# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**125276**

# OFFICE DIRECTOR MEMO

# Summary Basis for Regulatory Action

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| **Date** | January 8, 2010 |
| **From** | Curtis J Rosebraugh, MD, MPH<br>Director, Office of Drug Evaluation II |
| **Subject** | Summary Review |
| **NDA/BLA #<br>Supp #** | 125276 Complete Response |
| **Applicant Name** | Hoffmann-LaRoche |
| **Proprietary / Established (USAN) Names** | Actemra<br>Tocilizumab |
| **Dosage Forms / Strength** | Intravenous<br>4 mg/kg or 8 mg/kg every 4 weeks |
| **Proposed Indication(s)** | Moderately to severely active Rheumatoid Arthritis |
| **Action:** | *Approval* |

## 1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding the Complete Response (CR) filed by Hoffmann-LaRoche for tocilizumab (TCZ) and I refer the reader to the reviews in the action package, and from the first review cycle, for a more detailed discussion. I am in full agreement with Dr. Rappaport's review and conclusions. Tocilizumab is a recombinant human monoclonal antibody that selectively binds to soluble and membrane-bound human interleukin 6 receptor (IL-6R). The action of tocilizumab inhibits the binding of IL-6 to the receptor and therefore blocks the subsequent signaling cascade of IL-6. IL-6 is a cytokine that is a mediator of inflammation and is involved in the production of acute phase reactants, including C-reactive protein (CRP).

Please see my review from the Complete Response action taken on September 17, 2008 for complete details regarding safety and efficacy. TCZ has demonstrated efficacy for the 4 mg/kg and 8 mg/kg dose in subjects with incomplete response to MTX. In addition, TCZ at 8 mg/kg demonstrated that it is non-inferior (and may be superior) to MTX. The 8 mg/kg dose may have incremental improvement over the 4 mg/kg dose. However, there were deficiencies in the nonclinical program and manufacturing facilities and safety concerns that we felt required a REMS that led to the CR action.

Regarding the nonclinical pharmacology/toxicology deficiencies from the original application, the sponsor did not submit peri-natal and post-natal reproductive toxicology studies that have been required prior to approval of all biologic agents used to treat RA. This CR response has these data and the deficiency has been adequately addressed. Also, all deficiencies regarding manufacturing facilities have been resolved.

Tocilizumab demonstrated the following safety concerns, some expected from immunosuppressant therapy and some that may be unique to TCZ:

1) Increased incidence of serious infections that was dose related compared to placebo
2) Increased incidence of laboratory abnormalities compared to placebo including
    a) Decreased white blood cell count (WBC)
    b) Decreased platelets
    c) Increases in lipid parameters (appears dose related). The potential of this to translate into cardiovascular events is unknown
    d) Liver enzyme elevations
3) Gastrointestinal (GI) perforations that may be dose related
4) Demyelinating events, both central and peripheral

My original review discusses these further. The CR submission has updated safety information and post-marketing experience from other countries and Dr. Okada's review has an excellent safety summary based on this new information. During the first review cycle, we determined that the safety was appropriate to allow marketing if labeling could be agreed upon. Overall, the data in the update have not altered our conclusions and specifically the rates of deaths, serious adverse events (SAE), serious infectious events (SIE), and malignancies have remained consistent.

One safety concern identified in the original review was gastrointestinal (GI) perforation. The original submission had identified 16 events, the majority occurring in the lower GI tract. The update safety data has now identified 25 GI perforations. Dr. Okada has calculated that the exposure-adjusted incidence of lower GI events in the TCZ program has increased from 0.15 to 0.21 events per 100 patient-years, while the exposure-adjusted incidence of upper GI events remained the same. Both of these estimates are above rates found in RA patients in the United Health Care (UHC) and Marketscan databases. To put these numbers into context, Dr. Okada compares them to the incidence of GI perforations experienced with corticosteroids (0.39 per 100 patient-years) and TNF inhibitors (0.13 per 100 patient-years). It would appear that the risk for lower GI perforations is greater with TCZ than with TNF inhibitors and the label should reflect our concern.

TCZ is associated with increased ALT liver function tests. The ALT elevations > 3 x ULN seem to be to about the same extent as those demonstrated with MTX therapy. During the first review cycle, a subject was identified with abnormal liver function test and we wrestled with the issue of whether this was a case of Hy's Law or if the subject had Gilbert's disease so that it was not truly a Hy's Law case with all the accompanying ramifications. Ultimately, I concluded that while the subject may have had Gilbert's disease, they also had some degree of liver injury, some of which may have also been attributed to concomitant MTX therapy, but that TCZ was not totally absolved of risk. What is somewhat reassuring is that with the new data, there does not seem to be any cases that fulfill Hy's law criteria and there are theoretical reasons why TCZ may increase transaminase levels while not leading to overt liver disease as outlined in Dr. Okada's review.

During the first review cycle, an Advisory Committee meeting was held. Members expressed concern over the unknown cardiovascular effects that may occur because TCZ raises total cholesterol and LDL cholesterol. As Dr. Okada summarizes, in the original BLA, there were

15 cardiovascular events/4158 pt-yrs = 0.4/100 pt-yrs and this decreases to 24 events/8580 pt-yrs = 0.3/100 pt-yrs with the updated data. It is felt that the background rate in RA is 0.5 to 0.8/100 pt-yrs. While this is not conclusive data of the lack of a cardiovascular signal with TCZ use due to the paucity of events, it does give us some reassurance such that we can allow marketing while a definitive CV outcome trial is performed. It is interesting to note, that many consider CRP a marker of CAD risk (or at the least a marker of inflammation), much like LDL cholesterol is and as such it will be of scientific value to see if a drug that has such a profound effect on lowering CRP has a protective effect and actually reduces cardiovascular events.

With respect to CVA events, the background rate in RA is 0.1 to 0.8/100 pt-yrs. In the original BLA, there were 9 CVA events/4158 pt-yrs = 0.2/100 pt-yrs. In the updated All-Exposure population, there have been a cumulative 18 events/8580 pt-yrs = 0.2/100 pt-yrs, so this rate has remained stable and seems to be in line with what we would expect from this population.

After the first review cycle, we felt that TCZ marketing would require a REMS. The original REMS request from us required components including a Medication Guide, Communication Plan, and Elements to Assure Safe Use (ETASU) which would have a restricted distribution element. In discussion with the Office of Surveillance and Epidemiology (OSE) and the Division of Risk Management (DRISK), it was decided that ETASU were not appropriate for this product as the adverse events and laboratory abnormalities associated with tocilizumab treatment are similar to those observed with other products approved to treat Rheumatoid Arthritis and do not warrant ETASU to ensure that the benefits of tocilizumab outweigh the risks. Therefore the company was notified by teleconference on November 3, 2009, and by letter on November 16, 2009, that a modified REMS proposal should be submitted to the BLA and that the revised REMS need not contain the ETASU. The revised REMS that the sponsor submitted was reviewed by the Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK) and found acceptable.

**2. Conclusions and Recommendations**

TCZ has demonstrated efficacy for the 4 mg/kg and 8 mg/kg dose in subjects with incomplete response to MTX. In addition, TCZ at 8 mg/kg demonstrated that it is non-inferior (and may be superior) to MTX. The 8 mg/kg dose may have incremental improvement over the 4 mg/kg dose.

TCZ has also demonstrated several safety concerns many of which seem dose related, most associated with other immunosuppressant agents, although GI perforations, transaminitis and elevations in lipids (with unknown long term impact on cardiovascular outcomes) seem unique to this agent, or may occur at greater rates than other agents. Also noted was hypertension which the reviewers feel is infusion related (possible dose related) and transitory, although that has not been fully ascertained.

As I had mentioned in my previous review I am struck how the treatment of RA has some parallels to the treatment of HIV. Both are devastating diseases and both had lacked effective therapies until the recent past. With the first few therapies for HIV, we were willing to tolerate

a lot of unknowns with safety as we were desperate for therapies. But now, due to many effective therapies and the lengthening of the life span of those infected with HIV such that it is now considered a chronic disease, we are demanding more certainty and safety data with marketed and to be marketed drugs. We seem to now be in a similar position with therapies for RA. Where once we did not have much selection, we now have many options such that we can begin to be more concerned about the safety of new agents to a degree we were not afforded in the past.

Even though there are some safety concerns for TCZ, some of which may be unique, this drug is very effective, and for the most part, the safety profile associated with TCZ treatment appears to be consistent with the safety profile observed with other approved biologics. Adverse events related to TCZ-unique safety concerns appear to be rare. As such, it has the capacity to an important addition to the armamentarium of drugs used to treat RA and should be approved. However, until further clinical experience is obtained, its use should be recommended that therapy is limited to patients who have inadequate results with one or more DMARDs and who have inadequate response to one or more TNFs. This is in keeping with how we have approved agents for RA in the past and provides an effective agent to patients that have limited options. In addition, the sponsor will need an adequate REMs and also will need to conduct a cardiovascular outcome study as a PMR to further define whether the lipid effect (and potential blood pressure effect) increases the risk of cardiovascular thromboembolic events.