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CASE 4-20918/-/CIP

OFFICE OF PETITIONS

APPENDIX G

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

IND PERIOD

06/30/1999	Submitted an Investigation New Drug Application for ICL670 Dispersible Tablets – Indication: Iron Chelation. Two protocols are included, each with a question directed to the FDA reviewer (protocol CICL 670 0103 with Amendment No. 1 and draft protocol CICL670 0102).
07/12/1999	FDA LETTER acknowledging receipt on July 1, 1999 of the original IND dated June 30, 1999. Assigned IND No. 58,554.
07/22/1999	Telecon with FDA to discuss three recommendations for changes to Protocol 0103 submitted in the original IND.
07/22/1999	Fax to FDA providing Novartis' commitment to amend the clinical study protocol 0103 as recommended by FDA, discussed at telecon of even date.
07/27/1999	Fax to FDA clarifying the trial design description that appeared in protocol 0103 in response to the Agency's recent request.
08/04/1999	A corrected Form FDA 1572 was submitted to reflect changes to box 14.
08/04/1999	Official copies of the faxes dated July 22 and 27, 1999 are submitted.

08/19/1999 FDA LETTER referencing the agreement reached at the July 22, 1999 teleconference revising protocols 0103 and 0102 as well as requesting additional revision to same protocols. CMC issues to be addressed as the drug development proceeds are also listed.

10/06/1999 New protocol CICAL670 0104 (replaces 0103 and 0102 and incorporates all suggested changes from the Division) entitled: "Randomized, double-blind, placebo controlled, time-lagged, parallel-group study to evaluate the iron balance, safety and tolerability of multiple oral doses of ICL670A in patients with transfusion dependent beta-thalassemia". A revised investigator's Brochure is also included.

10/12/1999 Fax to FDA in response to a request from the Pharm/Tox reviewer for information on Klucel HF.

10/14/1999 This submission supersedes Serial No. 003. A complete 004 copy of all material (with the corrected protocol CICAL670 0104) previously sent is included. Initiation of this proposed study is planned for the second week of November and Novartis is asking the Division for any comments on or before November 1, 1999.

11/22/1999 FDA letter containing comments and recommendations from the review of the clinical protocol 0104 submitted on October 14, 1999, Serial No. 004

03/09/2000 This submission contains a full response to all CMC issues contained in the Agency's letter dated August 19, 1999.

05/02/2000 New investigator to Study No. CICAL670A 0104: Patricia Giardina, MD.

06/07/2000 Amendment No. 1 to Study No. ICL670A 0104.

07/27/2000 Amendment No. 2 to Study No. ICL670A 0104.

11/06/2000 Annual Report covering the period of July 1, 1999 through June 30, 2000. Includes preclinical and clinical study information and CMC changes.

11/06/2000                      Amendment No. 3 to Study No. 0104.

01/09/2001                      This amendment contains updated stability data for both the drug substance and drug product.

01/15/2001                      Amendment No. 4 to Study No. 0104.

03/23/2001                      Final Report for Study No. 0101 entitled "A double-blind, placebo-controlled, tolerability, safety and pharmacokinetic study with ascending single oral doses of ICL670A administered in a sequential order to patients with transfusion-dependent beta-thalassemia."

04/17/2001                      This correspondence requests a special protocol assessment on the two carcinogenicity protocols being submitted to determine whether the Division is in agreement with this study program as adequate to assess the risk for patients.

04/25/2001                      FDA letter stating that the April 17, 2001, request for a special protocol assessment will not be accepted. The protocols are to be resubmitted as separate submissions and for the rat carcinogenicity study protocol, a copy of the full report from the 26-week toxicology study in rats is to be included.

04/30/2001                      In response to an FDA letter dated April 25, 2001 concerning Novartis' April 17, 2001 request for special protocol assessment, this correspondence contains the resubmission of the rat carcinogenicity study protocol and a copy of the full report from the 26-week rat toxicology report.

04/30/2001                      In reference to the request for special protocol assessment (Serial No. 016) on the rat carcinogenicity study protocol, this submission contains additional information to clarify questions discussed by telephone.

06/07/2001                      Fax from FDA containing the final CAC report in response to Carcinogenicity Special Protocol Assessment Request, Serial No. 016, April 30, 2001.

06/19/2001 FDA letter containing comments and recommendations on the Request for Special Protocol Assessment amendments, Serial No. 16 and 17 (RAT CAR study protocol).

07/06/2001 In response to an FDA letter dated April 25, 2001, concerning Novartis' April 17, 2001, request for Special Protocol Assessment, this correspondence contains the draft mouse carcinogenicity protocol for review.

07/09/2001 This submission provides comments in response to an FDA letter dated June 19, 2001, regarding the 104-week carcinogenicity study in rats.

07/17/2001 FDA letter stating that the submission dated July 6, 2001, Serial No. 017, (special carcinogenicity protocol assessment) is under review and a written response will be coming within 45 days of its receipt.

08/21/2001 Fax from FDA containing the final CAC report in response to the Mouse Carcinogenicity Special Protocol Assessment Report.

08/31/2001 FDA letter containing comments and recommendations in response to a special carcinogenicity protocol assessment dated July 6, 2001, Serial No. 017.

10/26/2001 Eric Nisbet-Brown, MD; Protocol No. C1CL670 0104; rash maculopapular.

11/30/2001 This amendment contains updated documentation in support of minor changes to the drug substance manufacturing process.

12/20/2001 Patricia Giardina, MD; Protocol No. ICL670 0104; urticaria acute, body temperature increased, fatigue, pruritus NOS.

12/20/2001 Patricia Giardina, MD; Protocol No. ICL670 0104; urticaria acute, pruritus NOS.

01/04/2002 Patricia Giardina, MD; Protocol No. ICL670 0104; urticaria acute, body temperature increased, fatigue, transaminases increased, pruritus NOS; follow-up.

01/15/2002 Patricia Giardina, MD; Protocol No. ICL670 0104; urticaria acute, body temperature increased, fatigue, transaminases increased, pruritus NOS; follow-up.

01/17/2002 Patricia Giardina, MD; Protocol No. ICL670 0104; urticaria acute, blood in stool, pruritus NOS; follow-up.

02/05/2002 FDA letter requesting an Annual Report or a request to withdraw IND.

02/14/2002 Request for an end of Phase II meeting to discuss the registration program.

02/25/2002 Patricia Giardina, MD; Protocol No. ICL670 0104; urticaria acute, blood in stool, pruritus NOS; follow-up.

02/26/2002 Fax from FDA containing information on the meeting to be held on April 9, 2002.

03/12/2002 This Briefing Book is being submitted in preparation for the End of Phase II Meeting scheduled for April 9, 2002.

03/27/2002 Annual Report covers the period of July 1, 2000, through June 30, 2001. Includes preclinical and clinical information, CMC changes and a revised investigator's Brochure dated May 7, 2001.

04/05/2002 Fax to FDA containing the final list of Novartis attendees for the End of Phase II Meeting on April 9, 2002.

04/09/2002 Fax from FDA containing the April 9, 2002, meeting roster and a copy of the responses passed out at the meeting to all attendees.

04/10/2002 This submission contains copies of overheads presented by Novartis at the End-of-Phase II meeting.

06/03/2002 FDA letter containing the minutes of the April 9, 2002, End of phase 2 meeting.

08/08/2002 In response to an FDA letter dated August 31, 2001, concerning Novartis' July 7, 2001 Request for Special Protocol Assessment, this correspondence contains the revised draft mouse carcinogenicity protocol for review.

08/22/2002 FDA letter indicating that the request, Serial No 003, for a special carcinogenicity protocol assessment is being reviewed.

09/19/2002 Fax from FDA containing the final CAC report in response to the Carcinogenicity Special Protocol Assessment request.

10/07/2002 FDA Letter containing comments on recommendations on the amendment dated August 8, 2002 (Serial No. 033) which requested a special mouse carcinogenicity protocol assessment.

10/21/2002 Annual Report covering the period of July 1, 2001, through June 30, 2002. Includes preclinical and clinical study/safety information.

10/23/2002 In reference to the final CAC report for the proposed 26 week oral, mouse carcinogenicity study, this correspondence contains responses to the CAC recommendations and conclusions and asks for the Division's concurrence before the study proceeds.

11/14/2002 Fax from FDA containing the final CAC report in response to the Carcinogenicity Special Protocol Assessment request.

11/18/2002 Submission containing a request for a special protocol assessment for Protocol No. C1CL670A0107 entitled, "A randomized, comparative, open label phase III trial on efficacy and safety of long-term treatment with JCL670 (5 to 40 mg/kg/day) in comparison with deferoxamine (20 to 60 mg/kg/day) in beta-thalassemia patients with transfusional hemosiderosis."

11/18/2002 Submission containing a request for a special protocol assessment for Protocol No. C1CL670A0108 entitled, "A multi-center, open-label, non-comparative, phase II trial on efficacy and safety of ICL670 (5 to 40 mg/kg/day) given for at least 1 year to patients with chronic anemias and transfusional hemosiderosis unable to be treated with deferoxamine."

12/03/2002 FDA Letter containing comments and recommendations on the October 23, 2002 (Serial No. 035) request for a special carcinogenicity protocol assessment.

12/05/2002 Correspondence to the Division in reference to requests for special protocol assessment and a letter received from the Office of Orphan Products Development which notified Novartis that deferasirox qualifies for orphan-drug designation.

12/13/2002 In reference to the End-of-Phase 2 meeting held on April 9, 2002, this correspondence requests a Special Protocol Assessment for Protocol No. C1CL670A0109 entitled, "An open label, phase II study to evaluate the safety, tolerability, pharmacokinetics and the effects on liver iron concentration of repeated doses of 10 mg/kg/day of ICL670 administered to sickle cell disease in patients with transfusional hemosiderosis."

12/20/2002 In reference to FDA's recommendation during the End of Phase II meeting held on April 9, 2002, this submission contains an application for Fast Track Designation.

01/03/2003 FDA letter containing responses to questions submitted in the request for a special clinical protocol assessment (Serial No. 36).

01/03/2003 FDA letter containing responses to questions submitted in the request for a special clinical protocol assessment (Serial No. 37).

01/15/2003 FDA letter notifying Novartis that the submission (Serial No. 039), that requested a special protocol assessment, is being reviewed.

01/20/2003 In reference to January 3, 2003, FDA special protocol assessment, this correspondence requests clarification on two points raised.

01/21/2003 This amendment contains a stability protocol for review.

01/30/2003 FDA letter containing responses to questions submitted in the request for a special clinical protocol assessment (Serial No. 39).

02/19/2003 This correspondence notifies FDA of a possible data manipulation that occurred at Covance Laboratories, Geneva, Switzerland.

02/19/2003 This correspondence response to issues raised in the January 3 and 30, 2003, FDA Special Protocol Assessment for protocols C1CL670A0107, C1CL670A0108, and C1CL670A0109.

02/21/2003 FDA letter stating that the December 20, 2002 request for fast track designation has been granted.

03/19/2003 A Proposed Pediatric Study request is submitted for the treatment of patients with sickle cell anemia (Protocol No. C1CL670A0110).

03/24/2003 Request for FDA review of the proposed proprietary name: Exjade.

03/26/2003 Teleconference with FDA to discuss the review status of the proposed stability protocol submitted January 21, 2003.

04/04/2003 Amendment providing for minor specifications to the drug substance and two new dosage strengths: 150mg tablets/KN3766078 and 500 mg tablets/KN3756087.

04/23/2003 Request for teleconference to discuss the clarification points raised in the Novartis communication dated January 20, 2003, regarding the Special Protocol Assessment for protocols 0107 and 0108.

04/23/2003 Correspondence responding to an FDA request for additional information concerning the March 24, 2003 submission requesting a review of a proprietary name candidate for ICL670.

05/08/2003 Facsimile from the FDA confirming the teleconference scheduled for June 16, 2003.

05/09/2003 Request for teleconference with Division to discuss options that may bring this product to market significantly earlier for a certain subset of patients who are in most need.

05/19/2003 New Investigator to Study No. C1CL670A 0107: Dr. E. Vichinsky; Study No. C1CL670 0108: Dr. E. Vichinsky; Study No. C1CL670 0109: Dr. B. W. Clowney.

05/22/2003 FDA letter containing comments and recommendations on amendments dated January 20, 2003 (Serial No. 041) and February 19, 2003 (Serial No. 044).

05/22/2003 Briefing material for June 16, 2003, teleconference to discuss the clarification points raised in January 20, 2003 correspondence that remain outstanding.

05/30/2003 In reference to the April 9, 2002, End of Phase II meeting, this submission contains a preclinical protocol, Study No. 0370030, an oral neonatal and juvenile development study in rats for review.

06/02/2003 New Protocol to Study No. 0117 entitled "A protocol to allow treatment with ICL670 for patients with or at risk of life-threatening complications of transfusional iron overload who are unable to tolerate other iron chelators because of documented severe toxicity.

06/05/2003 Submission of toxicology report "An oral neonatal and juvenile development dose range-finding study in rats", Study No. 0370003.

06/09/2003 Correspondence and supporting documentation for the use of Crono 30 infusion pumps in the ongoing clinical trials.

06/10/2003 Correspondence on the resolution of clarification points raised concerning the Special Protocol Assessment.

06/16/2003 Submission of briefing materials for the July 18, 2003 teleconference.

06/24/2003 In reference to the January 3, 2003 FDA Special Protocol Assessment for protocol ICL670A0108, this submission contains Amendment No. 1 to this protocol.

06/24/2003 In reference to the January 3, 2003 FDA Special Protocol Assessment for protocol ICL670A0108, this submission contains Amendment No. 1 to this protocol.

07/01/2003 New investigators to Study No. 0107: Drs. A. Cohen, E. Neufeld; Study No. 0108: Drs. M. Cunningham, M.R. Jeng, A. Cohen, S.D. Rifkin; Study No. 0109: Drs. A. Kutlar, P. Swerdlow.

07/03/2003 This submission contains Amendment No. 1 to the Final Study Report for CICAL670A0101 submitted March 23, 2001 (Serial No. 013).

07/07/2003 This correspondence responds to an FDA for additional information for the SQUID machines in preparation for the July 18, 2003 teleconference.

07/09/2003 Facsimile from the FDA containing responses to questions listed in the June 16, 2003, package for the July 18, 2003 teleconference.

07/16/2003 Cancellation of teleconference with the Division to discuss regulatory options that may bring this compound earlier to the market.

07/17/2003 New investigators to Study No. 0107: Drs. P.J. Giardina, M.R. Jeng; Study No. 0108: Dr. P.J. Giardina; Study No. 0109: Drs. E. Vichinsky, O.C. Onyekwere; Study No. 0117: Dr. M. Cunningham.

07/18/2003 FDA letter containing issues to be addressed concerning the proposed pediatric study request dated March 19, 2003.

07/30/2003 Amendment No. 2 to Study No. 0109.

08/01/2003 FDA containing comments and recommendations on amendments dated March 9, 2000 (Serial No. 005), January 9, 2001 (Serial No. 011), November 30, 2001 (Serial No. 020) and April 4, 2003 (Serial No. 074).

08/01/2003 FDA letter containing comments and recommendations on the new preclinical protocol, 0370030 dated May 30, 2003 (Serial No. 053) and a preclinical report for Study 0370003 dated June 5, 2003 (Serial No. 055).

08/21/2003 Response to the August 1, 2003, FDA review of toxicology protocol #0370030 submitted May 30, 2003.

08/27/2003 Annual Report covering the period of July 1, 2002 through June 30, 2003. Includes clinical study information, preclinical study information, CMC changes and investigator's brochure.

09/05/2003 This submission response to the CMC questions in reference to the August 1, 2003 FDA letter containing comments and recommendations on amendments dated March 9, 2000 (Serial No. 005), January 9, 2001 (Serial No. 011), November 30, 2001 (Serial No. 020) and April 4, 2003 (Serial No. 074).

09/08/2003 New investigator to Study No. 0107: Dr. A.A. Thompson; Study No. 0109: Dr. F.L. Wilson.

09/16/2003 In reference to the August 1, 2003, FDA review of the neonatal rat toxicology protocol #0370030, this correspondence requests a Type A Meeting to discuss the necessity of conducting a neonatal marmoset toxicology study.

09/24/2003 In reference to the Special Protocol Assessment (SPA) provided by FDA for Study C1CL670A0109 on January 30, 2003, this correspondence requests a Type A Meeting to discuss possible amendments to the protocol as solutions for the recruitment issue for this study.

09/30/2003 Facsimile from FDA containing information on the telecom scheduled for October 30, 2003.

09/30/2003 In reference to the September 16, 2003, Type A Meeting request, this submission contains relevant background information regarding the toxicology development program for this compound.

09/30/2003 In reference to the September 16, 2003, Type A Meeting request, this submission contains relevant background information regarding the recruitment issues and possible protocol amendment solution for Study C1CL670A0109.

10/07/2003 New investigator to Study No. 0109: Dr. M. Francisco.

10/16/2003 Submission of an addendum to the Briefing Book dated September 30, 2003, in preparation for the October 30, 2003 teleconference to discuss the FDA request to perform a neonatal marmoset study.

10/22/2003 Facsimile from FDA containing their responses to the questions listed in the October 7, 2003 background package for a Type A meeting.

10/23/2003 Facsimile from FDA containing their responses to the questions listed in the October 7, 2003 background package for a Type A meeting.

10/20/2003 New investigator to Study No. 0107: Drs. T. Coates, L. Rice, R. Wise, P. Kelly, A. Adewoye.

10/30/2003 FDA minutes of a teleconference regarding the neonatal marmoset monkey study.

11/20/2003 FDA letter containing minutes of the October 23, 2003 Type A meeting.

11/24/2003 Dr. Alan Cohen; Rash maculo-papular, pyrexia, palpitations, rash erythematous.

12/03/2003 Dr. Alan Cohen; Rash maculo-papular, pyrexia, palpitations, rash erythematous; Follow-up #1.

12/16/2003 Dr. Alan Cohen; Rash maculo-papular, pyrexia, palpitations, rash erythematous; Follow-up #2.

12/19/2003 New Investigator to Study No. 109: Dr. Rita Bellevue.

12/19/2003 FDA letter containing comments and recommendations on the CMC amendment dated September 5, 2003 (Serial No. 070).

12/23/2003 Amendment No. 3 to Study No. 0109.

01/05/2004 FDA letter responding to the request for an evaluation of the tradename "Exjade".

01/05/2004 FDA letter responding to the questions contained in the April 18, 2003 amendment regarding the March 19, 2003 Proposed Pediatric Study Report and the Division's letter denying the PPSR.

01/19/2004 New investigator to Study No. 0109: Drs. K.L. Hassell, S. R. Cataland, W.C. Owen.

01/19/2004 Amendment No. 2 to Study No. 0107. Amendment No. 0108 to Study No. 0108.

02/02/2004 New protocol to Study No. 0107E1 entitled "A 3-year open label, non-comparative extension to a randomized, comparative, open label phase II trial on efficacy and safety of long term treatment with ICL670 (5 to 40 MG/KG/day) in comparison with deferoxamine (20 to 60 MG/KG/day) in B-thalassemia patients with transfusional hemosiderosis; New Protocol to Study No. 0108E1.

02/04/2004 Annual update, November 21, 2002, November 20, 2003, for the Orphan Drug Designation number 02-1610.

03/02/2004 This correspondence informs the Division that Novartis is actively working to obtain additional information regarding the death of a patient (PHHO2004TN02870) reported March 1, 2004.

03/12/2004 New investigator to Study No. 0109: Dr. Julia Margarita Cruz, MD.

03/17/2004 Alan Cohen: headache, illusion, anxiety.

03/18/2004 Facsimile from FDA containing advise on safety reports, SN-103, 104 and 105.

03/23/2004 New protocol 2101 entitled "A single center, open-label two treatment randomized, two period, crossover study to evaluate the absolute bioavailability of a single 375 mg oral dose of ICL670 in the form of tablets compared to 130 mg ICL670 as an intravenous infusion in healthy volunteers". Investigator: K.C. Lasseter, MD. Also included are CMC and toxicology information to support the new dosage form, 90 mg.5ml ICL670 concentrate for solution for intravenous administration.

04/02/2004 Alan Cohen: Headache, illusion, anxiety; Follow-up #1.

04/09/2004 New protocol to Study No. 2102 entitled "A single-center, open label, two treatment randomized, two-period cross-over study to evaluate the effect of a single oral 20 mg/kg dose of ICL670 on the pharmacokinetics of daily 0.25 mg. oral administration of digoxin in healthy volunteers.

04/09/2004 In reference to the October 23, 2003 meeting, this correspondence informs the Division that the clinical development plan for assessing iron overload will be submitted end of May 2004.

05/13/2004 Response to FDA request for information regarding safety reports; Serial No. 103, 104 and 105.

05/18/2004 This letter authorizes the FDA to refer to this IND in support of an IND that will be filed by P. Greenberg, MD.

05/19/2004 Request for a Type A meeting to discuss whether 4-hydrazinobenzoic acid meets the requirements for a starting material.

05/21/2004 Request for a Type A meeting to discuss the juvenile animal model that will provide sufficient information on potential biliary toxicities to support use of ICL670 in children.

05/21/2004 In reference to the Special Protocol Assessment for study C1CL670A 0109, this submission requests a Type A meeting to discuss the acceptability of a replacement study design (C1CL670A 2201) for the intended sickle cell patient population.

05/24/2004 Facsimile from FDA containing requests for information regarding Serial No. 109 and Serial No. 115.

05/26/2004 New investigator to Study No. 0109: Z. Yasin, MD.

05/27/2004 FDA request for information regarding Serial No. 109 and Serial No. 115

06/02/2004 Submission of additional, corrected copies of Briefing Book submitted May 19, 2004.

06/03/2004 FDA letter stating that the requested meeting concerning a starting material is unnecessary since adequate justification was provided in the May 19, 2004 submission.

06/03/2004 Alan Cohen: Headache, illusion, anxiety; Follow-up #2.

06/07/2004 FDA letter containing details for the type A meeting scheduled for June 28, 2004.

06/08/2004 Amendment No. 1 to Study No. 2102.

06/11/2004 E-mail to FDA containing a list of participants and questions from the Briefing Book for the June 28, 2004 meeting.

06/11/2004 Submission of 2 Briefing Books in preparation for the June 28, 2004 meeting to discuss juvenile toxicology studies and the development program in patients with sickle cell disease and clinical trials on cardiac safety.

06/16/2004 Addendum to Briefing Book for June 28, 2004 meeting.

06/22/2004 This submission contains a revised Investigator's Brochure (Edition 7) and addendum as noted in the submission dated May 13, 2004.

06/24/2004 Facsimile from FDA containing responses to meeting questions listed in the June 11, 2004, background package.

06/25/2004 New Investigator to Study No. 0109; Drs. T. Coates, L. Frankel.

06/29/2004 New Investigator to Study No. 0109; Dr. Liesl Mathias, MD.

06/30/2004 In reference to an agreement reached at the October 23, 2004 meeting to discuss recruitment issues and protocol changes for Study ICL67000109 in patients with sickle cell disease, this submission contains a Briefing Book on methods to assess iron overload.

07/01/2004 This letter authorizes the FDA to refer to this IND to support an IND that will be filed by C. Schiffer, MD.

07/08/2004 New investigator to Study No. 0109; Drs. R. J. Labotka, A. A. Thompson.

07/08/2004 Dr. Patricia Giardina: Klebsiella sepsis, urosepsis, pulmonary hypertension, electrocardiogram abnormal, chest pain, dyspnoea, cardiac murmur, back pain, pyrexia.

07/16/2004 Submission of the final clinical pharmacology report Study No. 0101.

07/26/2004 FDA letter containing a copy of the minutes on June 28, 2004 to discuss issues regarding QTc and the need for non-rodent study.

07/26/2004 FDA letter containing minutes of the minutes on June 28, 2004 to discuss issues regarding QTc and the need for non-rodent study.

07/27/2004 Request for pre-NDA meeting to discuss the content of the submission to support the indication: treatment of chronic iron overload due to repeated blood transfusions.

07/28/2004 New Investigator to Study No. 107E1: Dr. Alan Cohen, MD; Study No. 109: Drs. J. Eckman, P.A. Lane, Jr., L.J. Bengamin, P.J. Giardina, L. Krishnamurti, M. Heeney, J. Kwiatkowski.

08/03/2004 E-mail to FDA regarding the proposed juvenile mouse tox study protocol.

08/03/2004 In reference to the June 28, 2004, meeting with the Division, this correspondence requests a review of the draft juvenile mouse toxicology study protocol.

08/11/2004 FDA letter providing details about the requested (July 27, 2004) pre-NDA meeting scheduled for October 1, 2004.

08/11/2004 Facsimile from FDA containing a pre-NDA granted letter and a request for additional copy of the submission that included information on the SQUID and MRI.

08/16/2004 Clinical report for Study No. 0115 (2 volumes).

08/18/2004 In response to the August 11, 2004 request, this submission contains an additional desk copy of the Briefing Book on methods to assess iron overload submitted June 30, 2004.

08/18/2004 In reference to the June 28, 2004 meeting, this correspondence responds to a request from the Division to review a copy of the full protocol for Study No. C1CL670A2122.

08/20/2004 Telecon with FDA regarding the status of the review of preclinical and clinical protocols submitted August 3 and 18, respectively.

08/25/2004 Annual Report covering the period June 29, 2003 through June 30, 2004. Includes clinical study information, preclinical study information and CMC changes.

08/30/2004 New Investigator to Study No. 0108E1: Drs. E. Vichinsky, M. Cunningham.

08/30/2004 New Investigator to Study No. 0107E1: Drs. A. Cohen, E. Neufeld; Study No. 0108E1: Dr. Alan Cohen.

08/31/2004 FDA letter containing comments and recommendations on the final draft protocol in mice submitted August 3, 2004, Serial. No. 157.

08/31/2004 Briefing book submitted in preparation for the October 1, 2004, pre-NDA meeting.

09/15/2004 Dr. Lennette Benjamin: Hypersensitivity, pyrexia, headache, disease progression, oedema peripheral, breast oedema, face oedema.

09/16/2004 E-mail to FDA regarding the moving of the hematologic products to the Oncology Division and the impact on the review.

09/16/2004 Teleconference with FDA regarding the review status of the QT protocol (Study No. 2122).

09/22/2004 Teleconference with FDA regarding orphan drug designation issues for the preNDA meeting scheduled for October 1, 2004.

09/29/2004 FDA letter containing comments on the protocol for Study No. C1CL670A2122 submitted August 18, 2004.

09/29/2004 New investigator to Study No. 0107E1: Drs. E.Vichinsky, M.R. Jeng, A.A. Thompson; Study No. 0108E1: Dr. M.R. Jeng; Study No. 0109: Drs. R. Wise, I. Prasannan.

09/29/2004 Amendment No. 3 to Study No. 107 and Study No. 108.

09/30/2004 Facsimile from FDA containing response to the questions listed in the August 31, 2004 background package.

09/30/2004 Dr. Lennette Benjamin: Hypersensitivity, pyrexia, headache, disease progression, oedema peripheral, breast oedema, face oedema; Follow-up #1.

09/30/2004 Dr. Patricia Giardina: Klebsiella sepsis, urosepsis, pulmonary hypertension, electrocardiogram abnormal, back pain, pyrexia, chest pain, dyspnoea, cardiac murmur; Follow-up #1.

10/31/2004 FDA letter containing comments on the protocol revisions for Study No. 0107 submitted August 18, 2004.

10/15/2004 Dr. Spero Cataland: Pancreatitis, cholelithiasis, sickle cell anaemia with crisis, abnormal pain, nausea, vomiting.

10/19/2004 FDA letter containing minutes of the pre-NDA meeting held on October 1, 2004.

10/20/2004 New protocol to Study No. 0109E1 entitled "A one year open label, non-comparative extension to a randomized, multicenter, phase II study to evaluate the safety, tolerability, pharmacokinetics and the effects on liver iron concentration of repeated doses of 5-30 mg/kg/day of ICL670 relative to deferoxamine in sickle cell disease patients with transfusional hemosiderosis."

10/21/2004 New Investigator to Study No. 0107E1: Dr. Patricia J. Giardina; Study No. 0108E1: Patricia J. Giardina; Study No. 0109 E1: Dr. Onyinye C. Onyekwere.

10/22/2004 Request for a type A meeting to discuss issues that have become apparent since the pre-NDA meeting and to seek guidance and agreement regarding management of their impact.

10/29/2004 Amendment No. 2 to Study No. 0107E1.

11/02/2004 In reference to the FDA letter dated September 29, 2004, this correspondence responds to questions on protocol 2122 (Serial No. 161).

11/02/2004 FDA letter responding to a request for a meeting (Type A) and containing the meeting specifics.

11/04/2004 Submission of background information for the teleconference scheduled for November 10, 2004 to seek FDA's input on the acceptability of an amended definition of the population for primary analysis of non-inferiority in Trial 0107.

11/05/2004	E-mails to/from FDA regarding information to be presented at the November 10, 2004, teleconference.
11/10/2004	Facsimile from FDA containing responses to Novartis' questions regarding Study 0107.
11/10/2004	FDA minutes of a meeting held November 10, 2004, to discuss the proposed amended definition of the population for primary analysis for Trial 0107.
11/12/2004	This correspondence responds to the FDA letter dated October 13, 2004, that contained comments and recommendations on the change in protocol submission for Study No. C1CL670A0107.
11/16/2004	Amendment No. 2 to Study No. 0108E1.
11/17/2004	This revised Proposed Pediatric Study Request contains responses to the July 18, 2003 FDA letter.
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11/18/2004	New protocol to Study No. 2122 entitled "A randomized, blinded, active placebo controlled, parallel group study to evaluate the cardiac safety of single doses of ICL670 (20 to 40 mg/kg) in healthy volunteers.
11/18/2004	New investigator to Study No. 107E1: Dr. Thomas Coates, MD.
11/18/2004	E-mail to FDA regarding the status of various IND amendments and the CMC section for the NDA under the Pilot 1 guidance.
11/19/2004	Teleconference with FDA to discuss the protocol amendment for Study 109E submitted October 20, 2004, Serial No. 177.
11/22/2004	New protocols: Study No. US02 entitled "An open label, safety and tolerability study of deferasirox for treatment of transfusional iron overload in low-risk and INT-1 myelodysplastic patients." Study No. US03 entitled "An open label, safety and tolerability study of deferasirox for treatment of transfusional iron overload in low-risk and INT-1 myelodysplastic patients using serum ferritin monitoring."

11/30/2004	Submission of a final report for bioavailability Study 2101.
11/30/2004	Submission of additional desk copies of the Proposed Pediatric Study Request submitted November 17, 2004.
<del>12/01/2004</del>	New protocol to Study No. 2201 entitled "A randomized, open-label, multi-center, phase II study to evaluate the safety and efficacy of oral ICL670 (deferasirox) 20 mg/kg/day relative to subcutaneous deferoxamine in sickle cell disease patients with iron overload from repeated blood transfusions.
12/22/2004	Amendment No. 4 to Study No. C1CL670A0109.
12/23/2004	Investigator's Brochure (Edition 8, replacing Edition 7 dated 08-Feb-2004).
12/23/2004	New investigator to Study No. 2122: Dr. Jerry M. Herron, MD.
01/04/2005	Amendment No. 3 to Studies Nos. 0107E1 and 0108E1.
01/14/2005	This CMC amendment provides technical documentation in support of the introduction of an additional clinical trial service form "Market Form (MF)".
01/24/2005	Amendment No. 1 to Study No. US02.
01/28/2005	Submission of Clinical Study Report No. 0106.
02/07/2005	Telecon with FDA regarding the revised PPSR submitted November 17, 2004 (Serial No. 186).
02/11/2005	Submission of the final clinical pharmacology study report (Study No. 2120).
03/02/2005	Amendment No. 1 to Study No. 0109E1.
03/14/2005	New investigator to Study No. 0109E1; Drs. E. Vichinsky, L. Rice, P. Kelly, M.F. Gonzalez, W.C. Owen; Study No. 0117: Dr. Patricia J. Giardina, MD.

03/18/2005 New Investigator to Study No. 0109E1: Drs. Richard J. Labotka, MD, Cameron Tebbi, MD.

03/21/2005 Protocol Amendment: After this Protocol was submitted November 24, 2004 numerous changes were made which were incorporated into the protocol as a complete revision, rather than an amendment.

03/25/2005 Submission of final clinical reports for studies: A0105, A0105E1, A0105F, A2101, A2102.

03/28/2005 Teleconference with FDA regarding revised PPSR submitted in November.

04/05/2005 FDA letter stating that based on the review of the current (November 17, 2004) proposed pediatric study request, the Division is unable to issue a Written Request.

04/07/2005 Submission of Clinical Study Report No. 0104 (6 volumes).

04/14/2005 Teleconference with FDA regarding the PPSR and upcoming NDA submission.

04/14/2005 Submission of Clinical Study Report No. C1CL670A0105E2 (6 volumes).

04/15/2005 Teleconference with FDA regarding PPSR/Written Request.

04/15/2005 Dr. Jacqueline Madden: Lymphadenopathy, sickle cell anaemia with crisis, pyrexia, chills, blood alkaline phosphatase increased, pain, granuloma.

04/19/2005 Teleconference with FDA regarding the Division's letter on the PPSR dated April 5, 2005.

04/20/2005 Teleconference with FDA to discuss the PPSR submitted November 17, 2004 and the non-issuance of a WR.

04/21/2005 Dr. Billy Clowney, MD: Sickle cell anaemia with crisis, disease progression, otitis media, angiopathy, haemolytic anaemia.

04/27/2005

Dr. Billy Clowney, MD: Sickle cell anaemia with crisis, disease progression, otitis media, angiopathy, haemolytic anaemia; Follow-up #1.

04/29/2005

Dr. Zahida Yasin: Pulmonary embolism, lobar pneumonia, chest pain, dyspnoea, night sweats, feeling hot.

05/02/2005

New investigator to Study No. 0109E1: Drs. A. Kutlar, J. Cruz, B.W. Clowney, C.D. Scher, S. Cataland, Z. Yasin.

05/05/2005

Dr. Zahida Yasin: Pulmonary embolism, lobar pneumonia, night sweats, feeling hot, chest pain, dyspnoea; Follow-up #1.

05/05/2005

Dr. Jacqueline Madden: Tuberculosis, sickle cell anaemia with crisis, lymphadenopathy, pyrexia, chills, blood alkaline phosphatase increased, pain, granuloma; Follow-up #1.

05/05/2005

Dr. Zahida Yasin: Catheter related complication, superior vena caval occlusion, infection, jugular vein distension, face oedema, local swelling, neck pain, dyspnoea, apnoea.

05/12/2005

New Protocol to Study No. 2203 entitled "A study to provide expanded access of EXJADE (deferasirox) to patients with congenital disorders of red blood cells and chronic iron overload from blood transfusions who cannot adequately be treated with other locally approved iron chelators.

05/12/2005

New Investigator to Study No. 0109E1: Drs. K.L. Hassell, R. Nuss.

05/12/2005

Teleconference with FDA to discuss treatment protocol.

05/18/2005

Amendment No. 5 to Study No. 0109: Amendment No. 1 to Study No. 2201: Amendment No. 2 to Study No. US02.

05/18/2005

This submission responds to a request to submit a copy of the informed consent and the Investigator's Brochure in support of the protocol submitted May 12, 2005, Serial No. 226.

05/23/2005 New Investigator to Study No. 0109E1: Dr. Andrew S. Freiberg. Study No. 0117: Drs. Vichinsky, L. Rice. Study No. 2201: Drs. L. Krishnamurti, C. Tebbi, A.A. Thompson, M.J. Haut. Study No. US03: Dr. J.M. Feigert.

05/31/2005 FDA letter regarding treatment use under the treatment protocol received May 13, 2005.

06/06/2005 Facsimile from FDA containing comments from the review of the informed consent document for a treatment protocol.

06/06/2005 Teleconference with FDA to discuss the Division's comments on protocol 2203 and the informed consent.

06/07/2005 Clinical information submission containing final reports for studies: 0105, 0106, 0107, 2121, 2122, 0107 and 0108.

06/07/2005 Revised treatment protocol 2203 and informed consent in 232 response to comments made at the June 6, 2005 teleconference.

06/07/2005 Teleconference with FDA regarding revised treatment protocol 2203 and Informed Consent.

06/08/2005 New Investigator to Study No. 109E1: Dr. L. Krishnamurti. Study No. 0117: Drs. P. Kelly, G. Puthenveetil. Study No. 2201: Drs. M.F. Gonzales, M. Blinder, M.T. Lee.

06/09/2005 FDA letter stating that there is no objection to the May 12, 2005 proposed treatment use of this drug.

06/09/2005 Facsimile from FDA containing a safe to proceed letter for Serial No. 226.

06/13/2005 Amendment No. 2 to Study No. 0109E1.

07/07/2005 New Investigator to Study No. US02: Dr. Charles Schiffer. Study No. US03: Dr. Pradyumna Phatak. Study No. 109E1: Drs. C. Roberts, M. Heeney, A.A. Thompson. Study No. 117: Dr. Rita Bellevue. Study No. 2201: Drs. O. C. Onyekwere, R.L. Wise, W.C. Owen, M. Heeney, M. Torres.

07/15/2005 New Investigator to Study No. 0109: Drs. R. Wise, V. Deas; Study No. 0109E1: Drs. O.C. Onyekwere, V. Deas, T. Coates, P. Pederzoli, T. Tran.

07/21/2005 Dr. Zahida Yasin: Pulmonary embolism, lobar pneumonia, night sweats, feeling hot, thrombosis, concomitant disease progression, chest pain, dyspnoea; Follow-up #2.

07/26/2005 New Investigator to Study No. US03: Drs. S. Goldberg, E. Rich; Study No. 109E1: Drs. P.S. Swedlow, R. Gardner, Latha Prasannan; Study No. 2201: Drs. A. Kutlar, C.D. Scher, C. Minniti, W. Smith

08/12/2005 New Investigator to Study No. US03: Dr. S. Ganguly. Study No. 109E1: Drs. F.L. Wilson, P. Lane, L.J. Benjamin, T. Coates, P.J. Giardina, L. Mathias, J. Kwiatkowski, B.U. Mueller. Study No. 2201: Drs. R.J. Labotka, L. Mathias, A. Christodoulou-Pefkarou, S. Rao, Z. Yasin, J. Glass.

08/18/2005 Amendment No. 4 to Study No. 0108E1.

08/25/2005 Amendment No. 4 to Study No. 0107E1.

08/30/2005 Annual Report covering the period July 1, 2004 through June 30, 2005. Includes clinical study information, preclinical information and CMC changes.

08/31/2005 Amendment No. 1 to Study No. US03.

09/14/2005 New Protocol to Study No. US04 entitled "An open label trial evaluating cardiac T2 in B-thalassemia patients on deferasirox (ICL670) treatment for 18 months.

09/14/2005 New Investigator to Study No. US03: Drs. E. C. Besa, B. Powell, A. Raza, L. Rice, W.G. Harker; Study No. 2201: Drs. R. Gardner, A.D. Campbell.

09/21/2005 New Investigator to Study No. US02: Dr. C.A. Koller. Study No. US03: Drs. K. McDonagh, S. Cataland, N.J. DiBell, D.P. Steensma, K.R. Meehan. Study No. 0107E1: Dr. M.R. Jeng. Study No. 2201: Drs. E. Vichinsky, M. Heiny, B. Files, R.P. McCaffrey, L.S. Frankel, J.P. Cain, L. Hillard.

10/10/2005 New Investigator to Study No. US02: Dr. P. Greenberg. Study No. US03: Drs. C. Chay, J.R. Eckardt, B. Kaplan, A. Moreno-Aspitia. Study No. 109E1: Drs. M. Jeroudi, R. E. Ware. Study No. 2201: H.I. Saba. Study No. 2203: Dr. B. Lewis.

10/10/2005 Amendment No. 1 to Study No. 2203.

10/10/2005 New Investigator to Study No. US02: Dr. P. Greenberg. Study No. US03: Drs. C. Chay, J.R. Eckardt, B. Kaplan, A. Moreno-Aspitia. Study No. 109E1: Drs. M. Jeroudi, R. E. Ware. Study No. 2201: H.I. Saba. Study No. 3303: Dr. B. Lewis.

**NDA PERIOD**

12/15/2004                      Teleconference with the FDA for a preassigned NDA number (NDA 21-882).

01/04/2005                      Teleconference with FDA regarding filling out the user fee sheet and 356H form since the application is a rolling submission.

01/10/2005                      This submission contains a Reviewable Unit (RU) for the CMC section of the original application. The remaining sections will be submitted in April 2005. ICL670 is indicated for the treatment of chronic iron overloaded due to blood transfusions [1CD; electronic submission in REDI].

01/12/2005                      Emails to/from FDA regarding an Advisory Committee Meeting.

01/26/2005                      FDA letter acknowledging receipt of the reviewable unit of the CMC section of the original NDA for ICL670A (deferasirox) tablets, dated January 10, 2005.

04/29/2005                      In reference to the January 10, 2005 submission of the CMC Reviewable Unit, this submission completed the original NDA application.

05/10/2005                      CMC Amendment provides for updated product stability data.

05/16/2005                      Teleconference with FDA regarding applicant orientation meeting scheduled for June 29, 2005.

05/20/2005                      Response to request for information regarding patient enrolment by study center for studies 0107, 0108, and 0109 (paper submission).

05/27/2005                      In reference to the reviewable unit (CMC) submitted January 10, 2005 this submission contains Quality Overall Summary documents that were missing from that application.

06/03/2005 E-Mail to FDA regarding the agenda for the June 29, 2005 NDA orientation meeting, specifically the outline of clinical data presentation.

06/07/2005 Teleconference with FDA regarding revised treatment protocol 2203 and Informed Consent.

06/13/2005 Teleconference with FDA to discuss that ICL670 would be brought to the Blood Products Advisory Committee because it was a New Molecular Entity. FDA also reinforced that the Division would meet with NVS prior to the Advisory Committee meeting to discuss contents and issues that will be discussed at the meeting. FDA confirmed that the Priority Review Letter will be sent out within a week of this conversation.

06/17/2005 FDA letter acknowledging receipt of original NDA.

06/21/2005 Facsimile from the FDA requesting preclinical information, specifically datasets for the 2-year rat carcinogenicity study #17022 and the 26-week oral gavage carcinogenicity study in p53 heterozygous.

06/21/2005 Teleconference with FDA to discuss the applicant orientation meeting scheduled for June 29, 2005.

06/24/2005 E-mail to FDA listing the NVS attendees for the June 29, 2005 Advisory Committee Meeting. Additionally, NVS confirmed that the preclinical datasets, requested by FDA on June 21, 2005, will be FedExed by July 1, 2005 in electronic format.

06/29/2005 Minutes of the June 29, 2005 Applicant orientation review meeting (NDA review) with the Division of GI/Coagulation drug products.

06/29/2005 Response to FDA request for datasets for the 2-year rat carcinogenicity study #17022 and the 26-week oral gavage carcinogenicity study in p53 heterozygous mice.

07/07/2005

FDA Discipline Review Letter identifying deficiencies in the Drug Substance, Drug Product and Labeling sections of the Exjade NDA submitted under the Continuous Marketing Application (CMA)-Pilot-1 program.

~~07/08/2005~~

Amendment to a pending application providing the final juvenile mouse toxicology report 0480148. The version submitted in the original NDA has undergone QA by NVS and no changes to the results or conclusions have resulted by this QA. The only changes were editorial in nature.

07/11/2005

Facsimile from the FDA requesting the historical control data for the carcinogenicity rat study 017022 and mouse study 0270117 covering 3-5 years prior to the end of the in-life phase.

07/11/2005

Response to FDA request for information confirming that Exjade is not marketed in any country at this time.

07/12/2005

Emails to/from FDA for the period covering June 24 through July 12, 2005 regarding the list of NVS attendees for the June 29, 2005 review meeting. It further discusses NVS June 29, 2005 response to FDA's request for historical control data for the carcinogenicity rat study 017022 and the study in p52 mice.

07/14/2005

FDA Filing Communication Letter advising that FDA has completed the filing review of the new drug application and that it is sufficiently complete to permit a substantial review. FDA also identified potential review issues pertaining to the clinical information.

07/18/2005

Teleconference with FDA, Blood Products Advisory Committee, regarding the September 29, 2005 advisory committee meeting.

07/28/2005

Amendment to a Pending NDA (CMC) is in response to FDA e-mail, dated 21-Jul-2005, requesting submission of the categorical exclusion document of the environmental assessment.

08/03/2005 Teleconference with FDA during which was discussed the tentative agenda and logistics for the September 29, 2005 advisory committee meeting.

08/11/2005 Teleconference with FDA advising that they could not locate the SAS data sets for the rat carcinogenicity data. As per the FDA reviewer, it appeared that only the mouse data was included in the June 29, 2005 reply to a request for information. The rat carcinogenicity SAS data sets were submitted on CD-ROM to FDA via FedEx on August 15, 2005.

08/15/2005 This correspondence includes the SAS data sets for the rat carcinogenicity data requested by FDA and is a follow-up to the June 29, 2005 FDA request for information.

08/26/2005 Briefing Book submitted to FDA/CDER/SACS in paper and electronically for the blood products advisory committee meeting scheduled for September 29, 2005 for the proposed indication of the treatment of chronic iron overload due to blood transfusions in adults and pediatric patients.

08/29/2005 E-submission of the 120-day safety update.

09/08/2005 E-Mails to/from FDA containing the redacted FDA background package for the September 29, 2005 Blood Products Advisory Committee meeting.

09/09/2005 Facsimile from the FDA regarding CDRH reviewer's request for clarifications concerning BLS measurements using the SQUID magnetometer.

09/12/2005

Teleconference Pre-AC meeting to discuss presentations for the September 29, 2005 Blood Products Advisory Committee meeting. The focus was mainly on the pivotal study 0107, but commented that similar slides would be shown for studies 0108 and 0109. In response to FDA's inquiry regarding the efficacy data for study 0109, which was not presented in the NDA, NVS stated that it was submitted in the 120-day safety update. FDA stated that these data could only be brought in if there were a second review cycle or later as a supplement.

09/12/2005

FAX from FDA transmitting the meeting roster for the Pre-AC meeting scheduled for September 12, 2005.

09/16/2005

General Correspondence: Response to Information Request addresses the CDRH reviewer's request for clarifications concerning BLS measurements using the SQUID magnetometer.

09/19/2005

Email to FDA responding to request for a table, which provides an accounting of patients treated with ICL670 that was included in the NDA.

09/19/2005

PAD, C-ICL-1001 Coming Soon Ad, PLT, ICL-1004 Coming Soon teaser.

09/20/2005

General Correspondence: Response to Information Request addresses the CDRH reviewer's request for clarifications concerning BLS measurements using the SQUID magnetometer.

10/03/2005

TELECON with FDA regarding post-approval commitments. FDA outlined several criteria that the sponsor must meet with accelerated approval process. NVS confirmed the October 18 telecon with FDA to discuss commitments, at which time, NVS also confirmed that the PI submitted with the 120-day safety update, should be used for FDA review.

10/05/2005 E-MAIL to FDA as a follow-up to October 3, 2005 teleconference regarding clarification of post-approval commitments, namely, biopsy issue, the issue of safety in children 2-6 years, and accelerated approval impact on promotional materials, due to the lack of the final labeling.

10/06/2005 TELECON with DDMAC regarding pre-clearance of all promotional pieces as a commitment of the accelerated approval process. NVS informed DDMAC that we were not aware that Exjade would be undergoing accelerated approval and that on September 19, 2005, NVS submitted a Coming Soon AD and a Coming Soon Teaser upon first use.

10/12/2005 E-MAILS to/from FDA regarding proposed labeling, specifically dosage and administration section.

10/14/2005 This submission contains draft professional promotional material Expanded PI (ICL-OT-0031-A); Coming Soon Panel (ICL-EX-0058-A); Now Available Panel (ICL-EX-0030-A); Promotional Giveaways (ICL-PM-0065-A, ICL-PM-0065-B, ICL-PM-0065-C, ICL-PM-0065-D, ICL-PM-0065-E); Exjade Website Homepage - Version 1 (ICL-WS-0067-A).

10/18/2005 TELECON and meeting minutes from teleconference of October 18, 2005 with FDA regarding the Post-Approval Commitments.

10/19/2005 This submission is in response to FDA's post-approval commitment request for analyses of biopsy data on size and correlation with success rates, serum ferritin, and LIC. In addition, this submission constitutes the official copy of documentation sent to FDA via secure e-mail on October 17, 2005.

10/20/2005 TELECON with DDMAC requesting the review status of draft promotional material submitted October 14, 2005.

10/21/2005 E-MAIL from FDA regarding post-approval comments and instructions to disregard two comments, which have been addressed.

10/21/2005 TELECON with DDMAC regarding DTC promotional material. NVS plans to submit DTC pieces by the end of October or early November.

10/21/2005 This submission contains post-approval commitments based on comments received during the October 18, 2005 teleconference. In addition, this documentation constitutes the official copy of information sent to FDA via secure e-mail on October 21, 2005.

10/24/2005 TELECON w/DDMAC regarding professional promotion materials. DDMAC encouraged NVS to submit all our materials before the approval date, even though the label is not finalized, in order to avoid being locked out of using promotional materials during the 120 day post-approval.

10/25/2005 E-MAILS to/from FDA regarding the revised version of the post-approval commitments, as well as the dosage and Administration sections of the PI. FDA requested information on what is the mg/mL concentration after reconstitution for each vial size for each diluent amount to be added and what is the amount of total drug content after reconstitution.

10/25/2005 E-MAILS to/from FDA regarding comments received on the labeling received October 21, 2005, specifically the information contained within the parentheses, as well as the additional language added (do not chew or swallow whole). FDA confirmed that the language should be included and that the established name should appear in the parentheses.

10/27/2005 This submission contains revised draft labeling, as per FDA comments of October 21, 2005. The PI was sent to FDA via secure e-mail on October 26, 2005 and this submission constitutes the official copy.

10/27/2005	E-MAILS to/from FDA responding to FDA's request for information on what is the mg/mL concentration after reconstitution for each vial size for each diluent amount to be added and what is the amount of total drug content after reconstitution.
10/31/2005	This submission contains draft professional promotional materials for informational use only.
10/31/2005	This submission contains draft Direct-to-Consumer (DTC) promotional material.
10/31/2005	This submission contains Direct-to-Consumer (DTC) promotional material for informational use only.
10/31/2005	This submission contains draft professional promotional material.
11/01/2005	E-MAILS from FDA regarding post-approval commitments and language included in the PI.
11/01/2005	E-MAILS from FDA confirming that comment #5 does need study start and final report submission, as well as rewording.
11/01/2005	This correspondence contains revised draft labeling and post-approval commitments, which were received from FDA on October 28, 2005. This submission constitutes the official copy of these documents, which were sent to FDA via secure e-mail on October 31, 2005.
11/01/2005	This letter is to clarify that the EXJADE professional promotional materials submitted on October 14, 2005 were mistakenly submitted with FDA form 2253, when the intent of the submission is for Advisory Comments per sub-part H.
11/02/2005	E-MAIL from FDA containing the approval letter and approved PI.
11/02/2005	E-MAILS to/from FDA regarding PMC PIT and revisions to the PI.

11/02/2005 E-MAIL responding to FDA request for information on the NOEL study number 971974 for the PAC-PI commitment.

11/03/2005 FDA LETTER responding to NVS request for comments for proposed launch advisory submitted on October 14, 2005. These comments are provided using a draft version of the labeling and DDMAC advises NVS to update promotional materials to reflect the information available in the final approved PI. MACMIS ID # 13812

11/04/2005 TELECON from DDMAC confirming receipt of the Exjade launch DTC materials. However, FDA comments would not be received within 30 days.

11/04/2005 This correspondence contains a waiver request under CFR 314.90(a) to submit Form 3500A for adverse experiences determine to be both non-serious and labeled in the periodic safety report.

11/04/2005 TELECON with DDMAC to confirm receipt of the launch DTC materials. DDMAC stated that there is a backlog at DTC and would not be able to furnish comments within 30 days.

11/07/2005 TELECON w/DDMAC regarding advisory comments on the promotional pieces submitted on October 14, 2005.

11/08/2005 E-MAIL to FDA requesting information from the Agency regarding updated information for the PI and the correct method to report the changes.

11/08/2005 TELECON with DDMAC DTC group regarding the launch of the DTC materials. DDMAC requested that NVS identify which pieces were highest priority. NVS will identify the 5-6 priority items for DDMAC review and comment.

11/10/2005 PAD, ICL-AD-0018A Journal Ad. PEP, ICL-EX-0030A Convention panel.

11/15/2005

Final printed labeling for approved NDA 21-882. There was a minor editorial change made to the package insert included in the approval letter of November 2, 2005, regarding the tablet imprint. This minor change will be described in the annual report.

11/16/2005

E-MAIL to DDMAC-DTC group identifying the priority items for advisory comments.