

Tocilizumab (Actemra®)

Criteria for Use

November 2014

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient. Individual cases that are outside the recommendations should be adjudicated at the local facility according to the policy and procedures of its P&T Committee and Pharmacy Services.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or <http://vawww.pbm.va.gov> for further information.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive tocilizumab*

- Patient is currently receiving therapy with a biologic DMARD (see Issues for Consideration)
- Patient has a localized or active systemic infection (see Issues for Consideration)
- Patient has active hepatic disease or hepatic impairment (see Issues for Consideration)
- Patient declines transfer of rheumatologic care and follow-up with a VA rheumatology provider.
- Patient is non-compliant with requests for follow-up and laboratory appointments
- Baseline Absolute Neutrophil Count (ANC) < 2000/mm³
- Baseline platelet count < 100,000/mm³
- Baseline ALT and/or AST > 1.5x the upper limit of normal (ULN)

Inclusion Criteria *All of the following must be met:*

- Diagnosis of rheumatoid arthritis (RA) as defined by the ACR Classification Criteria
- Moderate to severe, active disease as defined by DAS-28, CDAI or SDAI*
- Inadequate disease control despite an adequate trial of non-biologic DMARD therapy that includes methotrexate (at maximally tolerated doses) or have a contraindication to methotrexate use or intolerance.

- Patient has discontinued at least **ONE** TNF-inhibitor despite a trial (at least 3 months-duration) due to inadequate disease control.
- OR
- Patient has discontinued at least **TWO** TNF-inhibitors due to intolerance issues.
- OR
- Patient has discontinued **ONE** TNF-inhibitor due to a severe, documented adverse event where the risk of attempting to trial another TNF-I may outweigh the benefit of therapy.
- OR
- Patient has a contraindication to the use of TNF-inhibitors

- Patient received vaccination for pneumococcal polysaccharide at least two weeks prior to first dose of tocilizumab OR if previously vaccinated, consider revaccination according to CDC guidelines (www.cdc.gov).

*DAS-28: Disease Activity Score; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index

Dosage and Administration

- Initial dose is 4 mg/kg given as an IV infusion in 100 ml 0.9% sodium chloride for intravenous infusion over 1 hour
- Repeat dose every 4 weeks
- For inadequate responders by weeks 12 - 16, dose can be increased to 8 mg/kg as an IV infusion over 1 hour
- Do not exceed a total tocilizumab dose of 800 mg/infusion.
- Dose-modifications may be needed for neutropenia, thrombocytopenia and elevated liver enzymes (see Package Insert for specific recommendations)

Monitoring

- Risk of gastrointestinal perforation. Instruct patients to report symptoms of severe, persistent abdominal pain to their provider immediately for evaluation and appropriate treatment.
- Risk of infection. Instruct patients to report symptoms of infection such as fever, sweating, chills, etc. to their provider for evaluation and appropriate treatment. Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including tocilizumab for rheumatoid arthritis. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Among opportunistic infections, tuberculosis, Cryptococcus, aspergillosis, candidiasis, and pneumocystosis were reported with tocilizumab. Other serious infections, not reported in clinical studies, may also occur (e.g., histoplasmosis, coccidioidomycosis,

listeriosis). Patients have presented with disseminated rather than localized disease. Viral reactivation has been reported with immunosuppressive biologic therapies and cases of herpes zoster exacerbation were observed in clinical studies with tocilizumab. Caution should be exercised in persons with evidence of chronic Hepatitis B infection (e.g., persons who are Hepatitis B Surface antigen-positive). No cases of Hepatitis B reactivation were observed in the trials; however patients who screened positive for hepatitis were excluded.

- Risk of neutropenia. Treatment is associated with a higher incidence of neutropenia. Monitor Absolute Neutrophil Count (ANC) every 4 – 8 weeks; dose modification may be needed. Discontinue tocilizumab if ANC < 500 cells/mm³.
- Risk of thrombocytopenia. Treatment is associated with a reduction in platelet count. Monitor platelets every 4 – 8 weeks; dose modification may be needed. Discontinue tocilizumab if platelet count < 50,000 cells/mm³.
- Risk of elevated liver function tests. Treatment is associated with elevated transaminase values. AST/ALT should be monitored every 4 – 8 weeks; dose modification may be needed. Discontinue tocilizumab if liver enzymes > 5x ULN.
- Risk of elevated lipid parameters. Assess lipid parameters 4-8 weeks after initiation, then at approximately 6-month intervals; patients should be managed per clinical hyperlipidemia guidelines (e.g. NCEP guidelines).
- Risk of gastrointestinal perforation. Instruct patients to report symptoms of severe, persistent abdominal pain to their provider immediately for evaluation and appropriate treatment.
- Drug interactions: Inhibition of IL-6 signaling with tocilizumab may increase CYP450 enzymatic activity thereby increasing drug metabolism, ultimately reducing drug exposure of CYP450 substrates. This effect may persist for several weeks even after tocilizumab discontinuation. Use caution and therapeutic monitoring in these situations (ie. oral contraceptives, simvastatin, etc.). Live vaccines should not be given with tocilizumab therapy.

Issues for Consideration

- Tocilizumab is FDA-approved for patients who have had an inadequate response to one or more TNF-antagonist therapies
- Tocilizumab has been studied in patients who have failed TNF-inhibitor therapy, similar to abatacept and rituximab. To date, there is no clinical data comparing these 3 agents or on the safety and efficacy of switching from abatacept or rituximab to tocilizumab or vice versa. There is greater long-term clinical experience with abatacept and rituximab in the setting of TNF-inhibitor failures.
- Combination therapy with tocilizumab and biologic DMARDs (e.g. infliximab, abatacept, rituximab, etc.) has not been evaluated. Such combination therapy may increase the risks of immune suppression and infection, whereas withholding tocilizumab until complete washout of previous biologic therapy carries a risk of disease flare. Based on the best available evidence, allow as long a latency period as clinically possible. Clinical trials used up to five half-lives (such as etanercept > 2 wks; infliximab > 8 wks; adalimumab > 8 wks; abatacept > 8 wks; anakinra > 1 wk; rituximab > 6 months). Shorter periods, such as one dosing interval (e.g., etanercept ≥ 1 wk; infliximab ≥ 8 wk; adalimumab ≥ 2 wks; etc.), have been used anecdotally but the risks and benefits are unknown.
- A Boxed Warning exists concerning the risk for serious infection.
 - Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections have occurred in patients receiving tocilizumab
 - If a serious infection develops, interrupt tocilizumab until the infection is controlled
 - Perform test for latent TB; if positive, start treatment for TB prior to starting tocilizumab
 - Monitor all patients for active TB during treatment, even if initial latent TB test is negative
- Use of tocilizumab is not recommended in those with active hepatic disease or hepatic impairment
- Live vaccines should not be given concurrently with tocilizumab; all vaccines should be brought up to date before initiating tocilizumab
- Pregnancy Category C. There are no well-controlled studies in pregnant women. Tocilizumab caused fetal harm in animal models. Discuss risk vs. benefit in women who are pregnant or may become pregnant. A pregnancy registry has been established.
- Geriatric patients: Use caution when providing tocilizumab to elderly patients. Serious infections occurred with greater frequency among those aged ≥ 65 years.
- REMS program consists of patient counseling and a medication guide.

Renewal Criteria

- Documented benefit of therapy, such as achievement of ACR20 or improvement in DAS28 score, SDAI or CDAI within 24 weeks of tocilizumab initiation.
- Discontinue tocilizumab if an adequate response is not achieved, at the maximally-tolerated dose, despite patient compliance, after a 24-week trial.
- Discontinue tocilizumab for the following laboratory abnormalities: liver enzyme abnormalities > 5x ULN; ANC < 500 cells/mm³, platelet count < 50,000 cells/mm³ (as noted under **Monitoring**).

Prepared: November 2014. Previous revisions: December 2010; June 2011. Contact: Francine Goodman, National PBM Clinical Pharmacy Program Manager – Formulary, VA Pharmacy Benefits Management Services (10P4P)