

ADDENDUM
to
Hoffmann-La Roche's Briefing Document

Arthritis Advisory Committee
July 29, 2008

10. RISK MANAGEMENT LABEL RECOMMENDATIONS

Hoffmann-La Roche has added the following risk management label recommendations to the Sponsor's Briefing Document:

10.1. INDICATION

ACTEMRA[®] (tocilizumab) is indicated for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who had an inadequate response to one or more DMARDs or TNF antagonists or in whom DMARDs cannot be used. ACTEMRA can be used alone or in combination with methotrexate or other DMARDs.

10.2. DOSAGE AND ADMINISTRATION

The recommended dose of ACTEMRA for adult patients with rheumatoid arthritis is 8 mg/kg given once every 4 weeks as a 60-minute single intravenous drip infusion. ACTEMRA may be used as monotherapy or concomitantly with methotrexate or other DMARDs. ACTEMRA has not been studied and should not be used in combination with biological DMARDs such as TNF antagonists, IL1R antagonist, anti-CD20 monoclonal antibody and Selective Co-Stimulation Modulators.

General Dose Advice

- The dose of 8 mg/kg is consistently more efficacious than 4 mg/kg in combination therapy in patients with an inadequate response to DMARDs or in patients having failed TNF antagonist therapy.
- Reduction of dose from 8 mg/kg to 4 mg/kg may be considered for management of dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia.
- In patients who have an inadequate response to one or more DMARD, a dose of 4 mg/kg may be considered followed by titration up to 8 mg/kg based on clinical response.
- Actemra monotherapy has only been studied at a dose of 8 mg/kg.

10.3. UPDATES TO SAFETY INFORMATION

Infections

- ACTEMRA treatment should not be initiated in patients with active infection.
- ACTEMRA should be interrupted if a patient develops a serious infection or an infection that could become serious until the infection is controlled.
- Patients should be screened for tuberculosis prior to initiating ACTEMRA. If positive, initiate tuberculosis treatment according to clinical practice guidelines
- Live attenuated vaccines should not be given while on ACTEMRA.

Neutrophils

- ACTEMRA should not be initiated in patients with Neutrophils < 2000 cells/mm³.
- Neutrophils should be monitored 4-8 weeks after the first infusion in all patients. Repeat labs as per good clinical practice

Lab Value (cells/mm³)	ACTEMRA Dose Modification
ANC ≥ 1000	Maintain dose
ANC 500-1000	Interrupt Actemra dosing When ANC >1000 cells/mm ³ resume Actemra treatment with 4 mg/kg and return to 8 mg/kg as clinically appropriate
ANC < 500	Discontinue Actemra

Gastrointestinal Perforations

- ACTEMRA should be used with caution in patients with a history of diverticulitis
- Patients presenting with abdominal symptoms should be promptly investigated

Lipids

- A lipid panel should be obtained after 4-8 wks of ACTEMRA
- Lipid levels should be maintained within target ranges (according to local guidelines) and managed with lipid lowering agents if appropriate

Platelets

- ACTEMRA should not be initiated in patients with Platelets < 100,000 cells/mm³.
- Platelets should be monitored 4-8 weeks after the first infusion in all patients. Repeat labs according to good clinical practice

Lab Value (cells/mm³)	ACTEMRA Dose Modification
Platelets 50,000-100,000	Interrupt Actemra dosing When platelets > 100,000 cells/mm ³ resume Actemra treatment at 4 mg/kg and return to 8 mg/kg as clinically appropriate
Platelets < 50,000	Discontinue Actemra

Liver Enzyme Elevations

- ACTEMRA should not be initiated in patients with ALT/AST > 1.5 x ULN
- ALT/AST should be monitored 4-8 weeks after the first infusion in all patients.
- Repeat labs as per good clinical practice

Lab Value	Action
> 1-3 x ULN	Dose modify concomitant DMARDs For persistent increases (in association with MTX, LFN, and sulfasalazine), dose modify ACTEMRA in order to normalize ALT/AST levels
> 3- 5 x ULN	Interrupt Actemra dosing until < 3 x ULN When values <3xULN resume ACTEMRA treatment at 4 mg/kg or 8 mg/kg dose. For persistent increases, discontinue ACTEMRA
> 5 x ULN	Discontinue ACTEMRA

Infusion Reactions

The infusion setting should be staffed with experienced personnel and appropriate medications and equipment to manage anaphylactic reactions