA requesting further clarification on 1) the method 'Appearance of Solution' 224-01S.02 and 2) characterization of the DS - the single crystal x-ray (STRU_MS_975_1, section 1.7).

08/08/00 Submitted a copy of a letter submitted to IND 43,240 in reference to the June 9, 2000, submission (Serial No.150) and to the June 28, 2000, teleconference.

08/08/00 FAX from FDA containing changes to the labeling based on the completion of the pharmacology review of the NDA.

08/14/00 Submitted a proposed package insert revised to reflect the change in infusion time from 5 to 15 minutes and precautions and administration recommendations to emphasizing safety measures for the use of Zometa®.

08/14/00 FAX from FDA containing comments and requests following completion of a preliminary review of renal toxicity.

08/15/00 FDA LETTER listing deficiencies in the biopharmaceutics section of the NDA and containing labeling comments concerning the biopharmaceutics review.

08/18/00 Submitted a copy of a letter submitted to IND 43,240 in reference to the August 8, 2000 submission (Serial No.162) and the August 17, 2000, teleconference.

08/22/00 Response to an August 15, 2000, FDA letter, regarding the biopharmaceutics section of the NDA.

08/25/00 Request for a refund of the user fee regarding designation of orphan drug status.

08/25/00 Submitted a copy of a letter submitted to IND 43,240 in reference to an August 14, 2000, facsimile from the FDA and to an August 17, 2000, teleconference.

08/29/00 FAX to FDA containing a copy of an e-mail response regarding Dr. Hon's site and the attachment from the February 2, 2000, submission.

09/01/00 E-mail to FDA containing vial and carton labels.

09/08/00 Submitted safety update summarizing the information communicated since the April 19, 2000.

09/14/00 Submitted response to the preliminary preclinical labeling comments received August 8, 2000, by facsimile.

09/20/00 E-mails to FDA containing information on the ongoing Zometa[®] clinical trials.

09/21/00 Submitted copies of the cover letters of the unblinded data from the ongoing studies submitted to IND 43,240 in support of the pending NDA.

09/21/00 FDA LETTER finding the original NDA, as amended, approvable.

09/29/00 Correspondence submitted in reference to the September 21, 2000, approvable letter, notifying FDA of Novartis' intent to file an amendment and also requests a meeting to discuss the format and content of the amendment.

10/10/00 Submitted follow-up to the meeting request of September 29, 2000.

10/12/00 FAX to FDA containing the Form 356H which was inadvertently left off the October 10, 2000, submission.

11/06/00 Submitted briefing book for the End of Review Meeting scheduled for December 14, 2000.

12/13/00 Submitted materials in preparation for a Novartis End of Review Meeting scheduled with the Division for December 14, 2000.

12/14/00 FDA minutes of an End of Review meeting held on Dec. 14, 2000.

12/14/00 Novartis minutes of a Drug Regulatory Affairs and FDA meeting held on December 14, 2000 to discuss the safe use of Zometa® in Hypercalcemia of Malignancy.

12/21/00 Submission complying with Division request of December 14, 2000 and addressing some lingering concerns expressed in the approvable letter and the December 14 meeting.

12/22/00 Fax to FDA in response to request for slides presented at the December 14, 2000 Zometa® End of Review FDA Meeting.

02/01/01 TELECON from FDA with comments on the renal safety data submitted in December 2000 to support the lift of the clinical hold.

02/19/01 Submitted amendment providing Novartis' Complete Response to the Approvable Letter issued September 21, 2000. Reference is also made to a December 21, 2000 Novartis letter and a January 8, 2001 telephone call when FDA accepted Novartis' proposal for this Complete Response.

03/26/01 Submission made in reference is to a February 19, 2001 letter with Novartis' Complete Response to the Approvable Letter and in response to requests made in an FDA telecon on March 22, 2001.

03/27/01 FDA LETTER acknowledging receipt of the resubmission to the Zometa® application, submitted on February 19, 2001.

03/29/01 Submitted, in response to an FDA request, a diskette containing the Kaplan-Meier figures for the pre amendment period for Study 10.

04/02/01 Official copy of telefax dated March 30, 2001 containing the running text of the proposed package insert which complies to the September 8, 2000, requests from the Division.

04/09/01 Submitted, in response to an FDA request, an official copy of telefaxes dated April 4 and 6, 2001, which contained patient narratives found in Novartis' Complete Response submission dated February 19, 2001.

04/11/01 Submitted the correct Tables 4 and 5 of the Complete Response submitted on February 19, 2001 to the Approvable Letter, issued to Novartis on September 21, 2000.

04/11/01 Fax to FDA with an attached section entitled, "Update of Renal Event Analyses".

04/30/01 Submitted approved labeling for the EU and Australia in reference to the February 19, 2001, Complete Response to the Approvable Letter.

05/03/01 Submission of an electronic and paper copy of a revised draft package insert which highlights changes made from the electronic version of the draft PI sent to the Division on April 25, 2001.

05/16/01 Notification to FDA stating Novartis accepts the terms issued in the NO OBJECTION FOR IMPORTATION LETTER dated August 31, 2000 with a correction that the material will be packaged by Novartis at the Suffern, N.Y. facility.

05/30/01 FAX from FDA containing information on financial disclosure by clinical investigators.

05/31/01 Fax to FDA, as a follow-up to a May 30, 2001 teleconference, regarding clinical investigator's financial disclosure information.

05/31/01 FAX to FDA containing financial disclosure information.

06/01/01 Submission of an official copy of the May 31, 2001, facsimile on financial disclosure.

06/08/01 Fax from FDA with comments regarding the Zometa[®] label.

06/12/01 Submission in response to FDA labeling comments of June 8, 2001.

06/22/01 FAX from FDA containing labeling comments from the clinical review.

07/10/01 Sent, in response to an FDA request, official copies of the draft labeling.

07/17/01 TELECON to FDA to discuss the timing and status of the NDA review and the timing and type of the bone mets application to the Oncology Division.

08/03/01 In response to an FDA request, this general correspondence submission contains samples of the Zometa[®] carton for purposes of color clarification.

08/09/01 FAX to FDA concerning the agreement reached between FDA and Novartis to use a two-hour administration of Aredia for the TIH program.

08/16/01 Sent letter notifying the Division that the Phase 4 Commitment to conduct a pharmacokinetics and pharmacodynamics study in patients with impaired renal function has been completed.

08/20/01 Submitted final revised labeling (carton and PI) that reflects all agreed changes made during telephone conversations held on August 15-17 and 20, 2001.

08/20/01 Received FDA LETTER via fax approving the new drug application for the use of Zometa[®] for the treatment of hypercalcemia of malignancy.

Public Health Service

Food and Drug Administration

4035 '02 JAN 15 A9:40
Memorandum

Date: January 11, 2002

From: Claudia Grillo, Paralegal Specialist
Regulatory Policy Staff (HFD-007)

Subject: Patent Term Restoration Application
for Zometa

To: Dockets Management (HFA-305)

Attached please find a copy of the Application for Extension of Patent Term Under 35 U.S.C. § 156 for the above-referenced human drug product, together with the cover letter from the Patent and Trademark Office. The applicant is Novartis Corporation and the product's trade name is Zometa. Please assign a docket number to this application for patent extension and advise me of same.

If you have any questions, please contact me at 594-5645. Thank you for your assistance.

Attachment

RAF-0020