Risk Management Plan

Actemra® (tocilizumab) 162mg for SC Injection

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Actemra (tocilizumab) SC Injection Post-marketing Risk Management Plan

I Introduction

Tocilizumab is a humanised monoclonal antibody created by grafting the complementarity determining region (CDR) of the mouse anti-human interleukin-6 receptor (IL-6R) monoclonal antibody onto a human IgG1k antibody framework. The IL-6 cytokine is a multi-functional cytokine produced by a variety of cell types which has been shown to be involved in such diverse physiological processes as T-cell activation, induction of acute phase proteins, stimulation of haemopoietic precursor cell growth and differentiation, proliferation of hepatic, dermal and neural cells, bone metabolism, lipid metabolism and hepatoprotection. The cytokine has also been implicated in the pathogenesis of a variety of disease states including inflammatory diseases, osteoporosis, neoplasia and ageing. It exerts its effect through a ligand-specific receptor (IL-6R) that exists in both soluble and membrane-bound forms. The membrane-bound IL-6R is physiologically expressed on a variety of human cells including monocytes, T-lymphocytes, B-lymphocytes, hepatocytes, osteoblasts and keratinocytes. Receptor expression can also be induced by a variety of stimuli in pathological states including inflammation and neoplasia.

As a therapeutic agent, tocilizumab has been approved in Taiwan in July 2011 as IV infusion solution for treatment of rheumatoid arthritis. Since approval, its risk management plan has been implemented extensively.

Considering convenience of drug administration, new formulation of subcutaneous injection of tocilizumab 162mg has been developed. From clinical approach, SC formulation given by patients' self-injection exempted the patients traveling to hospitals to receive IV infusion. In the meantime, unlike IV infusion route, clinical study results indicated that tocilizumab s.c. administration can be given in fixed dose. The new formulation provides more options for physicians to make the best choice based on patients' condition.

The proposed indication of Actemra SC Injection in Taiwan is as follows:

"Actemra, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more DMARDs or tumor necrosis factor (TNF) antagonists. In these patients, Actemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate."

Recommended dosage for Actemra SC Injection is 162 mg subcutaneous injectionevery two weeks.

II Worldwide regulatory status

Tocilizumab was first approved in Japan for the treatment of Castleman's disease on 11 April 2005, which marks its International Birth Date (IBD). In 2008, it has also been approved in Japan for treatment of moderate to severe RA in adult patients, pJIA and sJIA.

The IV infusion form has been approved in over 120 countries globally for treatment of adult RA and over 30 countries for systemic juvenile idiopathic arthritis (sJIA).

The SC formulation has already been approved in countries and regions including Japan, US and EU for treatment of adult RA.

III Rheumatoid arthritis in Taiwan

Rheumatoid arthritis is characterized as disabling chronic systemic inflammatory autoimmune disease. The onset of disease occurs in adults in their fourth and fifth decade of life. The disease is characterized by symmetric synovitis and erosive arthritis, often rapidly progressive with joint damage soon after the onset of symptoms. This feature typically leads to a progressive decline in functional status and work disability.

The majority of studies carried out in Northern European and North American estimate a prevalence of 0.5-1% and a mean annual incidence of 0.02-0.05%[(1)]. In Taiwan, it was reported that the annual incidence rate is 0.03%, similar as worldwide epidemiological data[(1)].

Timely diagnosis and early aggressive treatment with the goal of rapidly controlling symptoms, limiting joint damage, improving function and preventing disability is essential. Traditional, principles of the treatment of RA is to use analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) for the control of pain and inflammation, in combination with DMARDs (Disease Modifying Anti-Rheumatic Drugs) to slow the process that result in joint destruction. Over the past decade, treatment of RA has changed considerably with biological agents such as anti-IL-1, anti-TNF, anti-IL-6, anti-CD20 B cells, and T-cell co-stimulation modulator. By selectively blocking the effect of specific cytokines or inflammatory cells, these biological agents largely improved treatment effect of traditional agents.

IV Overview of TCZ safety profile in clinical trial experiences

Multiple phase I, phase II and phase III studies were conducted to prove clinical safety and efficacy of tocilizumab SC formulation, as well as to bridge clinical data with IV formulation. In the two phase III pivotal studies, 1095 patients were treated with tocilizumab SC for at least 24 weeks, and 239 patients were treated for at least 48 weeks. Study WA22762 is a phase III, randomized, double-blind, active-controlled trial designed to demonstrate non-inferiority of tocilizumab SC (given 162 mg weekly) vs. IV (8mg/kg q4w) in patients with moderately to

severely active RA who had an inadequate response to stable dose of DMARDs that may have included one of more anti-TNF biological agents. Study NA25220 is a phase III, randomized, double-blind, placebo-controlled trial comparing tocilizumab SC (given 162 mg q2w) versus placebo SC in patients with moderately to severely active RA with an inadequate response to DMARDs that may have included one or more anti-TNF biological agents.

Study results indicated that tocilizumab SC was well tolerated and the overall safety profile is consistent with the known and well-established profile of tocilizumab IV, with the exception of a higher incidence of injection site reactions (ISRs) in the SC arm, as would be expected with a subcutaneous route of drug administration. The majority of ISRs were single occurrence, manageable, of CTC Grade 1 intensity, and resolved without sequelae. No patients discontinued the study treatment due to an ISR.

Consistent with AEs previously reported for tocilizumab IV, the most common system organ classes (SOC: ≧10% in at least one treatment arm) in which AEs were reported following tocilizumab SC were infections and infestations (most commonly upper respiratory tract infection [URTI], nasopharyngitis and urinary tract infection [UTI], investigations (mainly elevation in hepatic transaminases), gastrointestinal disorders (most commonly diarrhea), musculoskeletal and connective tissue disorders (most commonly arthralgia and RA), general disorders and administration site conditions (most commonly injection site erythema and pain), skin and subcutaneous tissue disorders (most commonly rash and pruritus), and nervous system disorders (most commonly headache).

During the initial 24-week treatment period there was one death (Sepsis) in the IV arm of WA22762 and there were three deaths (two sepsis and one lower respiratory tract infection) in the TCZ SC treatment group of NA25220.

The majority (≧94%) of AEs reported were Grade 1 or 2 in intensity. In the TCZ arms, the most common SOCs in which Grade ≧3 AEs were reported were infections and infestations, investigations and blood and lymphatic system disorders.

During the long term extension period, in both studies WA22762 and NA25220, the safety profile of TCZ SC was generally consistent with the safety observed during the first 24-week blinded period, and no new safety issues emerged with the longer duration of tocilizumab SC treatment. The event rates per 100 PY of exposure for SAEs and AEs leading to withdrawal were sustained after week 24 and in the extension phase, whereas rates for all-grade AEs were lower in the extension phase. Two additional deaths (one per arm) were reported in study WA22762 during the extension phase (shock in the SC arm and idiopathic pulmonary fibrosis in the IV arm) and

one more death (angina pectoris) in the TCZ SC arm.

V. **Special safety concerns in Taiwan**

Tuberculosis infection is one of high epidemic communicable disease listed as a national disease control program by Taiwan CDC. New cases reported during year 2005-2008 are 16,472 (72.5/100,000 population), 15,378 (67.4/100,000 population), 14,480 (63.2/100,000 population) and 14,265 (62.0/100,000 population), respectively. The overall trend is down-slope, but still needs attention[(2)]. Considering the immune response of RA patients receiving biological immune modulators may be altered, it is strongly recommended to conduct TB screening and routine monitoring for patients prior to Actemra use.

Prevalence rate of chronic hepatitis B and hepatitis C are also higher in Taiwan, comparing with other countries. Estimated prevalence rate of adult hepatitis B carrier in Taiwan is 15-20%[(3)]. It is strongly recommended to conduct viral hepatitis screening to exclude active hepatitis patients from receiving Actemra treatment. In order to close monitor hepatitis-related safety issues during Actemra use, symptom-free hepatitis B or hepatitis C carriers, if necessary to start Actemra treatment, are highly advised to accept routine safety monitoring.

In the past 3 years of experience with Actemra IV Infusion formulation, only two cases were reported for TB infection and one case for suspect hepatitis B re-activation. The low incidence is because well-implemented communication plan provided to health care providers. Awareness of TB and viral hepatitis has been highly elevated during the past several years among medical professionals and patient groups. In the SC formulation, such efforts shall be continued.

VI **Details of important identified and potential risks:**

Identified risks:

Review of the safety data for tocilizumab from phase I-III clinical trials has indicated the following identified risks:

- Serious infections (including hepatitis B reactivation)
- Serious hypersensitivity reaction
- Complications of diverculitis (including GI perforation)

Potential risks for further evaluation:

The following potential risks for further evaluation were identified on the basis of clinical trials data with tocilizumab:

- Neutropenia and the potential risk of infections
- Thrombocytopenia and the potential risk of bleeding
- Liver enzyme elevations and bilirubin elevations and the potential risk of

hepatotoxicity

- Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events
- Malignancies
- Demyelinating disorders
- Immunogenicity

Potential risks of drug interaction:

- CYP450 substrates

VII Post-marketing risk management plan

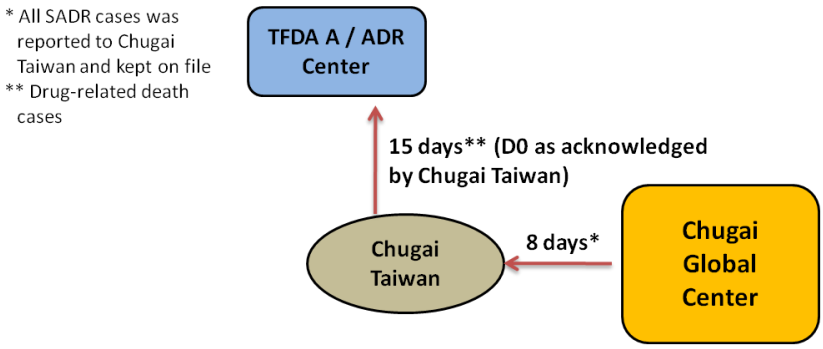
1. AE report: (timeline and reporting scheme)

a、 Serious AE reporting of Taiwan cases: all serious adverse events shall be reported to Taiwan ADR center by the sponsor within 15 calendar days, and also reported to Chugai Drug Safety Department within 3 calendar days after Chugai Taiwan was acknowledged. Chugai Taiwan will also reinforce training and education to health professionals to report SADR to Taiwan ADR center within the following timeline:

- ◆ Death or life-threatening SAEs: initial report within 7 calendar days; follow-up report within 15 calendar days after the health professional become aware of the event.
- ◆ Disability, birth defect, hospitalization / prolonged hospitalization: within 15 calendar days after the health professional become aware of the event.

F. Hoffmann-La Roche Ltd. (hereafter referred to as “Roche”) holds the global safety database for tocilizumab. Therefore, Chugai Drug Safety Department will forward all SAE reports to Roche, according to the joint pharmacovigilance contractual arrangement between Roche and Chugai.

b、 Serious AE reporting outside Taiwan cases: foreign serious SAE cases will be reported to Chugai Taiwan from Chuagi Global Center. These reports will be checked and filed. All drug-related death cases will be reported to TFDA ADR center within 15 days after Chugai Taiwan was acknowledged.



c、 Guided questionnaire

The use of Guided Questionnaires (GQs), will be implemented for designated events of special interest in newly initiated clinical trials or post-marketing experiences, in order to ensure that appropriate data are collected thoroughly and consistently. A GQ is defined as a questionnaire designed to elicit specific information for a particular adverse event term when observed during clinical use of Actemra, to allow better characterization of the nature, occurrence of potential risk factors, as well as assessment of the effectiveness of risk minimization measures. Such GQs are intended to further improve the quality of adverse event data, to provide the Global Drug Safety Database with consistent data that will fully describe events in order to medically evaluate cases, and to analyze data consistent with the objectives of the pharmacovigilance plan. (see appendix 1 for GQs of each potential and identified risks)
GQs have been prepared for the following potential and identified risks:

- Infections (including all opportunistic infections and non-serious infections as defined by those treated with IV anti-infectives)
- Myocardial infarction /acute coronary syndrome
- Gastrointestinal perforations and related events
- Malignancies
- Anaphylaxis / hypersensitivity reactions
- Demyelinating disorders
- Stroke
- Bleeding events
- Hepatic events

Adverse event information collected by Guided Questionnaires will be entered into the tocilizumab Global Drug Safety Database and the result of analysis will be appropriately described in the global PBRER. The report will be submitted to Taiwan FDA / ADR center upon PSUR submission timeline defined by TFDA. For AE cases reported in Taiwan, if a Guided Questionnaire is used for this case, the information

collected in Guided Questionnaire will be included with the Taiwan reporting format made to Taiwan ADR center as follow-up documents.

2. Dose adjustment plan (Refer to the latest PI)

   If laboratory abnormality was detected, the dose of tocilizumab use should be given in reduced frequency or interrupted according to the instruction provided in product labeling. During treatment period, ALT, AST, ANC and platelet count should be carefully monitored.

3. PSUR

   After license approval, the sponsor will submit global PBRER to TFDA ADR center every 6 months for first two years, and then annually for three years.

4. Maintenance of safety information update

   Labeling change: approved professional labeling, describing the conditions in which tocilizumab can be used safely and effectively, will be reviewed periodically and updated as necessary to incorporate information from post-marketing surveillance or studies revealing new benefits or safety concerns. All newly acquired safety information will continue to be actively monitored in accordance with Guidance for Good Pharmacovigilance Practice (藥品優良安全監視規範), including regular review and evaluation of cumulative data. When newly detected safety information become applicable that lead to revision of CCDS (company core data sheet), the sponsor shall file the application of labeling change to TFDA within 60 days of global CCDS revision.

   If product labeling has been revised to include updated safety information and approved by TFDA, the new version of package insert should be delivered to all prescribers and hospital pharmacies with proper notification letter.

5. Communication plan

   a. Internal training of company personnel (first-line contact with health professions, safety information management specialists). Disease and product knowledge training has been implemented since IV formulation obtained license approval three years ago. For the new SC formulation, additional? training will be focused on SC-specific safety information such as injection site reaction and self-injection instruction.

   b. Physician and nurse training
      i. “Risk communication plan” (Appendix 2).
      ii. Notification of product safety information.(Appendix 3)
      iii. Dear HCP letter whenever important safety information shall be updated and require immediate communication
      iv. Notification of product labeling change
      v. Instruction of self-administration (Appendix 5)

   c. Pharmacist training
      i. Notification of product safety information.(Appendix 3).
      ii. Dear pharmacist letter whenever important safety information updated

iii. Notification of product labeling change

d. Patient education

i. Patients' medication guide (Appendix 4)

ii. Instruction of self-administration (Appendix 5)

iii. Articles or videos for disease management

e. Records for training / education for internal / external programs

i. Trainings provided to medical professionals will include at least "Risk communication plan" and "Notification of product safety information". The training should be delivered to prescribers after hospital formulary listing. Potential training target include Rheumatology and Immunology specialists.

ii. The communication plan should be delivered by qualified trainers. All training records should be reserved will signature and date by the trainer.

iii. All versions of training material should be retained and keep filing.

VIII References

(1) Epidemiology of adult rheumatoid arthritis. Alamanos *et., al.* Autoimmunity Reviews 4 (2005) 130-136

(2) Taiwan tuberculosis control report 2009. Taiwan CDC

(3) Hepatitis B. Taiwan CDC

IX Appendix

Appendix 1: Guided Questionnaire

Appendix 2: Risk communication plan

Appendix 3: Notification of product safety information

Appendix 4: Patients' medication guide

Appendix 5: Instruction of self-administration