

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125276

OTHER REVIEW(S)



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: December 17, 2009

To: Bob Rappaport, M.D., Director
Division of Analgesia, Anesthesia, and Rheumatology Products

Through: Kellie Taylor, Pharm.D., M.P.H., Team Leader *Kellie Taylor 12/17/09*
Carol Holquist, R.Ph., Director *Carol Holquist 12/17/09*
Division of Medication Error Prevention and Analysis

From: Tara Turner, Pharm.D., Safety Evaluator *T. Turner 12/17/09*
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Actemra (Tocilizumab) Injection
80 mg/4 mL; 200 mg/10 mL; 400 mg/20 mL

Application Type/Number: BLA# 125276/0

Applicant: Hoffmann-LaRoche Inc.

OSE RCM #: 2009-1377

CONTENTS

1	BACKGROUND	1
1.1	Introduction	1
1.2	Regulatory History	1
2	METHODS AND MATERIALS.....	1
3	RECOMMENDATIONS	1
3.1	Comments to the Division.....	1
3.2	Comments to the Licensee.....	2
	APPENDICES	4

1 BACKGROUND

1.1 INTRODUCTION

This review is written in response to a July 31, 2009 request from the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) for evaluation of the labels and labeling of Actemra to identify areas that could contribute to medication errors. The Licensee submitted proposed container labels, carton and insert labeling for our review and comment.

1.2 REGULATORY HISTORY

During the first review cycle for the subject BLA, DMEPA reviewed the draft labels and labeling submitted by the Licensee (see OSE RCM # 2007-2566; dated July 28, 2008). These comments were communicated to the Applicant. At the conclusion of the first review cycle, the Agency issued a complete response letter, dated September 17, 2008. A resubmission, dated July 8, 2009, was received from the Licensee, including revised labels and labeling in addition to a Risk Evaluation and Mitigation Strategy (REMS). The REMS will be reviewed by OSE under separate cover. The revised labels and labeling do not reflect all of the revisions suggested in OSE review # 2007-2566.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used the principles of Human Factors and Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels, carton and insert labeling submitted July 8, 2009 (see Appendices A through C).

3 RECOMMENDATIONS

Our evaluation noted areas where the presentation of information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. We provide general recommendations for all product labels and labeling in *Section 3.1 Comments to the Division* for discussion during the review team's labeling meetings. *Section 3.2 Comments to the Licensee* contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Licensee prior to approval. Please note that some of these recommendations were outlined in DMEPA's previous review (see OSE RCM# 2007-2566; dated July 28, 2008), but were not implemented by the Licensee in the revised proposed labels and labeling.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Licensee with regard to this review. If you have further questions or need clarifications on this review, please contact Abolade (Bola) Adeolu, Project Manager, at 301-796-4264.

3.1 COMMENTS TO THE DIVISION

A. General Comments for All Labels and Labeling

1. We defer to the Office of Biotechnology Products (OBP) review team for designation of the established name and dosage form of this product. It is currently presented as "tocilizumab _____ for IV infusion" on the container labels and carton labeling and as "tocilizumab (_____ for intravenous infusion" in the insert labeling. It is our understanding that OBP intends to recommend the following presentation of the dosage form and route of administration: "Injection" and "For Intravenous Infusion". We concur with this recommendation and find that it provides improved clarity. The approved established name and dosage form should be revised accordingly and presented consistently across all product labels and labeling.

b(4)

- We note that the Licensee submitted two distinct panels each for the 80 mg/4 mL and 400 mg/20 mL container labels and carton labeling [strength presented in white font (Figures 1 and 3) versus black font (Figures 2 and 4)] in accordance with a previous OBP request. DMEPA prefers the white font because of improved contrast and readability compared to the black font on the green and red color bars. The 200 mg/10 mL strength was only presented with a yellow color bar and black font, which is acceptable to DMEPA (Figure 5).

Figure 1

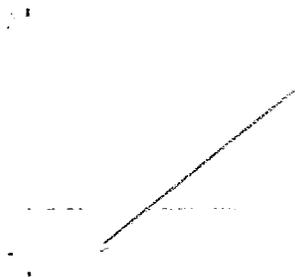
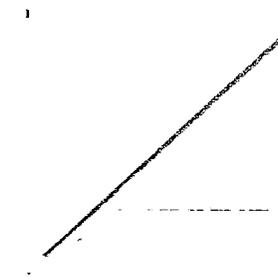


Figure 2



b(4)

Figure 3

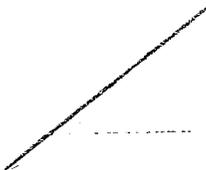


Figure 4

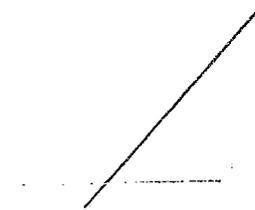
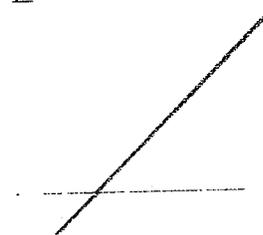


Figure 5



b(4)

B. Insert Labeling

- No comments at this time.

3.2 COMMENTS TO THE LICENSEE

A. Container Labels and Carton Labeling

- For all container labels and carton sizes, delete the number "1" which precedes "mL" in the statement of strength ("20 mg in 1 mL") located immediately beneath the total drug content. Revise to read as follows:

80 mg/4 mL	200 mg/10 mL	400 mg/20 mL
(20 mg/mL)	(20 mg/mL)	(20 mg/mL)
- Revise the route of administration and single use statements, which are currently presented as one combined statement "For IV single use only after dilution" as follows:
 - "For intravenous infusion only after dilution"
 - "Single use only; discard unused portion"

B. Container Labels

1. If space permits, add "Protect from light" to the storage requirements (as presented on the carton labeling).

10 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Other Reviews- 1



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: December 8, 2009

To: Bob A. Rappaport, MD, Director
**Division of Anesthesia, Analgesia, and Rheumatology
Products (DAARP)**

Through: Mary Willy, PhD, Deputy Director *Mary Willy 12/8/09*
Division of Risk Management (DRISK)

LaShawn Griffiths, MSHS-PH, BSN, RN *LaShawn Griffiths*
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Sharon R. Mills, BSN, RN, CCRP *Sharon R. Mills 12/8/09*
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): ACTEMRA (tocilizumab)

**Application
Type/Number:** BLA 125276/0

Applicant/sponsor: Hoffman La-Roche

OSE RCM #: 2009-1376

1 INTRODUCTION

On July 9, 2009, Roche submitted a Complete Response to the Agency's Complete Response (CR) letter dated September 17, 2008. In the CR letter, the Agency cited deficiencies in the application, including nonclinical, labeling, and other areas. Additionally, the Applicant was informed that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for ACTEMRA (tocilizumab). This review is written in response to a request by the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) included as part of their Complete Response. Please let us know if DAARP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant. The proposed REMS is being reviewed by DRISK and will be provided to DAARP under separate cover.

2 MATERIAL REVIEWED

- Draft ACTEMRA (tocilizumab) Prescribing Information (PI) submitted July 9, 2009
- Draft ACTEMRA (tocilizumab) Medication Guide (MG) submitted on July 9, 2009

3 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

15 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

CC list:

DARP:

Bob A. Rappaport
Sarah Okada
Jeff Siegel
Kathleen Davies

OSE:

Claudia Karwoski
Mary Willy
Mary Dempsey
LaShawn Griffiths
AboladeAdeolu
Cherye Milburn

DDMAC:

Twyla Thompson
Wayne Amchin

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: August 27, 2008

TO: Sharon Turner-Rinehardt, Regulatory Project Manager
Sarah Okada, M.D. Medical Officer
Jeffrey Siegel, M.D. Medical Team Leader
Division of Anesthesia, Analgesia and Rheumatology Products

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125276

APPLICANT: Hoffman-La Roche

DRUG: Actemra (tocilizumab)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Treatment of moderately to severely active Rheumatoid Arthritis (RA)

CONSULTATION REQUEST DATE: March 5, 2008

DIVISION ACTION GOAL DATE: September 16, 2008
PDUFA DATE: September 18, 2008

I. BACKGROUND:

Tocilizumab is a humanized monoclonal antibody targeting the interleukin-6 receptor (IL6R). The application represents the first for this class of agents (IL-6 inhibitors) and tocilizumab is a new molecular entity. IL-6 is a pleiotropic pro-inflammatory cytokine that has been shown to be involved in multiple processes, including inflammatory processes pathogenic in Rheumatoid Arthritis (RA). The application seeks approval for tocilizumab alone or in combination with methotrexate (MTX) or other disease modifying anti-rheumatic drugs (DMARDs) in the treatment of adult patients with moderately to severely active Rheumatoid Arthritis. Tocilizumab is currently approved only in Japan.

The goals of the inspections were assessment of safety and of the primary efficacy endpoint of the proportion of subjects with an ACR20 response (a validated composite index of response) at week 24. The ACR core set variables are:

1. Swollen/tender joint count (SJC/TJC). 66 joints are assessed for swelling and 68 joints are assessed for tenderness
2. Patient's global assessment of disease activity as assessed on a 100mm horizontal Visual Analogue Scale (VAS)
3. Physician's global assessment of disease activity as assessed on a VAS
4. Patient's assessment of pain assessed on a VAS
5. Acute Phase Reactants: high sensitivity C-reactive protein (CRP) or Erythrocyte Sedimentation Rate (ESR). The CRP is preferred because it is analyzed centrally. The ESR is to be used if CRP is missing.
6. Health Assessment Questionnaire Disease Index (HAQ-DI) using the Stanford HAQ-DI

For the US sites, site selection was based on the sites enrolling the largest number of subjects. The following are the reasons for the Mexican sites:

- Dr. Lugo's results did not appear excessive or remarkable; however, he enrolled the highest number of subjects among the investigators, with 53 subjects total in studies WA17822, WA17824, and WA18063.
- Dr. Ramos-Remus' subjects' results for WA17822 were perhaps better than expected, however his 22 subjects comprised only 3.5% of the total study population. He also enrolled a high number of subjects overall, with 43 subjects total in studies WA17822, WA17824, and WA18062.
- Dr. Irazoque's site was chosen because, for WA17823, subjects demonstrated a very low placebo response rate. She also enrolled the second highest number of subjects with 34 (2.8% of the total). She did not participate in other pivotal studies.

The protocols inspected were:

- A. WA 17822 entitled "A randomized, double-blind, parallel group study of the safety and reduction of signs and symptoms during treatment with MRA (tocilizumab) versus

placebo, in combination with methotrexate, in patients with moderate to severe rheumatoid arthritis.”

- B. WA 17823 entitled “A randomized, double-blind, parallel group study of the safety and prevention of structural joint damage during treatment with MRA (tocilizumab) versus placebo, in combination with methotrexate, in patients with moderate to severe active rheumatoid arthritis.
- C. WA 17824 entitled “A randomized, double-blind, double-dummy, parallel group study of the safety and efficacy of MRA (tocilizumab) monotherapy, versus methotrexate (MTX) monotherapy, in patients with active rheumatoid arthritis.
- D. WA 18062 entitled “A randomized, double-blind, placebo-controlled, parallel group study of the safety and reduction of signs and symptoms during treatment with MRA (tocilizumab) versus placebo, in combination with methotrexate in patients with moderate to severe active rheumatoid arthritis and an inadequate response to previous anti-TNF therapy.
- E. WA 18063 entitled “A randomized, double-blind, placebo-controlled, parallel group study of the safety and efficacy of MRA (tocilizumab) in patients with moderate to severe active rheumatoid arthritis and an inadequate response to current DMARD therapy.

II. RESULTS (by Site):

Name of CI or Sponsor Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
/	WA 17823/ 30 subjects, WA18062/ 10 subjects	April 29 to May 5, 2008	VAI
CI: Michael Fairfax Arthrocare-Arthritis Care & Research, 3330 N. 2nd Street, Suite 601, Phoenix, AZ 85012	WA17824/ 5 subjects, WA18063/ 21 subjects	April 15 to 25, 2008	NAI

b(4)

CI: Gustavo Lugo-Zamudio Hospital Juarez de Mexico Av. Instituto Politecnico Nacional No. 5160, 3° Piso, Servicio de Reumatologia, Col. Magdalena de las Salinas, 07760 Mexico City, Mexico	WA17822/ 23 subjects WA17824/ 10 subjects WA18063/ 20 subjects	July 7 to 11, 2008	Pending (Preliminary classification OAI)
CI: Cesar Ramos-Remus Unidad de Enfermedades Cronico Degenerativas, Colomos 2292, Col. Providencia Guadalajara, 44620, Jalisco, Mexico	WA17822/ 22 subjects WA17824/ 14 subjects WA18063/ 7subjects	June 23 to 27, 2008	Pending (Preliminary classification VAI)
CI: Fedra Irazoque- Palazuelos Centro Medico Nacional "20 de Noviembre" ISSSTE, Av. Felix Cuevas No. 540, Torre de Consulta Externa, Piso 8, Col. Del Valle, 03229, Mexico City, Mexico	WA17823/ 34 subjects	June 30 to July 4, 2008	Pending (Preliminary classification VAI)
SPONSOR Hoffman-La Roche 340 Kingsland Street, Nutley, New Jersey 07110- 1199	WA17822, WA 17823 WA17824, WA18062 WA18063	April 15- May 22, 2008	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1.

b(4)

- a. **What was inspected:** For Protocol WA 17823, 30 subjects were enrolled. All consent documents were reviewed and data for 15 subjects were reviewed. For Protocol WA18062, ten subjects were enrolled and all consent documents and

data were reviewed. The assignment originally requested inspection of WA17824 that contained 3 subjects. In discussion with the sponsor, it was determined that [redacted] was not the primary investigator at this site and inspection of these records was not conducted.

b(4)

- b. **General observations/commentary:** Concerning data integrity, verification of subject questionnaires and VAS was not possible because the subject instruments did not have a place for initials of the person completing the form. The site does not calculate the HAQ-DI directly so there is no source document for this component of the ACR at the site to compare to data listings submitted in the BLA.

For Study WA18062 [redacted] did not ensure that the investigation was conducted according to the investigational plan. Specifically:

b(4)

- The protocol stated that subjects with a "History of severe allergic or anaphylactic reactions to human, humanized or murine monoclonal antibodies" should be excluded from the study, but Subject 5894 was enrolled with a history of anaphylactic reaction to Remicade in violation of the exclusion criterion.
- The protocol stated that subjects within 1 year prior to randomization, were to have experienced an inadequate response to treatment with etanercept, infliximab or adalimumab because of toxicity or inadequate efficacy (etanercept \geq 3 months at 25 mg twice a week (or 50 mg weekly), or at least 4 infusions of infliximab at \geq 3 mg/kg or adalimumab at a minimum of 40 mg every other week for \geq 3 months), but Subject 5893 who had not had etanercept since January 11, 2003 was enrolled and had study drug administered on February 1, 2006.

These violations were reported in the BLA by the sponsor. The clinical investigator (CI) reported these violations to the IRB and took corrective action in a memo dated August 22, 2006.

- c. **Assessment of data integrity:** Data for this site appear acceptable in support of the pending application.

2. Michael Fairfax
Arthrocare-Arthritis Care & Research
3330 N. 2nd Street
Suite 601
Phoenix, AZ 85012

- a. **What was inspected:** For protocol 17824, at this site, five subjects were screened and three subjects completed the study. For protocol 18063, at this site, 21 subjects were screened and 20 subjects completed the study. Review of all consent forms for WA17824 and 10 of 21 consent forms for Protocol WA18063 did not show any objectionable findings. All enrolled subjects met all inclusion/exclusion criteria and

records existed documenting screening. No discrepancies were found in the comparison of source documents to sponsor supplied databases. The following databases were compared to the source documents: swollen joint count, tender joint count, patient global VAS, Physician VAS, Patient pain VAS, and ESR. For the five subjects enrolled Protocol WA17824, patient diaries were also reviewed with no discrepancies.

- b. **General observations/commentary:** Concerning data integrity, verification of subject questionnaires and VAS was not possible because the subject instruments did not have a place for initials of the person completing the form. Verification of the Health Assessment Questionnaire Disease Index (HAQ-DI) could not be done at the site because the value for the HAQ-DI was calculated centrally. There were no objectionable findings.
- c. **Assessment of data integrity:** Data for this site appear acceptable in support of the pending application.

- 3. Gustavo Lugo-Zamudio
Hospital Juarez de Mexico Av.
Instituto Politecnico Nacional No. 5160, 3° Piso, Servicio de Reumatologia,
Col. Magdalena de las Salinas, 07760
Mexico City, Mexico

Note: Observations noted for this site are based on the Form FDA 483, Inspectional Observations and communications from the FDA Investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** For Protocol WA 17822, Dr. Lugo-Zamudio screened 28 subjects, enrolled 23 subjects, 22 subjects completed the study and 2 records were reviewed during the inspection. For Protocol WA 17824, Dr. Lugo-Zamudio screened 16 subjects, enrolled 10 subjects who all completed the study and 2 records were reviewed during the inspection. For Protocol 18063, Dr. Lugo-Zamudio screened 31 subjects and enrolled 20 subjects. No records were reviewed for this study.
- b. **General observations/commentary:** The following observations were noted on the Form 483 and in other communications:
 - Dr. Lugo-Zamudio did not conduct the investigation in accordance with the investigational plan. Specifically,
 - The blinded assessor joint count duties were delegated to study personnel who were performing laboratory results review.
 - Drug dispensing records for Subject 4910's Week 8 visit revealed that the person administering product to the subject was not authorized to perform this function and the records state that 20.7mL was removed from each vial while, according to the IVRS, only 6.9 mL was to be removed from each vial.

- For Protocol WA 17822 Dr. Lugo-Zamudio in did not stop study drug infusions for subject 4910 after a 3.7% increase in the ALT levels at Study visit 12.
 - Formal readings of electrocardiograms and chest x-rays were not completed as per the Study.
 - Laboratory values were not reviewed as per protocol:
 - Shipments of study drug that were outside of the storage temperature range were accepted.
 - Dr. Lugo-Zamudio did not maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Specifically,
 - An ECG that appears to have been created in 1998 was placed into a subject's file and was represented as being the subject's baseline ECG.
 - Concerning Subject 4912 in Protocol WA 17822, the Week 2 study visit examination was recorded as being performed on a 30 year old female, but the subject is a 28 year old male.
 - Qualifications of the joint assessors was not documented adequately. (However, verbal Communications from the field investigator revealed that 90% of the assessments were performed by a rheumatologist, three of the four assessors were physicians, and the fourth assessor was a medical student.)
 - Source documents were not maintained for the collection, storage, shipment and disposition of blood or urine samples.
 - Case report forms for tender and swollen joint counts contain the initials of the person completing the form, but no date.
 - Dr. Lugo-Zamudio did not report to the IRB all unanticipated problems involving risk to human subjects. Specifically, Subject 3695 experienced a serious adverse event on August 25, 2005 that was reported to the IRB by the sponsor monitor rather than by the study staff, (no note of whether this was reported by CI to sponsor) and the SAE experienced by Subject 3092 on August 1, 2005 was reported to the sponsor on August 12, 2005 which was outsider the protocol required 24 hours.
 - Dr. Lugo-Zamudio failed to report to the sponsor adverse effects that may reasonably be regarded as caused by or probably caused by an investigational drug. Specifically, the adverse events of itching, nausea and dizziness that occurred on day after the infusion of investigational product was not reported to the sponsor or IRB.
 - Dr. Lugo-Zamudio failed to maintain adequate drug disposition records. Specifically,
 - There are no records showing by whom and when infusion bags were prepared.
 - The authorization to receive study medication was not delegated to any staff members.
- c. **Assessment of data integrity:** This inspection report is preliminary classified OAI based on 483 items that pertain to inadequate recordkeeping and human subject

protection issues; however, at this time, there is no indication that data integrity has been compromised. As such, data are considered acceptable at this time.

4. Cesar Ramos-Remus

Unidad de Enfermedades Cronico Degenerativas,
Colomos 2292, Col. Providencia Guadalajara, 44620,
Jalisco, Mexico

Note: Observations noted for this site are based on the Form FDA 483, Inspectional Observations and communications from the FDA Investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** Dr. Ramos-Remus enrolled 22 subjects in Protocol WA 17822 and 14 subjects in Protocol WA 17824.
- b. **General observations/commentary:** Concerning data integrity, verification of subject questionnaires and VAS was not possible because the subject instruments did not have a place for initials of the person completing the form. Verification of the Health Assessment Questionnaire Disease Index (HAQ-DI) could not be done at the site because the value for the HAQ-DI was calculated centrally. The following observations were noted on the Form 483:
 - Dr. Ramos-Remus did not maintain adequate drug disposition records with respect to quantity and use by subjects. Specifically records that documented the infusion for each subject receiving treatment did not show the quantity that was infused at each visit.
- c. **Assessment of data integrity:** Data for this site appear acceptable in support of the pending application.

5. Fedra Irazoque-Palazuelos

Centro Medico Nacional "20 de Noviembre" ISSSTE, Av.
Felix Cuevas No. 540, Torre de Consulta Externa, Piso 8, Col. Del Valle, 03229
Mexico City, Mexico

Note: Observations noted for this site are based on the Form FDA 483, Inspectional Observations and communications from the FDA Investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** For Protocol WA 17823, Dr. Irazoque-Palazuelos screened 57 subjects, enrolled 34 subjects, 24 subjects completed the study and 12 subject records were reviewed during the inspection.
- b. **General observations/commentary:** Concerning data integrity, verification of subject questionnaires and VAS was not possible because the subject

instruments did not have a place for initials of the person completing the form. Verification of the Health Assessment Questionnaire Disease Index (HAQ-DI) could not be done at the site because the value for the HAQ-DI was calculated centrally.

The following observations were noted on the Form 483:

- Dr. Irazoque-Palazuelos failed to report to the sponsor adverse effects that may reasonably be regarded as caused by or probably caused by an investigational drug. Specifically, the adverse events of bacterial pharyngitis in Subject 2125 and urinary tract infection Subject 2131 were not reported to the sponsor.
- Dr. Irazoque-Palazuelos failed to maintain adequate and accurate case histories. Specifically,
 - There were no signatures and dates obtained for the efficacy assessments of SF-36, HAQ, FACT-F, EQ-5D, Pain-VAS (Subject Assessment), Pain-VAS (Physician Assessment), and Joint counts.
 - For subject 2126, joint assessor “MMB” completed all assessments from Screening to Week 24. Changes to the joint counts were made by a sub-investigator over one month after completing the assessment.
- Dr. Irazoque-Palazuelos did not conduct the investigation in accordance with the investigational plan. Specifically,
 - Shipments of study drug that were outside of the storage temperature range were accepted.
- Dr. Irazoque-Palazuelos did not promptly report to the IRB all unanticipated problems to the IRB.

c. **Assessment of data integrity:** Data for this site appear acceptable in support of the pending application.

6. Sponsor

Hoffman-La Roche
340 Kingsland Street,
Nutley, New Jersey 07110-1199

a. **What was inspected:** The inspection audited protocols WA 17822, WA 17823, WA 17824, WA 18062, WA 18063. Investigator CVs, 1572s and financial disclosure forms were reviewed for approximately 10% of the 4211 clinical sites. The inspection included review of standard operating procedures and monitoring audits.

b. **General observations/commentary:**

- Hoffman-La Roche did not either promptly secure compliance or discontinue shipments of the investigational drug to the investigator and end the investigator’s participation in the investigation for an investigator who was not complying with the general investigational plan. Specifically, non-compliance was noted by a monitor beginning as early as the second

monitoring visit on October 28, 2005, but no attempt was made to bring the CI into compliance until the tenth monitoring visit on August 30, 2006.

- Hoffman-La Roche did not maintain adequate records showing the receipt, shipment, or other distribution of the investigational drug. Specifically, for six of seven study centers reviewed for investigational drug accountability for protocols WA 17822, WA 17824, WA 18062, and WA 18063, there is no documentation for the final disposition of the investigational products.
- Hoffman-La Roche did not submit for each clinical investigator who participates in a covered study, either a certification that none of the financial arrangements described in 21 CFR 54.2 exist, or disclose the nature of those arrangements to the agency; or where they acted with due diligence to obtain the information required in this section but were unable to do so, certify that despite their due diligence in attempting to obtain the information, they were unable to obtain the information and include the reason. For example, for the following investigators Hoffman-La Roche did not submit until July 23, 2008 financial information or a certification stating that despite their due diligence in attempting to obtain the information, they were unable to obtain the information, including the reason: b(4)

- c. **Assessment of data integrity:** Data monitored by the sponsor appear acceptable in support of the pending application.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Concerning data integrity, verification of subject questionnaires and VAS was not possible because the subject instruments did not have a place for initials of the person completing the form. Verification of the Health Assessment Questionnaire Disease Index (HAQ-DI) could not be done at the site because the value for the HAQ-DI was calculated centrally.

The inspection of Dr. Michael Fairfax found no significant regulatory violations. The inspection of Hoffman-La Roche found regulatory violations as mentioned above. The inspections of Drs. — Ramos-Remus, Lugo-Zamudio and Irazoque-Palazuelos found regulatory violations as mentioned above. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR. Data appear acceptable in support of the pending application.

b(4)



Susan Leibenhaut, M. D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:



Constance Lewin, M.D., M.P.H
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations



Shari L. Targum, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993
Tel (301) 796-1151

Memorandum

DATE: August 27, 2008

FROM: Shari L. Targum, M.D., Team Leader *Shari Targum 8/27/08*
Division of Cardio-Renal Drug Products, HFD-110

THROUGH: Norman Stockbridge, M.D., Ph.D., Director *Norman Stockbridge 8/27/08*
Division of Cardio-Renal Drug Products, HFD-110

TO: Sharon Turner-Rinehardt, RPM, Division of Anesthesia, Analgesia and Rheumatology Products

Sarah Okada, M.D., Medical Officer, Division of Anesthesia, Analgesia and Rheumatology Products

SUBJECT: BLA 125276

NAME OF DRUG: Tocilizumab

TRADE NAME: Actemra

FORMULATION: Intravenous

RELATED APPLICATIONS: N/A

APPROVED INDICATIONS: N/A

SPONSOR: Hoffman-LaRoche

DOCUMENTS AVAILABLE FOR REVIEW: 1. Primary medical review for BLA 125276; 2. Selected slides from DAARP advisory committee meeting (7/29/2008)

DATE CONSULT RECEIVED: August 14, 2008

DESIRED COMPLETION DATE: August 28, 2008

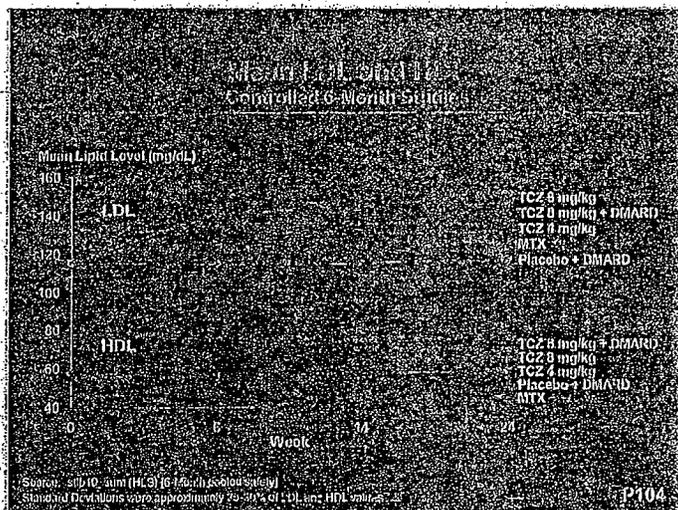
DATE CONSULT COMPLETED: August 27, 2008

BACKGROUND & RATIONALE:

Tocilizumab (TCZ), a recombinant monoclonal antibody targeting the interleukin-6 (IL-6) receptor, has been proposed for the treatment of moderately to severely active rheumatoid arthritis (RA). The TCZ RA program included 4200 RA patients in 5 randomized, controlled trials (4 placebo-controlled and one active-controlled) in which the primary endpoint was the proportion of ACR 20 responders at Week 24. Patients completing the 24-week core studies were allowed to enroll in long-term open-label extensions for a total of 5 years. Data from the

long-term extensions are still accruing, but at present include approximately 1500 patients treated for up to 18 months, and 500 patients treated for up to 2 years.

According to the consult request, the liver expresses high levels of IL-6 receptors, and IL-6 plays a large role in acute phase reactant production. Treatment with TCZ resulted in dramatic decreases in acute phase reactants such as C-reactive protein. However, treatment with TCZ also resulted in mild to moderate increases in all lipid parameters, shown below (from the applicant's slide-set, Arthritis Advisory Committee meeting, July 29, 2008):



Mean Low-Density Lipoprotein (LDL) Values Over Time
Controlled 6-Month Studies

	TCZ 0 mg/kg n=250	TCZ 4 mg/kg + DMARD n=215	TCZ 8 mg/kg + DMARD n=714	TCZ 8 mg/kg + DMARD n=1467	DMARD n=1060
Baseline	115 ± 31	114 ± 33	114 ± 33	115 ± 35	114 ± 34
Week 14 (2 Weeks from Infusion)	144 ± 44	117 ± 34	133 ± 38	137 ± 43	115 ± 34
Week 24 (4 Weeks from Infusion)	140 ± 43	118 ± 35	127 ± 36	135 ± 42	117 ± 35

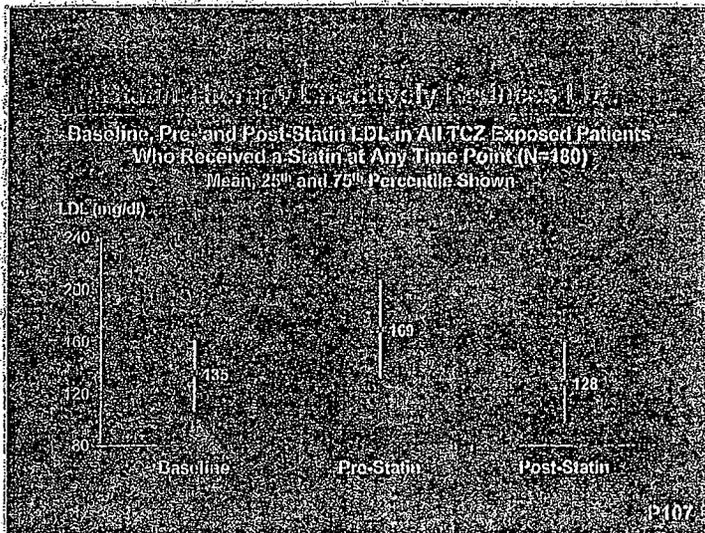
P105

Best Possible Copy

**Baseline to Last Observation
LDL-C/ATPIII Guidelines
Controlled 6-Week Studies**

LDL-C (mg/dL)	TCZ 4 mg/kg DMARD n=291	TCZ 8 mg/kg DMARD n=277	TCZ 8 mg/kg DMARD n=166	DMARD n=172
< 130 to ≥ 130	22.6%	11.3%	15.4%	8.8%
< 160 to ≥ 160	17.4%	6.7%	11.0%	3.5%

P106



Best Possible Copy

Questions:

1) Given the lipid parameter changes (see above), and the lack of corresponding cardiovascular adverse event signal detected in the time frame of the clinical trials and long-term extensions, do you believe that these lipid parameter changes are sufficient to be worrisome for an increased risk of cardiovascular events?

Response:

In reviewing serious adverse events in the TCZ pivotal studies (Table 24, primary medical review, not shown in this memo), this reviewer observed one myocardial infarction (MI) event, two coronary artery disease events and one congestive heart failure event in the "all TCZ" column (N=2644: 10 total cardiac events, incidence < 1%); in the "placebo + DMARD" column, there are two MI events and one angina/acute coronary syndrome events (N=1170: 5 total cardiac

events, incidence < 1%). In the "all TCZ" column, two adverse cardiac events (<1%) led to discontinuation from the pivotal studies (one acute coronary syndrome event and one myocardial ischemia event, respectively).

From Table 20 (RA controlled pivotal studies) in the primary medical review (not shown) there were two cardiac deaths in total, one (patient # 3298) in the placebo + DMARD (N=1170) group and one (patient # 4929) in the TCZ 8 mg/kg (N=288) group. In the pooled TCZ long-term extensions (N=2562), four cardiac deaths are noted (#3739, 5883, 5687, 4943); in addition, one death is listed as "unknown" (5151).

According to the primary medical review, as of the final data cut-off for the 120-day safety update (January 31, 2008), 15 MI were diagnosed in 4158 patient-years exposure for a rate of 0.35 per 100 patient-years (lower than published rates of MI in RA patients, which range from 0.47 per 100 patient-years [ARAMIS database] to 0.76 per 100 patient-years in the National Data Bank for Rheumatic Diseases).

This reviewer agrees that no adverse cardiac signal was observed in the available tocilizumab RA data. However, the event rates are low in all treatment groups (TCZ as well as comparator); therefore this reviewer is unable to make definitive conclusions. While it is possible that TCZ use may not lead to increased risk, it is also possible that the highest risk patients were not studied, or that the duration of treatment was not long enough to allow for the occurrence of an adequate number of events. Since you are comparing MI rates in RA patients to historical (i.e., nonconcurrent) controls, it is also possible that the risk of MI in RA has changed over time.

Is drug-associated dyslipidemia (e.g., elevated LDL) a safety risk? Or is any potential safety risk posed by TCZ mitigated by other drug effects such as a decrease in inflammation and CRP?

While we accept the premise that increased LDL is a risk factor for cardiovascular events, and that lowering LDL is a surrogate for risk reduction, it is not evidence-based (although perhaps a reasonable assumption) that increasing LDL by some degree will lead to increased risk. Moreover, even if we thought that drug-associated increases in LDL conferred an increased risk, how much of an increase in LDL is needed to elevate risk and magnitude of that increased risk are not known.

Other drugs have known associations with dyslipidemia. For example, hydrochlorothiazide has been associated with increases in cholesterol and triglycerides (1). There have also been published concerns about beta-blocker-associated increases in triglycerides and decrease in HDL (2). However, outcome trials with hydrochlorothiazide (e.g., SHEP) and beta-blockers (e.g., MERIT, BHAT) have shown a net benefit of therapy in target patient populations at risk for cardiac events.

Antiretroviral drugs have also been associated with dyslipidemia; as survival for HIV patients has increased, so has the concern for cardiac outcomes. However, there are no long-term adequately powered cardiovascular outcome studies in patients taking antiretroviral drugs. Interestingly, the SMART study (3) showed an increase in cardiac events in the group receiving interrupted retroviral therapy, compared to the group receiving continuous therapy.

On the other hand, the development of torcetrapib as a treatment to increase HDL (presumably to improve cardiovascular risk) was stopped due to an increased rate of cardiovascular events and death in a 15,000-patient study (4, 5).

This reviewer concludes, from the above examples, that at the present time one cannot predict net cardiovascular risk on the basis of drug-associated lipid increases due to multiple and complex effects of drugs.

2) If so, given the limited numbers of RA patients who might be available for a cardiovascular outcomes study, how would you recommend this question be addressed?

Comments/Recommendations:

1. An appropriately designed, adequately powered cardiovascular outcome study would provide the most definitive answer to the question of cardiovascular risk. Short of an outcome study, this reviewer is concerned that postmarketing epidemiologic studies may be limited in that the outcome measured will likely be common; hence these studies will only be informative if there is a clear temporal relationship with drug, or if there is a large and/or consistent signal. Thus far, a large signal has not been observed in the current database.

2. The LDL effect should appear in labeling. An example of labeling of lipid elevations can be found in the package insert for KALETRA (see below).

Kaletra labeling (Precautions):

Lipid Elevations

Treatment with KALETRA has resulted in large increases in the concentration of total cholesterol and triglycerides (see ADVERSE REACTIONS – Table 16). Triglyceride and cholesterol testing should be performed prior to initiating KALETRA therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate.

This type of labeling language, adapted to reflect TCZ data, may be reasonable with the caveat (or incongruity) that you may be recommending initiating treatment for a side effect of another treatment.

3. We also recommend that you acknowledge, in labeling, what relative and absolute risk can be ruled out by available data.

Thank you. If you have any further questions please feel free to contact me or the Division.

References:

- 1) Hydrochlorothiazide package insert.
- 2) Shaw J, et. al. Beta-blockers and plasma triglycerides. Br Med J. 1978 April 15; 1 (6118): 986.
- 3) The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ Count-Guided Interruption of Antiretroviral Treatment. New England J of Medicine 2006 Nov 30; 355(22): 2283-96.
- 4) FDA Statement (December 3, 2006): Pfizer Stops All Torcetrapib Clinical Trials in Interest of Patient Safety. <http://www.fda.gov/bbs/topics/news/2006/new01514.html>
- 5) Barter PJ et. al. Effects of torcetrapib in patients at high risk for coronary events. New England J of Medicine 2007 Nov 22; 357 (21): 2109-22.

**Food and Drug Administration
Center for Drug Evaluation and Research**

CONSULTATION

DATE: Consult requested: 30 July 2008
Desired Completion date: 11 August 2008
Date of review: 7 August 2008

FROM: Eileen Craig, M.D.
Division of Metabolism and Endocrine Products (DMEP)

THROUGH: Eric Colman, M.D., Deputy Director
Division of Metabolism and Endocrine Products *EC 8/7/08*

TO: Sharon Turner-Rinehardt, RPM/ Sarah Okada, MO
Division of Anesthesia, Analgesics and Rheumatology *EC 8/25/08*

SUBJECT: Potential cardiovascular risk associated with lipid parameter changes seen with Actemra (Tocilizumab)

I. Basis for Consult Request

BLA 125276 is an original submission for tocilizumab, a recombinant monoclonal antibody targeting the interleukin 6 receptor, proposed for treatment of moderately-to-severely active rheumatoid arthritis (RA).

The tocilizumab RA program included approximately 4200 RA patients in 5 randomized, controlled trials. The primary endpoint for the trials was the proportion of ACR 20 responders at Week 24. Patients completing the 24-week core studies were allowed to enroll in long-term open-label extensions for a total of 5 years. Data from the long-term extensions are still accruing, but at present includes approximately 1500 patients treated for up to 18 months, and 500 patients treated for up to 2 years.

This biologic target is unique in that the liver expresses high levels of IL-6 receptor, and IL-6 plays a large role in a number of hepatic processes, such as acute phase reactant production. Treatment with tocilizumab resulted in dramatic decreases in these acute phase reactants, including C-reactive protein. However, treatment with tocilizumab also resulted in mild-to-moderate increases in all lipid parameters, shown in slides from the applicant's slide-set from the Arthritis Advisory Committee Meeting July 29, 2008:

DAARP's analysis of the sponsor's data did not reveal an increased risk of myocardial infarction during the time frame of the clinical trials (24 weeks) and long-term extensions.

II. Material Reviewed for Consult

- Division of Anesthesia, Analgesia, and Rheumatology Products' Overview of the July 29, 2008 AAC Meeting to Discuss BLA 125276 for tocilizumab for the treatment of moderately to severely active rheumatoid arthritis (RA)
- Hoffmann-LaRoche's briefing document for Tocilizumab Biologic License application 125276 for the 29 July 2008 Arthritis Advisory committee
- Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005 Oct 8; 366(9493):1267-78.
- Boers M, Dijkmans B, Gabriel S, Maradit-Kremers H, O'Dell J, Pincus T. Making an impact on mortality in rheumatoid arthritis. *Arthritis Rheum* 2004; 50(6):1734-1739.
- Del Rincon ID, Williams K, Stern MP, et al. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001; 44:2737-2745.
- Dhawan SS, Quyyumi AA. Rheumatoid arthritis and cardiovascular disease. *Curr Atheroscler Rep*. 2008 Apr; 10(2):128-33
- Gonzalez-Juanatey C, Llorca J, Martin J, Gonzalez-Gay MA. Carotid Intima-Media Thickness Predicts the Development of Cardiovascular Events in Patients with Rheumatoid Arthritis. *Semin Arthritis Rheum*. 2008 Mar 11
- Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis. *Arthritis Rheum* 2005; 52(2):402-411.
- Naranjo A, Sokka T, Descalzo MA, Calvo-Alén J, Hørslev-Petersen K, Luukkainen RK, Combe B, Burmester GR, Devlin J, Ferraccioli G, Morelli A, Hoekstra M, Majdan M, Sadkiewicz S, Belmonte M, Holmqvist AC, Choy E, Tunc R, Dimic A, Bergman M, Toloza S, Pincus T; QUEST-RA Group. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. *Arthritis Res Ther*. 2008; 10(2):R30. Epub 2008 Mar 6.
- Pereira IA, Borba EF. Multiple factors determine the increased prevalence of atherosclerosis in rheumatoid arthritis. *Acta Reumatol Port*. 2008 Jan-Mar; 33(1):47-55.
- Sattar N, McInnes I. Vascular comorbidity in rheumatoid arthritis: potential mechanisms and solutions. *Curr Opin Rheumatol* 2005, 17:286—292
- Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, Stampfer MJ, Curhan GC. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation*. 2003 Mar 11; 107(9):1303-7.
- Wolfe F, Freundlich B, Straus WL. Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis. *J Rheumatol*. 2003; 30(1):36-40.
- Chait A, et al. Lipoprotein-associated inflammatory proteins: markers or mediators of cardiovascular risk. *J Lipid Res*. 2005;46:389-403.

- McQueen M, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *Lancet*. 2008;327:224-233.

III. Background

Tocilizumab (TCZ) is a recombinant human monoclonal antibody directed against the interleukin-6 receptor. By preventing the binding of interleukin-6 to its receptor tocilizumab inhibits the biological activity of interleukin-6. The clinical development program for tocilizumab included studies of 4 mg/kg and 8 mg/kg and studied tocilizumab monotherapy and tocilizumab use in combination with methotrexate and other disease modifying anti-rheumatic drugs (DMARDs). The majority of patients in the tocilizumab RA pivotal studies were female, Caucasian, and rheumatoid factor (RF) positive, with a mean age in the early fifties.¹ Roche studied over 3200 patients at 8 mg/kg and over 1,100 patients at 4 mg/kg. Of the 3,778 patients in the tocilizumab safety database, 2121 had been exposed for at least 12 months, 1463 had been exposed for at least 18 months, 640 had been exposed for at least 24 months, and 113 had been exposed for at least 30 months (Table 9, pg 43 of FDA AAC Briefing Document).

Serum lipids, total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides increased in patients in both the tocilizumab monotherapy and 4 mg/kg or 8 mg/kg combination therapy groups more than in patients in the placebo and MTX groups (refer to Roche's Table 44 below, pg 86 of AAC background package).

Table 44 Baseline (SD) and Week 14 Lipid Parameters – Double-blind Controlled Studies

	TCZ 8 mg/kg +DMARD N = 1467		TCZ 4 mg/kg + DMARD N = 714		Placebo + DMARD N = 1068		TCZ 8 mg/kg N = 260		MTX N = 253	
	BL	14 wks	BL	14 wks	BL	14 wks	BL	14 wks	BL	14 wks
Total cholesterol (mg/dL)	199	230	195	226	199	199	199	238	193	195
LDL (mg/dL)	114	137	114	133	114	115	115	144	114	117
HDL (mg/dL)	57	62	57	62	57	57	56	60	53	55
Triglycerides (mg/dL)	129	159	123	163	129	144	133	171	131	129

Week 14 is used in this analysis because it is the last fasting assessment prior to patients being eligible for escape therapy. These are patients with fasting samples at baseline.

DMEP reviewer's comments:

Note that the baseline LDL value for TCZ 8 mg/kg +DMARD is reported as 115 mg/dL in Slide P105 and as 114 mg/dL in Table 44 of Roche's background package.

At Week 14 (source-Roche's Table 44):

¹ Division of Anesthesia, Analgesia, and Rheumatology Products' Overview of the July 29, 2008 AAC Meeting to Discuss BLA 125276 for tocilizumab for the treatment of moderately to severely active rheumatoid arthritis (RA)

TCZ 8 mg/kg: 25% increase in LDL-C (difference of 29 mg/dL or 0.8 mmol/L)
 TCZ 8 mg/kg +DMARD: 20% increase in LDL-C (difference of 23 mg/dL or 0.6 mmol/L)
 TCZ 4 mg/kg +DMARD: 17% increase in LDL-C (difference of 19 mg/dL or 0.5 mmol/L)
 Placebo +DMARD: <1% increase in LDL-C (difference of 1 mg/dL or 0.03 mmol/L)
 MTX: 3% increase in LDL-C (difference of 3 mg/dL or 0.08 mmol/L)

At Week 24 (source-Roche's Slide P105):

TCZ 8 mg/kg: 22% increase in LDL-C (difference of 25 mg/dL or 0.7 mmol/L)
 TCZ 8 mg/kg +DMARD: 17% increase in LDL-C (difference of 20 mg/dL or 0.5 mmol/L)
 TCZ 4 mg/kg +DMARD: 11% increase in LDL-C (difference of 13 mg/dL or 0.3 mmol/L)
 Placebo +DMARD: 3% increase in LDL-C (difference of 3 mg/dL or 0.08 mmol/L)
 MTX: 4% increase in LDL-C (difference of 4 mg/dL or 0.1 mmol/L)

In the double-blind studies, serum LDL increased from < 130 mg/dL at baseline to \geq 130 mg/dL at the last observation in 23% of patients in the tocilizumab 8 mg/kg group, 22% of patients treated with 8 mg/kg tocilizumab + DMARD, 15% of patients treated with 4 mg/kg tocilizumab + DMARD, 9% of patients treated with DMARDs, and 11% of patients in the MTX group.

Serum LDL increased from < 160 mg/dL to above 160 mg/dL in 17% of patients on tocilizumab 8 mg/kg, 13% of those treated with 8 mg tocilizumab + DMARD, 11% of those treated with 4 mg tocilizumab + DMARD, 4% of patients treated with DMARDs, and 7% of patients in the MTX group.

Lipid increases occurred as early as 6 weeks after initiation of tocilizumab treatment and remained stable through treatment in the open-label extension studies.²

Through its blockade of IL-6R, tocilizumab is expected to lower CRP. For the 4 mg/kg dose, a moderate decrease in mean CRP trough levels was observed up to Week 24. Mean trough levels ranged from 1.62 to 2.66 mg/dL (baseline 3.07 mg/dL) and from 1.19 to 2.13 mg/dL (baseline 2.8 mg/dL) for Study WA18062 and WA17822, respectively. Levels fluctuated within the dosing interval with considerably lower levels 2 weeks post-dose (weeks 2, 6 and 14), ranging from 0.36 to 0.45 mg/dL and from 0.12 to 0.23 mg/dL in studies WA18062 and WA17822, respectively. For the 8 mg/kg dose, a pronounced and sustained decrease in mean CRP trough levels was observed. Mean CRP levels at week 4 ranged from 0.53 to 0.99 mg/dL with mean baseline levels ranging from 2.55 to 2.99 mg/dL. Mean trough levels decreased with time and ranged from 0.22 to 0.28 mg/dL at week 24. Furthermore, mean levels at 2 weeks post-dose were similar for patients treated with 4 and 8 mg/kg. For 8 mg/kg, mean CRP levels 2 weeks post-dose ranged from 0.07 to 0.20 mg/dL (Roche's AAC background package, pgs.28-29).

According to the FDA AAC briefing document, the overall rate of myocardial infarctions (MI) in the RA Phase 3 studies and long term extensions remained consistent over time. As of the final data cut-off for the 120-day safety update (January 31, 2008 for deaths and

² Hoffmann-LaRoche's briefing document for Tocilizumab Biologic License application 125276 for the 29 July 2008 Arthritis Advisory committee, page 89

SAE), 15 MI were diagnosed in approximately 4158 patient-years exposure for a rate of 0.35 per 100 patient-years. This rate is not elevated compared to published rates of MI in RA patients, which range from 0.47 per 100 patient-years in the ARAMIS database to 0.76 per 100 patient-years in the National Data Bank for Rheumatic Diseases.

Similarly, the rate of cerebrovascular accident events in patients treated with TCZ during the Phase 3 studies is not elevated compared to published rates. Nine CVA were diagnosed in 4158 patient-years exposure for a rate of 0.22 per 100 patient years. Published rates range from 0.11 per 100 patient-years in female RA patients within the Nurse's Health Study to 0.76 per 100 patient-years in the UK General Practice Research database.³

DMEP reviewer's comment: The long-term safety database for tocilizumab (640 exposed for ≤ 24 months and 113 exposed for ≤ 30 months) is limited when the goal is to assess cardiovascular morbidity and mortality. Using patient-years of exposure may be misleading if the study does not have an adequate number of subjects studied for a sufficient duration to assess this long-term safety risk.

Cardiovascular disease (CVD) is recognized as the leading cause of death in RA patients, accounting for nearly 40% of their mortality.⁴ Patients with rheumatoid arthritis (RA) are at a two-fold increased risk for myocardial infarction (MI) and stroke, with younger patients at higher risk^{4,5}. A study by Solomon et al. compared incidence rates of myocardial infarction and stroke in women with and without RA among the 114,342 women in the Nurses' Health Study. Multivariate pooled logistic regression was used to adjust for potential cardiovascular risk factors. A total of 527 incident cases of RA and 3622 myocardial infarctions and strokes were confirmed during 2.4 million person-years of follow-up. The adjusted relative risk of myocardial infarction in women with RA compared with those without was 2.0 (95% CI, 1.23–3.29). Women who had RA for at least 10 years had a risk for myocardial infarction of 3.10 (95% CI, 1.64–5.87). Thus, the risk increased to nearly three-fold in patients who have had the disease for 10 years or more^{6,7}. RA patients are also twice as likely to have an unrecognized MI and sudden cardiac death, and less likely to report symptoms compared with non-RA patients⁸. Some of the medications used to treat RA, such as nonsteroidal anti-inflammatory drugs and cyclooxygenase 2 inhibitors, may also increase the risk for MI and CV morbidity. The increased risk of CV disease in RA patients seems to be independent of traditional CV

³ Division of Anesthesia, Analgesia, and Rheumatology Products' Overview of the July 29, 2008 AAC Meeting to Discuss BLA 125276 for tocilizumab for the treatment of moderately to severely active rheumatoid arthritis (RA), page 22.

⁴ Dhawan SS, Quyyumi AA. Rheumatoid arthritis and cardiovascular disease. *Curr Atheroscler Rep*. 2008 Apr; 10(2):128-33

⁵ Solomon DH, Goodson NJ, Katz JN, et al.: Patterns of cardiovascular risk in rheumatoid arthritis. *Ann Rheum Dis* 2006, 65:1608–1612.

⁶ Solomon DH, Karlson EW, Rimm EB, et al.: Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003, 107:1303–1307.

⁷ Sattar N, McInnes I. Vascular comorbidity in rheumatoid arthritis: potential mechanisms and solutions. *Curr Opin Rheumatol* 2005, 17:286—292

⁸ Maradit-Kremers H, Crowson CS, Nicola PJ, et al.: Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum* 2005, 52:402–411.

risk factors. Pathogenic mechanisms include pro-oxidative dyslipidemia, insulin resistance, prothrombotic state, hyperhomocysteinemia, and immune mechanisms such as T-cell activation that subsequently lead to endothelial dysfunction, a decrease in endothelial progenitor cells, and arterial stiffness, which are the congeners of accelerated atherosclerosis observed in RA patients.⁹

IV. Recommendations

The following questions have been posed by DAARP to DMEP:

Questions:

1) Given the lipid parameter changes discussed below, and the lack of corresponding cardiovascular adverse event signal detected in the time frame of the clinical trials and long-term extensions, do you believe that these lipid parameter changes are sufficient to be worrisome for an increased risk of cardiovascular events?

DMEP Response: The relationship between LDL-C and risk for CVD (CVD) is direct and linear. A 1% increase in the level of LDL-C is associated with a 1% increase in the risk for CVD. Thus, on a population level, the average increase in LDL-C observed following treatment with 8 mg/kg TCZ would presumably increase the risk for CVD by as much as ~ 20%. However, inflammation is believed to play an important role in the pathogenesis and risk for CVD. It is known, for example, that IL-6 reduces levels of ApoA-I, a protein component of HDL-C that is involved in reverse cholesterol transport, and accounts in part for the inverse relationship between HDL-C levels and risk for CVD. That TCZ reduced levels of CRP, an additional serum protein directly correlated with risk for CVD, and increased levels of HDL-C, raises the possibility that the drug may induce physiologic changes that could contribute to a reduction in the risk for CVD. Hence, it is anyone's guess if long-term use of TCZ in subjects with RA will increase, decrease, or have a neutral effect on CVD risk.

Given that there were only a total of ~ 57 serious cardiac events and only ~ 18 acute coronary syndrome events in subjects treated with TCZ 4 mg/kg, TCZ 8 mg/kg, and control agents (slide p115 from Roche's AC presentation) the number and duration of patient exposure is inadequate to accurately define TCZ's cardiovascular profile.

2) If so, given the limited numbers of RA patients who might be available for a cardiovascular outcomes study, how would you recommend this question be addressed?

DMEP: Provided below is a table of various sample sizes for a non-inferiority trial comparing the incidence of major cardiovascular events (MACE) – CHD death, non-fatal MI, and stroke – in patients treated with standard anti-arthritic therapy to standard anti-arthritic therapy + TCZ.

⁹ Dhawan SS, Quyyumi AA. Rheumatoid arthritis and cardiovascular disease. *Curr Atheroscler Rep.* 2008 Apr; 10(2):128-33

Total sample sizes ¹ for a non-inferiority outcome trial comparing an arthritis drug to control group on a major cardiovascular event (MACE) endpoint

Control annual event rate ²	Trial duration (yrs)	Control total event rate ³	Non-inferiority margin for hazard ratio λ_t / λ_c (total # events needed ⁴)			
			1.2 (944)	1.3 (456)	1.4 (277)	1.5 (191)
2%	2	4%	24900	12000	7300	5100
	3	6%	16600	8000	4900	3400
	4	8%	12500	6000	3700	2600
3%	2	6%	16600	8000	4900	3400
	3	9%	11100	5400	3300	2300
	4	11%	9100	4400	2700	1900
4%	2	8%	12500	6000	3700	2600
	3	12%	8300	4000	2500	1700
	4	15%	6700	3200	2000	1400

1 Sample sizes rounded up to nearest 100

2 Control event rate assumed equal to test drug event rate.

3 Event rate for trial duration = $1 - (1 - \text{annual event rate})^{\text{yrs}}$

4 Total # events calculated analytically and verified using EAST

To cite one scenario, assuming 1:1 randomization, an annual MACE rate of 4% in the control group, and a study duration of 2 years, to rule out, with 80% power, a 40% increase in the risk for MACE in TCZ vs. non-TCZ subjects, would require a total of approximately 1850 subjects per group.

The sample size increases as the level of risk one wishes to rule out decreases, the event rate in the control group decreases, and the duration of the study decreases.

We would also mention that while there are articles in the literature touting imaging studies, such as intima-media thickness (CIMT) of the common carotid artery and intravascular ultrasound (IVUS) of the coronary arteries, as useful noninvasive surrogate markers of macrovascular atherosclerosis disease in RA and other patient populations,¹⁰ this division, for reasons beyond the scope of this consult, has found these imaging techniques problematic when attempting to assess drug-induced changes in CVD risk.

If you do not believe that it is feasible to conduct an outcomes trial to characterize the long-term cardiovascular profile of TCZ in patients with RA, we recommend that the labeling include the changes in lipoprotein lipids levels (including Apo B and Apo A) observed in the clinical trials. Moreover, it would be prudent to instruct healthcare providers to periodically monitor lipid levels, particularly during the first 3 months of

¹⁰ Gonzalez-Juanatey C, Llorca J, Martin J, Gonzalez-Gay MA. Carotid Intima-Media Thickness Predicts the Development of Cardiovascular Events in Patients with Rheumatoid Arthritis. *Semin Arthritis Rheum.* 2008 Mar 11

TCZ use, and when indicated per clinical guidelines, treat to goal with an HMG-CoA-reductase inhibitor (statin) as first line therapy.

You can consult the recommendations from the National Cholesterol Education Program at the following web address:

<http://www.nhlbi.nih.gov/guidelines/cholesterol/>

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

DATE: 12 August 2008

FROM: John R. Senior, M.D., Associate Director for Science, Office of Surveillance and Epidemiology (OSE)

TO: Sarah Okada, M.D. Medical Reviewer, Division of Anesthesia, Analgesic, and Rheumatology Products (DAARP)
Bob Rappaport, M.D., Director, (DAARP)

CC: Mark Avigan, M.D., Director, DAEA I/OSE
Gerald Dal Pan, M.D., Director, OSE

SUBJECT: Addendum to consultation of 8 August 2008, following resubmission of data. OSE consultation #2008-1259

Documents reviewed:

- 1) Additional data sent by sponsor (Roche) on 8 August in response to request by Dr. Sarah Okada of 7 August 2008.
- 2) Previously submitted information about the case, as reviewed in my consultation of 8 August 2008 concerning BLA 125276 for tocilizumab (ACTEMRA[®], Roche)
- 3) Roche justification for revision, reference to Kratz and Lewandrowski, 1998.

After I spoke with Dr. Okada on 7 August, she promptly forwarded a request to the sponsor that same day a request to:

- 1. Provide the data for that patient from the lab at which the tests were performed, along with the normal ranges for the women at that laboratory (include data from all available sampling dates).**
- 2. Include all bilirubin values; include direct bilirubin as well as total bilirubin and indirect bilirubin. Also, provide the corresponding values for AST, ALT, and alkaline phosphatase in the same data.**

Roche very quickly sent back an amended set of data for the case, drastically revising downward the reported serum ALT and AST values from those reported to us in their previously submitted "attachment4 lab listings" that had been forwarded to me for my initial consultation request. The revised data for the ALT and AST are all lower than those reported originally in attachment4 lab listings, and are stated to have been done at the — central laboratory, with reference or "normal" ranges that differ somewhat from the standard Roche Reference Ranges submitted as "attachment6 lab data handing" previously, and quite drastically from the upper limits of normal (ULN) provided previously in attachment4. The result of this transformation may be seen in the following table:

b(4)

date	event	attachment4 listed data			resubmitted 8Aug08 Roche transformed data		
		ULN 55 ALT	ULN 40 AST	ULN 115 ALP	x34/55 ALT	x34/40 AST	x123/115 ALP
21-Aug-06		31	27		19	23	
29-Aug-06	start MRA 8 mg IV			119			127
12-Sep-06		42	31	98	26	26	105
26-Sep-06	MRA 8 mg IV	61	39	103	38	33	110
10-Oct-06		44	27	108	27	23	116
24-Oct-06	MRA 8 mg IV	36	26	93	22	22	99
21-Nov-06	MRA 8 mg IV	40	26	97	====> 25	22	104
5-Dec-06	MRA 8 mg IV	34	25	87	21	21	93
19-Dec-06		42	29	78	26	25	83
16-Jan-07	MRA 8 mg IV	40	25	69	25	21	74
13-Feb-07	end core study;mtx20	39	31	78	24	26	83
20-Feb-07	MRA 8 mg IV mtx20						
6-Mar-07	mtx20	44	25	66	27	21	71
20-Mar-07	MRA 8 mg IV mtx20	118	56	76	73	48	81
3-Apr-07	mtx20	222	95	74	137	81	79
17-Apr-07	mtx10	920	422	80	569	359	86
3-May-07	stop mtx10 LTE62-77	92	45		57	38	
15-May-07	MRA 4 mg IV mtx10	47	26	90	29	22	96
6-Jun-07	stop all	269	115		166	98	
11-Jun-07	withdrawn from study	254	74	88	157	63	94
27-Jun-07		199	89	108	123	76	116
10-Jul-07		40	27	122	25	23	130
7-Aug-07		36	28	111	22	24	119

Note: MRA=tocilizumab; mtx=methotrexate

Comment: It remains unclear where the data provided originally in the laboratory listings in attachment4 came from. The ULN values given there are for men and are all quite a bit higher than those for women, as specified in the Roche Reference Ranges originally provided to us as attachment6: ALT for men 55, women 30; AST for men 40, women 25; ALP for men 115, for women 100. I had used the values for women, rather than men in my consultation of 8 August sent last week. Since the patient was in Peru, can we be sure that the ——— central laboratory did all the tests, and why did the reference ranges keep changing? The revision by adjusting the results according to a formula that really amounts to dividing a new ULN for women by the previous ULN for men does make the numbers smaller, but what is true?

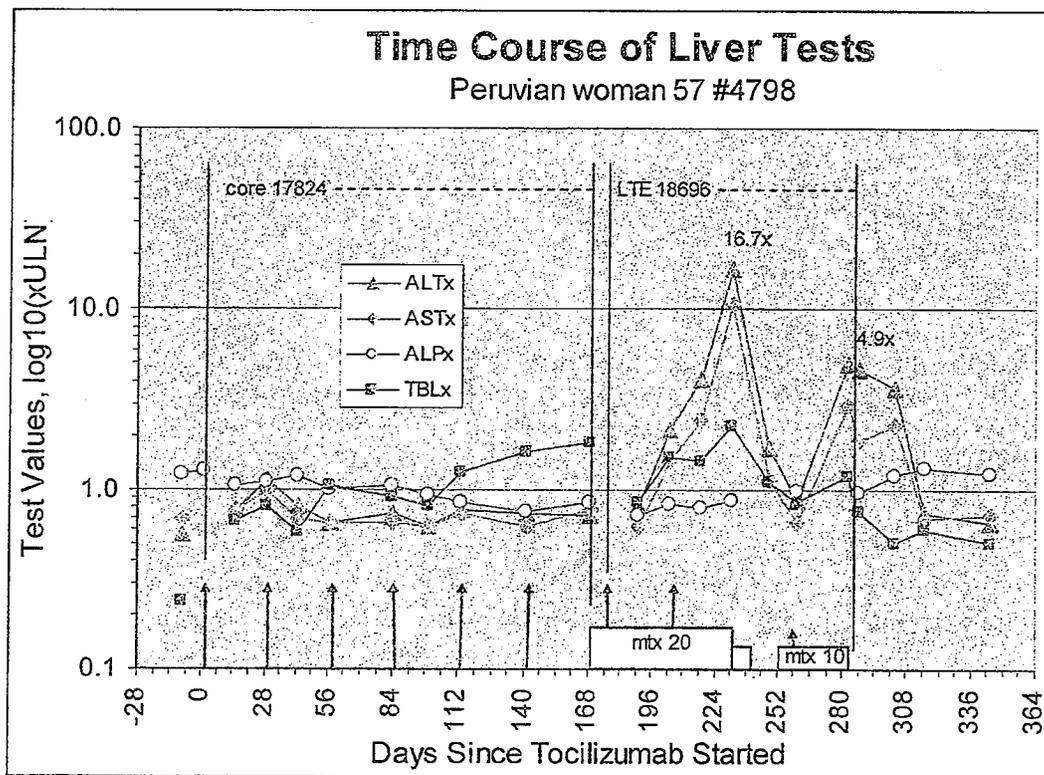
b(4)

The resubmitted information included some additional data about hematological values during the core study, but none for the long-term extension study during which the abnormal laboratory values were seen. The revised listing states that bilirubin values were changed from micromoles per liter to mg/dL in the extension study.

Comment: The hematological data are of no particular interest, since they were stable and there was never a question that the high calculated "indirect" bilirubin levels had been caused by

hemolysis. The revised listing seems to mix up the bilirubin fractions, and to imply the indirect bilirubin was being measured, which is wrong. Only direct-reacting (at 1 minute) and total bilirubin concentrations in serum are actually measured; the indirect fraction is calculated by difference as $IBL = TBL - DBL$. Actually it is well known that direct-reacting bilirubin by the standard diazo test grossly overestimates the true amount of glucuronidated bilirubin at low or normal levels, and underestimates it when the TBL is elevated. It is also well known that women tend to have lower TBL values than men, although not all laboratories recognize this.

Using the resubmitted data generally lowers the numerical values of the serum transaminases but does not change the pattern of obvious liver injury that occurred during the extension period during which tocilizumab was given in combination with methotrexate.



Comment: The appearance of the graph is not much changed by the downward revision of the serum transaminase values. The pattern of acute hepatocellular injury is still evident, and the timing continues to suggest a tocilizumab-methotrexate combination injury. The rechallenge after half-doses of both agents is prompt and impressive, and makes a drug-induced injury very likely or definite, although other possible causes (acute viral hepatitis A, B, C, autoimmune hepatitis, biliary tract disease, etc) have not been adequately excluded. The lone TBL value of 2.25 xULN on day 232, when the transaminases peaked, does not constitute a Hy's Law case, for the reasons discussed in the consultation of 8 August. It is very likely that the patient had constitutional hyperbilirubinemia (Gilbert syndrome) and that the bilirubin elevation was not significant, compared to her previous values on Days 113-169. The bilirubin appears to have

been raised by reduced capacity to conjugate bilirubin with glucuronide, because of inherited genetic aberrations, and not because of drug-induced hepatocellular damage. However, having Gilbert's syndrome does not protect a person against DILI, and the data here continue to show that she did have DILI. It cannot be resolved whether the DILI was from one drug or the other, or from the combination, because of the way the study was carried out.

The sponsor's justification for the manipulation and revision of the data appears to be expressed in the previously submitted "attachment6 lab data handling" in which it is explained that different laboratories use different methods, resulting in different reference ranges. While this may have been so in the past,¹ in recent years the almost universal use of machines to carry out multiple tests on the same sample of serum has led to standardization of results. The major differences in laboratory-reported "normal" ranges now has become due to differences in the way they select individuals to constitute the so-called "normal" reference sample of the population. It has become realized that in some sample selections, people have been included despite the fact that they may be overweight or obese and very likely to have fatty liver disease with or without steatohepatitis, and may have elevated ALT values that are not really normal or healthy. In addition, the prevalence of low grade chronic hepatitis C, often asymptomatic and of unknown origin or duration, may further contribute to elevating the ULN in a reference population sample.² The differences in people selected as "normal" has become greater than the differences in laboratory methods used. It is questionable that simply changing the data to some idealized reference range is valid.

The sponsor's document on "Handling and Reporting of Laboratory Safety Data" that was provided as attachment6 previously, also states that "laboratory test values were converted from the investigator reported units to SI units." This has not been done for the serum enzyme activities for ALT, AST, and ALP. The units reported both in the original and revised submission were in U/L, or international units per liter of serum. These units are based on micromoles of substrate changed per minute per liter of serum. The Systeme International (SI) units are expressed in micromoles per second per liter of serum, called a microkatal, and have values 1/60th of those expressed in U/L. Thus, 30 U/L would be 0.5 μ kat/L, as listed in the reference they cited from the Massachusetts General Hospital laboratory.¹

All in all, not a very credible performance by this sponsor on reporting data to us.

Recommendations:

1. This revised data do not alter my opinion that this case does not meet a definition of "Hy's Law case." The woman apparently had an underlying reduced capacity to conjugate bilirubin with glucuronide (constitutional hyperbilirubinemia, or Gilbert syndrome).
2. It looks very likely or even definite that she suffered hepatocellular injury of Level 1 severity, caused by either the combination of methotrexate and tocilizumab, or possibly by methotrexate alone. Again, having Gilbert syndrome does not prevent a person from having a superimposed drug-induced liver injury.
3. The sponsor has not clarified the data, and it remain unclear in which laboratory the tests were carried out or what the ranges of normal should be. The sponsor has not explained the discrepancies between the data previously submitted as attachment4, and the resubmitted downward revision of the numbers.
4. No further reporting on the exact dates of drugs and doses administered has been provided, to resolve the discepancies between what they reported to us and what they told their consultant, _____
5. No information has been provided as to the patient's height and weight, and body mass index, nor whether they tested her for acute viral hepatitis A, B, C and for autoimmune hepatitis, biliary tract disease, and possible cardiovascular evidence of congestive heart failure or hypotension. She could also be studied to confirm a diagnosis of Gilbert syndrome (constitutional hyperbilirubinemia).
6. I do not think that this case justifies a recommendation for monitoring, but some mention of it should be included in the labeling, with suggestion that future cases should be looked for, especially in patients taking combinations of drugs with tolizumab, and that cases that occur be investigated thoroughly and reported completely. The sponsor needs to be informed of how to do a rechallenge if anything is to be learned from it.

b(4)

JR Senior

John R. Senior, M.D.

cc: M. Avigan, OSE/DAEA I
G. Dal Pan, OSE
R. Rappaport, DAARP
S. Okada, DAARP
R. Temple, CDER/DMP

REFERENCES

1. Kratz A, Lewandrowski KB. Normal reference laboratory values. N Engl J Med. 1998 Oct 8;339(15):1063-75. [PMID [9761809](#)]
2. Prati D, Taioli E, Zanella A, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med. 2002 Jul;137(1):1-10. [PMID [12093239](#)]

1 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Administrative - 1

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

DATE: 8 August 2008

FROM: John R. Senior, M.D., Associate Director for Science, Office of Surveillance and Epidemiology (OSE)

TO: Sarah Okada, M.D. Medical Reviewer, Division of Anesthesia, Analgesic, and Rheumatology Products (DAARP)
Bob Rappaport, M.D., Director, (DAARP)

CC: Mark Avigan, M.D., Director, DAEA I/OSE
Gerald Dal Pan, M.D., Director, OSE

SUBJECT: Request dated 3 August 2008 for review of possible Hy's Law case, by 15 August 2008; received at OSE 6 August and assigned #2008-1259

Documents reviewed:

- 1) Consultation request from Dr. Sarah Okada concerning a 57-year-old Peruvian woman with rheumatoid arthritis patient who developed increased serum aminotransferase activities and also had elevated serum total bilirubin levels, on investigative treatment with the monoclonal antibody tocilizumab (ACTEMRA,® Roche) and methotrexate
 - 2) Brief narrative report submitted by sponsor, with table of test results in extension period
 - 3) Roche document on handling of laboratory safety data and normal ranges **b(4)**
 - 4) Consultation to Roche by _____ dated 5 October 2007
 - 5) Roche tabulation of data from both 6-month and extension periods
 - 6) Fragment of clinical review of BLA 125276 by Dr. Okada, pages 71-77
 - 7) Selected medical literature citations
-

The case which is of special concern was that of a 57-year-old Peruvian female with a 9-year history of rheumatoid arthritis who was participating in a clinical trial of a monoclonal antibody to the interleukin-6 receptor (IL-6R), ACTEMRA (tocilizumab, Roche), given intravenously at four-week intervals. The drug was given alone for the first 6 months, 8 mg/kg, then with oral methotrexate 20 mg weekly during a long-term extension period.

Comment: There are numerous discrepancies in the data and ancillary information provided by the sponsor concerning this case. The sponsor's narrative and that of their consultant _____ refer to several laboratory values that do not correspond, compounded by at least three different statements of what the laboratory normal ranges should be, in the material provided for my review. It is unclear whether the data tabulated for the long-term extension study WA18696 in the sponsor's narrative (transbilresp.pdf) were "adjusted" by the sponsor in some way, but they differ markedly from the listing of the serial data for both the core trial WA 17824 and the

b(4)

extension provided (attachment4lablistings.pdf), particularly with respect to the ALT and TBL values, and their so-called normal ranges.

The critical question concerns the serum bilirubin values of 17 April 2007 (day 232 of the core study or day 57 in the extension study). Serum bilirubin is measured by adding a diazo reagent to measure color developed "directly," then methanol or ethanol is added to solublize more of the bilirubin to give a "total" bilirubin measure. The reactivity and color development depends on the water solubility of the bilirubin, and is a rough and very inaccurate estimate of how much bilirubin is conjugated to make glucuronide derivatives by uridinediphosphopyridine glucuronosyl transferase, an enzyme called UGT1A1. It is a very old test, dating back to van den Bergh¹ and Muller in 1916, modified by Malloy and Evelyn² in 1937, to make it "quantitative." Bilirubin itself, derived from oxidation of heme via biliverdin, is very insoluble in water and is carried in the plasma by loose albumin binding; the glucuronides are much more water-soluble. In laboratory practice the direct-reacting bilirubin is subtracted from the total measured to give a calculated difference, called "indirect" bilirubin. Therefore as reported, TBL - DBL → IBL. However, there really is very little truly mono- and diglucuronidated bilirubin in normal plasma or serum (<1 μmol/L), so the measured DBL overestimates amounts of conjugated bilirubin at low TBL levels, and underestimates them at high TBL concentrations.

In the genetic aberration of constitutional hyperbilirubinemia, also known as Gilbert syndrome, TBL fluctuates from the normal range to slightly or somewhat elevated, mostly up to 2 and 3 mg/dL. This results from reduction in the rate of bilirubin conjugation with glucuronide, found to be due to a group of inherited mutations of the superfamily of genes coding for the enzyme uridine diphosphoglucuronosyltransferase (UGT) and identification of UGT1A1 as the isoform catalyzing glucuronidation of bilirubin to mono- and diglucuronides that are excreted into the bile by the hepatocytes. This results in a reduced fraction of the TBL that shows up as DBL, and correspondingly increased IBL is calculated by subtraction. In the 5-7% of the Caucasian population (I don't know the distribution in Peru) who have these mutations, there may be insertion of extra adenine-thymidine (A-T) nucleotides, causing reduced expression of the gene and about 30% reduction in glucuronidation.^{3,4} This causes no impairment whatsoever in other liver functions, most people who have it don't know it, it causes no restriction in their lives, and is not really a disease at all.⁵

The listing shows the peak bilirubin value at 38H, with an ULN of 17 micromoles/liter of serum but in Table 2 of the sponsor's narrative shows 2.7H mg/dL, with ULN of 1.2. Using the listing values, the total bilirubin concentration was 2.2 xULN (38/17 = 2.24), about the same as using the narrative table values (2.7/1.2 = 2.25 xULN). However, the ULN of 1.2 mg/dL does not equal 17 μmoles/L, but is 21 μmoles/L, and 38/21 = 1.81 xULN. Converting from mg/dL to μmoles/L is done using a factor of 17.1 (based on 10,000 micrograms per liter divided by the molecular weight of bilirubin of 584.66 micrograms per micromole; 10,000/584.66 = 17.1). All this is very confusing in the material provided for review here. Using the ——— narrative, the listing of data provided in attachment4, and the values for ULN in the sponsor's statement of normal ranges provided as attachment6, a composite synthesis may be constructed of what went on and will serve as a basis for my remarks. Obviously, the sponsor provided more detailed information to their consultant, ———, than they reported to us in their narrative.

b(4)

The patient in question here was reported to have started tocilizumab 8 mg/kg intravenously on 29 August 2006, and had repeat doses every 4 weeks for 6 months. _____ reported that she was also taking low-dose prednisone 5 mg/day, and the sponsor's narrative said she also was on aluminum hydroxide as an antacid, paracetamol (acetaminophen), piroxicam, and folic acid. The data listing (attachment4) showed normal levels of TBL before study and for 4 months, but then slightly elevated levels at 16, 20 and 24 weeks after starting the study at 1.2, 1.7, and 1.8 xULN assuming an ULN of 17 μ mol/L. However, the data listing also shows that all the bilirubin was "indirect" (actually more than all, since it lists IBL as >TBL on study days -8, 113, and 141; this is just one more error in the sponsor's data). If the sponsor's measurements are to be believed, then the patient had no measurable DBL on all the days of the 6-month core study, and also continued this in the long-term extensions study.

b(4)

Comment: This is strongly suggestive that she had the Gilbert syndrome of constitutional hyperbilirubinemia and that her later rise in TBL was not due to drug-induced hepatocellular injury, and hence what was observed should not be considered a "Hy's Law case." The bilirubin elevation was not the consequence of hepatocellular drug-induced liver injury but was due to a constitutional and harmless gene mutation. The ALT rise was substantial, and occurred after methotrexate was added to her regimen, and recurred after rechallenge.

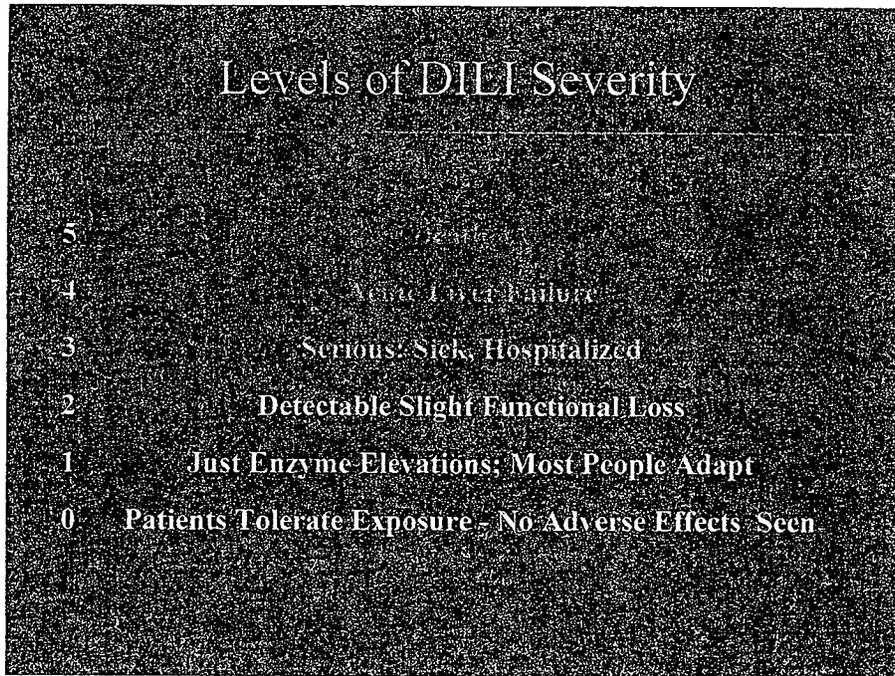
Although it may be more detail than you asked for, let us consider the origins of the concept. The term 'Hy's Law' was coined by Bob Temple shortly after a Fogarty Conference at NIH in 1978,⁶ where by consensus of the assembled experts the "markedly abnormal" level of ALT was set at >3 xULN and bilirubin at >2 xULN. Bob then referred to "Hy's Law" verbally and privately on many occasions over the next two decades, and found it a valid and useful tool for assessing the clinical and regulatory importance of cases. His first public use of it that I know of was at the CDER course on "Drugs and the Liver: What They Do To Each Other" held in April 1999 (see: www.fda.gov/cder/livertox/courses.pdf), at the Shady Grove Campus in Gaithersburg, attended by about 325 CDER reviewers. The late Dr. Hyman J. Zimmerman was present, but was unable to speak because of the lingual carcinoma that caused his death three months later. He did tell me, by writing notes, that he believed it was so but did not want his name used in an eponymic sense. He declined to specify how he determined a case was "drug-induced" or "hepatocellular" or what levels of ALT should be used to call it hepatocellular injury or what level of serum TBL was required for "jaundice."

Bob had written his definition that he called "Hy's Law" in November 2000 in a white paper sent out in advance (see pages 6-7 in: www.fda.gov/cder/livertox/clinical.pdf) to the registrants signed up to attend a large, public meeting at Chantilly VA in February 2001. Bob then referred openly to it at the meeting www.fda.gov/cder/livertox/presentationssss/im1389/sld012.htm (slides 12-15). The term was catchy, became rather widely used informally, and was discussed as a landmark finding in HEPATOLOGY.⁷ In response to a challenge by Jim Lewis of Georgetown,⁸ Kaplowitz, Temple, and I were asked to write accompanying editorials⁹⁻¹¹ to explain it further. He has recently upgraded his definition in the draft guidance to industry made public in the Federal Register in October 2007 (www.fda.gov/cder/guidance/7507dft.pdf pages 3-6), which was discussed in some detail at the March 2008 public conference at the nearly National Labor College (see 2008 Meeting at: www.fda.gov/cder/livertox). The term has been very widely used,

but is also widely misunderstood, as evidenced by the behavior of the staff at study site 14 who were observing patient 916 and reported in the narrative summary provided.

What Dr. Temple has defined and used is not exactly what Hy Zimmerman said, wrote, or meant when he talked about it repeatedly, although it captures the principle. The first mention I have found to what the late Dr. Hyman J. Zimmerman meant was in his distinguished George M. Kober Lecture given in 1968, published in *Perspectives in Biology and Medicine*.¹² From what we can learn from those who trained under him and knew very intimately what patients he was alluding to, the Zimmerman observation referred to a mixed group of patients, many of whom were rather sick, disabled, hospitalized patients who were visibly jaundiced. He described them as having "drug-induced hepatocellular jaundice," which he characterized as a "grave illness with an estimated mortality rate of 10-50 per cent." He continued to believe in the correctness of the observation, referring to it as a "serious lesion, [whose] mortality rate ranges from 10 to 50 percent," in his textbook editions of 1978¹³ and 1999.¹⁴

What Bob Temple defined as Hy's Law indicated a level of liver injury that could be somewhat less severe than what Hy Zimmerman was describing, but more severe than the widely used pharmaceutical industry definition of ALT >3xULN. The Temple definition depended on laboratory measures of elevated serum activities of transaminase enzymes AND total bilirubin concentration. However, the Zimmerman description, terse though it was, described clinically serious injury with all the FDA adjectives of disabling, requiring or prolonging hospitalization, life-threatening effects used to define serious adverse reactions. In an attempt to clarify this rather widespread confusion, we have recently¹⁵ proposed five levels of severity of DILI (Figure 2), which are in accordance with the current thinking of the NIH-sponsored drug-induced liver injury network (DILIN) principal investigators. The subject of was recently discussed again by Adrian Reuben¹⁶ in his presentation at the March 2008 conference on DILI.



Best Possible Copy

It is usually observed that lower levels of severity are detected more frequently, and that some of those people may show more serious levels of DILI. However, the finding of a given level of DILI in an individual person does not predict what will happen if exposure to causative drug is continued, because many people adapt by changes in expression of liver enzymes, transporters, and other processes, and repair and regeneration, so they become tolerant to drugs that caused transient injuries. However, finding cases of more severe injury than just transient enzyme rises in some ("Hy's Law cases") may suggest that other people may fail to adapt and progress to the higher levels 3 to 5 of clinically serious DILI if administration of the drug is not stopped. In this context, what Hy Zimmerman seemed to be referring to were cases of level 3 DILI severity, who showed the 10 to 50% mortality rate (or its more recent equivalent of liver transplant).

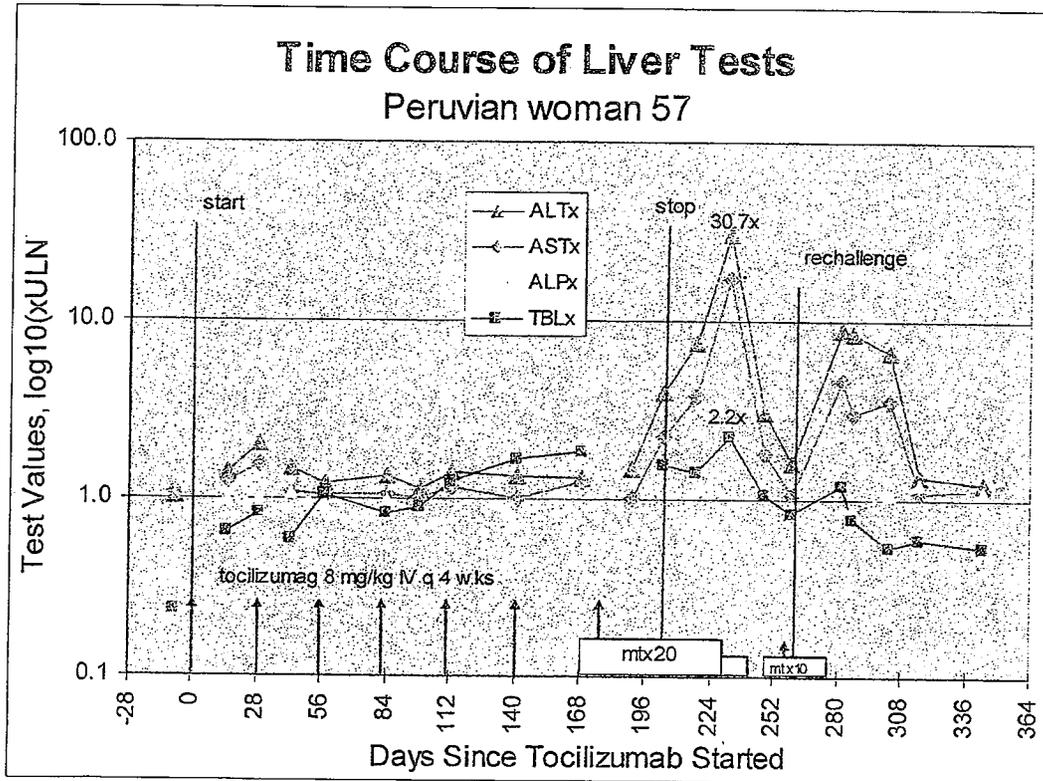
For some reason, despite all that's been written and discussed, many people don't fully understand what Temple meant by applying a definition that may reflect only Level 2 severity to assessing cases of DILI, while the pharmaceutical industry standard and practice had been to stop administering a study drug if ALT or AST activities exceeded 3x ULN, Level 1 severity. Defining Hy's Law as biochemical elevations of ALT as >3x ULN with concurrent or immediately subsequent TBL >2x ULN is therefore a conservative rule, aimed at casting a great deal more attention on the level 2 DILI cases in hope of avoiding progression to or incidence of the more serious levels 3 to 5 among future patients exposed to the drug. It is too late now, but perhaps we should be talking about "*Temple's Rule, based on the Zimmerman observation.*" The rule, or law, is really a regulatory device to help sort out cases of drug-induced hepatotoxicity that merit special attention and careful work-up. If a case is really a "Hy's Law case," then it has much more clinical and regulatory importance than simple ALT or AST elevations, whatever level of peak or highest observed serum activity is chosen.

Comment: This case exemplifies the confusion that appears to remain widespread among not only among many of the investigators and sponsors of clinical trials, but also to some extent among regulatory reviewers, and even consultants in hepatology. This Peruvian woman had constitutional hyperbilirubinemia (Gilbert syndrome) of no clinical importance, and fluctuating elevations of TBL with apparently very little or no DBL. She also showed minimal fluctuating elevations of serum ALT activity that have not been explained and raise the question of whether she had fatty liver or undiagnosed mild chronic hepatitis C, or some other underlying liver problem, details about which have not been given to us in the sponsor's narrative. The data provided do not support assessment of this as a "Hy's Law" case or anything more than simple Level 1 serum enzyme elevations. Based on the time course of the changes (see Figure) and the positive rechallenge, it would seem very likely or even "definite" (almost certain) that she showed acute drug-induced liver injury (DILI), but it cannot be established to what drug. Was it caused by methotrexate alone, or by tocilizumab in combination with methotrexate?

As the investigator carried out the rechallenge, no answer is provided. After subsidence of the peak injury during dose reduction and interruption of methotrexate administration, she was then rechallenged by half-doses of both drugs and showed a positive response. If they had given just methotrexate, or just tocilizumab for the rechallenge, they might have learned something. Such acute DILI is not typical of methotrexate-related DILI, which is more often slow and insidious, with hepatosteatosis and fibrosis appearing after long-term methotrexate administration as in

treatment of psoriasis, so tocilizumab is not necessarily completely innocent in this case. To appreciate this, please look carefully at the graphic display of the time-course of the liver test abnormalities, using the details of when the drugs were started and stopped, doses changed and restarted, as reported in [redacted] consultation.

b(4)



Comment: Based on a likelihood scale of 1 to 5 (from almost certainly or definitely not drug-related, to almost certainly or definitely drug-related), this case would appear to be a 4 or 5, but to the combination of methotrexate and tocilizumab. Because of what we have known for many years about methotrexate and how little we know about possible tocilizumab-induced hepatotoxicity, I would estimate that this reaction was possibly caused by methotrexate alone and definitely caused by the combination of the two drugs. The fact that she tolerated six monthly injections of tocilizumab without hepatotoxicity makes a combination effect much more likely. With regard to the severity of the case, I would rate it as Level 1 and not a Hy's Law case, since she showed a consistent reduction in DBL throughout all the measurements made, if the data provided are credible. The patient could of course be checked for having Gilbert syndrome, by both repeat serum bilirubin fractionations using standard tests, by more accurate fractionations using one of a variety of chromatographic measures, and by genetic testing of her UGT1A1 activity and TATA boxes.

Recommendations:

1. **This case would not meet a definition of "Hy's Law case" in my estimation. She apparently had an underlying reduced capacity to conjugate bilirubin with glucuronide (constitutional hyperbilirubinemia, or Gilbert syndrome). It must be understood, however, that having Gilbert syndrome does not prevent a person from having a superimposed drug-induced liver injury.**
2. **It looks very likely or even definite that she suffered hepatocellular injury of Level 1 severity, caused by either the combination of methotrexate and tocilizumab, or possibly by methotrexate alone.**
3. **The sponsor should clarify the data, and confirm the exact dates of laboratory testing and the normal ranges in the laboratory(ies) used, exact dates of drugs and doses administered, to resolve the discrepancies in what they have reported.**
4. **Additional information should be provided as to the patient's height and weight, and body mass index, whether they tested her for acute viral hepatitis A, B, C and for autoimmune or alcoholic hepatitis, biliary tract disease, and possible cardiovascular evidence of congestive heart failure or hypotension. She could also be studied to confirm a diagnosis of Gilbert syndrome (constitutional hyperbilirubinemia).**
5. **It is unlikely that the confirmation of the reported values, normal ranges, and supplementary information will change my opinion based on new data, but the sponsor should do a better job in reporting the facts to us.**
6. **I do not think that this case justifies a recommendation for monitoring, but some mention of it should be included in the labeling, with suggestion that future cases should be looked for, especially in patients taking combinations of drugs with tolizumab, and that cases that occur be investigated thoroughly and reported completely.**

JR Senior

John R. Senior, M.D.

cc: M. Avigan, OSE/DAEA I
G. Dal Pan, OSE
R. Rappaport, DAARP
S. Okada, DAARP
R. Temple, CDER/DMP

References

1. van den Bergh AAH, Muller P. Über eine direkte und indirekte Diazoreaktion auf Bilirubin. *Biochem. Z.* 1916;77:90-103.
2. Malloy HT, Evelyn KA. The determination of bilirubin with the photoelectric colorimeter. *J Biol Chem.* 1937;119:481-90.
3. Tukey RH, Strassburg CP. Human UDP-glucuronosyltransferases: metabolism, expression, and disease. *Annu Rev Pharmacol Toxicol.* 2000;40:581-616. [PMID [10836148](#)]
4. Rossi F, Francese M, Iodice RM, et al. Inherited disorders of bilirubin metabolism. *Minerva Pediatr.* 2005;57(2):53-63. [PMID [15985997](#)]
5. Bailey A, Robinson D, Dawson AM. Does Gilbert's disease exist? *Lancet* 1977;1(8018):931-3. [PMID [67389](#)]
6. Davidson CS, Leevy CM, Chamberlayne EC, eds. Guidelines for Detection of Hepatotoxicity Due to Drugs and Chemicals. Washington, National Institutes of Health Publication No. 790313, 1978.
7. Reuben A. Hy's Law. *Hepatology* 2004;39(2):574-8. [PMID [14768020](#)]
8. Lewis JH. 'Hy's Law,' the 'Rezulin Rule,' and other predictors of severe drug-induced hepatotoxicity: putting risk-benefit into perspective. *Pharmcoepidemiol Drug Saf.* 2006;15(4):221-9. [PMID [16444771](#)]
9. Kaplowitz N. Rules and laws of drug hepatotoxicity. *Pharmcoepidemiol Drug Saf.* 2006;15(4):231-3. [PMID [16552791](#)]
10. Temple R. Hy's Law: predicting serious hepatotoxicity. *Pharmcoepidemiol Drug Saf.* 2006;15(4):241-3. [PMID [16552790](#)]
11. Senior JR. How can 'Hy's law' help the clinician? *Pharmcoepidemiol Drug Saf.* 2006;15(4):235-9. [PMID [16552792](#)]
12. Zimmerman HJ. The spectrum of hepatotoxicity. (Kober Lecture). *Perspect Biol Med.* 1968;12(1):135-161. [PMID [4387099](#)] (page 155)
13. Zimmerman HJ. Hepatotoxicity. The Adverse Effects of Drugs and Other Chemicals on the Liver. New York, Appleton-Century-Crofts, 1978. (page 353)
14. Zimmerman HJ. Hepatotoxicity. The Adverse Effects of Drugs and Other Chemicals on the Liver. 2nd edition. Philadelphia, Lippincott Williams & Wilkins, 1999. (page 433)
15. Senior JR. Lessons from isoniazid --- would it be approved today? www.fda.gov/cder/livertox/presentations2008/C-Senior2.pdf
16. Reuben A. Hy's law explained. www.fda.gov/cder/livertox/presentations2008/E-Reuben2.pdf

Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Anesthesia, Analgesia, and Rheumatology Products

Application Number: BLA 125276

Name of Drug: ACTEMRA (tocilizumab)

Applicant: Roche Laboratories

Material Reviewed:

Submission Date: November 19, 2007

Receipt Date: November 19, 2007

Submission Date of Structure Product Labeling (SPL): November 19, 2007

Type of Labeling Reviewed: WORD

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

1. Delete the modifier "RA" from the Highlights **INDICATION AND USAGE** and **DOSAGE AND ADMINISTRATION** sections.
2. Delete dash lines from the Highlights **INDICATION AND USAGE** and **DOSAGE AND ADMINISTRATION** sections.
3. Delete underline from references throughout entire label; for example, [*see Warnings and Precautions (5.4)*] and not [*see Warnings and Precautions (5.4)*]. See "Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements" at <http://www.fda.gov/cder/guidance/6005dft.htm>].

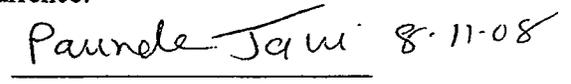
4. The first statement under Highlights and Full Prescribing Information (FPI): **DOSAGE AND ADMINISTRATION** section, "ACTEMRA is administered by intravenous infusion." should be deleted due to redundancy.
5. Indent all paragraphs under headings and subheadings throughout the FPI. For overall formatting, refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for examples of labeling in the new format.
6. Under FPI: **ADVERSE REACTIONS**, subsection 6.1, remove the bold font from the subheadings (Infections, Infusion Reactions, Laboratory Tests, and Other Adverse Reactions), and consider using italics or underline to distinguish subheadings.
7. Under FPI: **CLINICAL PHARMACOLOGY**, subsection 12.3, remove the bold font from the subheadings (Distribution, Elimination, Pharmacokinetics in Special Populations, Hepatic Impairment, and Renal Impairment) and consider using italics or underline to distinguish subheadings.

Recommendations

Labeling revisions, deficiencies, and issues should be communicated to the Sponsor with a request that updated labeling be submitted to the application. This updated version of labeling will be used for further labeling discussions.


Sharon Turner-Rinehardt 1-15-08
Regulatory Health Project Manager

Supervisory Comment/Concurrence:


Parinda Jani 8-11-08
Chief, Project Management Staff

Drafted: STR/010708
Revised/Initialed:
Finalized:
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT