

# Biologics in Psoriasis and Psoriatic Arthritis

(Adalimumab, Etanercept, Golimumab, Infliximab, and Ustekinumab)

## Criteria for Use

June 2013

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. A monograph with literature review is also available at [www.pbm.va.gov](http://www.pbm.va.gov). The monograph tabulates dosing regimens, contraindications, warnings and precautions that were current at the time of document preparation.*

### Exclusion Criteria

Contraindication to biologic therapy or other condition that would preclude the use of a biologic agent

#### **Adalimumab, etanercept, golimumab, infliximab, ustekinumab:**

- Active or severe infection including tuberculosis
- Hypersensitivity to product ingredients
- Hypersensitivity to murine proteins (infliximab)
- Administration of live vaccine concomitantly with or during biologic therapy.
- Administration of BCG vaccination within one year of starting ustekinumab. Administration of therapeutic intravesical BCG should also be considered a contraindication.
- Has Wegener's granulomatosis and is receiving immunosuppressives (etanercept)
- Concomitant therapy with another tumor necrosis factor (TNF) inhibitor
- Concomitant therapy with abatacept or anakinra
- History or development of reversible posterior leukoencephalopathy syndrome (RPLS) (associated with ustekinumab)

#### **Adalimumab, etanercept, golimumab, infliximab:**

- Multiple sclerosis or other demyelinating disease, or first-degree relative who has multiple sclerosis
- Has heart failure that has not been cleared by cardiology for biologic therapy. (Administration of infliximab doses > 5 mg/kg to patients with moderate to severe (NYHA class III or IV) heart failure is a contraindication.)

### Inclusion Criteria

#### **I. For Adalimumab, Etanercept or Infliximab in Chronic Plaque Psoriasis WITHOUT Psoriatic Arthritis**

- Physician is experienced in the systemic treatment of moderate to severe psoriasis; AND
- Previous biologic agents are discontinued and one biologic agent is used at a time; AND  
(There is insufficient evidence to support efficacy and safety of combination biologic therapy.)
- Adult with chronic ( $\geq 6$  months) moderate to severe plaque psoriasis; AND
- Patient is a candidate for systemic therapy (antipsoriatic or ultraviolet); AND
- Current tuberculosis test is negative or patient receives therapy for prevention or treatment of tuberculosis as clinically indicated prior to starting biologic therapy (also see Issues for Consideration, Infections); AND
- Pre-therapy laboratory tests and appropriate treatment and vaccinations recommended in the prescribing information for the biologic agent and as clinically indicated have been performed (e.g., tuberculin skin test or interferon-gamma release assay (IGRA), chest X-ray, anti-TB therapy if indicated, hepatitis B virus screening (HBsAg and anti-HBc), age-appropriate immunizations, CBC, liver enzymes); AND

Meets one of the following criteria:

- Patient has contraindication, risk factor for serious adverse effect, inadequate response, intolerance, or hypersensitivity to both methotrexate AND ultraviolet therapy (PUVA or narrow-band UVB / UVB, with or without oral retinoids, e.g., acitretin)

See *Issues for Consideration, Methotrexate Contraindications and Risk Factors for Serious Adverse Effects.*

Relative contraindications to ultraviolet therapy: history of skin cancer, melanoma or strong likelihood of developing them (e.g., pale skin, easily sunburns, many moles).

Adequate trial durations:

- For methotrexate: NO or minimal response after 3 months at doses of 15–25 mg/wk (or lower if limited by toxicity); inadequate partial response to treatment after 6 months at doses of 15–25 mg/wk (or lower if limited by toxicity).
- For PUVA and UVB: NO or minimal response after 12 treatments; inadequate partial response after 24 treatments

- Has contraindication, risk factor for serious adverse effect, inadequate response, intolerance, or hypersensitivity to methotrexate, AND ultraviolet therapy is inaccessible;

AND

- The biologic agent is prescribed at the FDA-approved dose for plaque psoriasis.

*Off-label doses may be considered on a case-by-case basis.*

*Etanercept induction doses of 25 mg or 50 mg once weekly may be considered in lieu of 50 mg twice weekly for the first 12 weeks.*

## II. For Ustekinumab in Chronic Plaque Psoriasis WITHOUT Psoriatic Arthritis:

- Meets criteria in Section I AND

Meets one of the following criteria:

- Has contraindication or risk for serious adverse effect (e.g., demyelinating disease, first-degree family member with multiple sclerosis, or heart failure) to TNF inhibitors; OR
- Patient has NO or minimal response after 3 months; inadequate partial response after 6 months; OR intolerance or hypersensitivity with two other TNF inhibitors (adalimumab, etanercept 50 mg/wk, or infliximab)

## III. For Adalimumab, Etanercept, or Infliximab in Psoriatic Arthritis With or Without Psoriasis

- Biologic therapy is prescribed and monitored by a VA or VA-affiliated rheumatologist; AND

- Active psoriatic arthritis; AND

- Current tuberculosis test is negative or patient receives therapy for prevention or treatment of tuberculosis as clinically indicated prior to starting biologic therapy; AND

- Pre-therapy laboratory tests and appropriate treatments and vaccinations as recommended in the prescribing information for the biologic agent and as clinically indicated have been performed (e.g., tuberculin skin test or interferon-gamma release assay (IGRA), chest X-ray, anti-TB therapy if indicated, hepatitis B virus screening (HBsAg and anti-HBc), age-appropriate immunizations, CBC, liver enzymes); AND

Meets one of the following criteria:

- Patient has erosive disease, enthesitis, axial disease, uveitis or dactylitis
- Patient does not have the manifestations above AND has documented contraindication, risk factor for serious adverse event, inadequate response, intolerance, or hypersensitivity with one of the following agents: methotrexate or leflunomide
- *Although methotrexate has been shown to lack efficacy in reducing joint symptoms / synovitis in psoriatic arthritis, experts believe that a subgroup of patients may respond.*
  - *An adequate trial duration is considered to be 3 months, of which at least 2 months is at the standard target dose, unless intolerance or toxicity limits the dose.*

AND

- The biologic agent is prescribed at the FDA-approved dose for psoriatic arthritis.

*Off-label doses may be considered on a case-by-case basis.*

#### IV. For Golimumab in Psoriatic Arthritis With or Without Psoriasis

Meets criteria in Section III AND

Patient has NO or minimal response after 3 months; inadequate partial response after 6 months; OR intolerance or hypersensitivity with two other TNF inhibitors (adalimumab, etanercept or infliximab)

#### Dosage and Administration

Refer to current Product Information.

#### Issues for Consideration

##### General

- Severity of Plaque Psoriasis
  - Moderate to severe psoriasis may be described as psoriasis in which one cannot achieve or would not be expected to achieve adequate control using topical agents, with adequacy defined by the patient's own perception of the disease and its burdens.
  - Severe psoriasis may be described as disease that is disabling or impairs the patient's quality of life (self-reported), including ability to work and activities of daily living AND the disease does not have a satisfactory response to treatments that have minimal risks, the patient is willing to accept life-altering adverse effects to achieve less disease or no disease, AND generally more than 10% of body surface area is involved with disease. Psoriasis may also be considered severe when other factors apply such as the patient's attitude about the disease; location of disease (e.g., face, hands, fingernails, feet, genitals); symptoms (e.g., pain, tightness, bleeding, or severe itching); arthralgias or arthritis.
- Patients with first-degree relatives who have MS are contraindicated from receiving TNF inhibitors because they have an increased risk of developing MS, with a sibling relative risk of 18 to 36. Ustekinumab is not a TNF inhibitor and is not contraindicated in demyelinating disease or in first-degree family members with MS.
- During biologic therapy, patients should be periodically re-evaluated for new signs and symptoms, such as those potentially due to infection or malignancy.
- Consider biologics in perspective: Methotrexate (cirrhosis, pulmonary fibrosis), cyclosporine (renal impairment, hypertension), and acitretin (teratogenicity, mucocutaneous toxicity, hyperlipidemia) are associated with major, relatively predictable treatment-limiting organ toxicities. However, TNFIs are associated with relatively unpredictable major harms including serious infections (e.g., sepsis, tuberculosis, and viral infections), autoimmune dysfunction (e.g., lupus, demyelinating disorders), and malignancies (e.g., lymphoma). TNFIs have also been associated with paradoxically inducing psoriasis and psoriasiform lesions.

##### Infections

- Prior to starting biologic therapy, patients should be screened for tuberculosis and assessed for risk of other infections such as hepatitis B and HIV. Vaccinations, prophylaxis and treatment for exposure or infection should be considered in accordance with Center for Disease Control or other appropriate guidelines.
- Patients who test positive because of latent TB infection (LTBI) should preferably complete at least 2 months of an appropriate course of drug therapy for prophylaxis before starting biologic therapy whenever the clinical situation allows biologic therapy to be delayed; the purpose of this delay is to ensure patient adherence to and tolerance of therapy for LTBI. Weigh the risks of delaying biologic therapy with the risks of activating TB. When delaying biologic therapy or timing the initiation or re-initiation of biologic therapy relative to TB prophylaxis is a concern, consider consulting an infectious disease / TB management expert.
- Perform screening tuberculin skin testing (i.e., PPDs) and/or interferon-gamma release assay (IGRA) with good history taking, symptom assessment and physical exam on an annual basis, and consider an annual chest X-ray if suggested by symptoms in patients on biologic therapy. If a patient develops LTBI, they should be treated with appropriate drug therapy for prophylaxis; it is not necessary to stop the biologic agent unless the patient is unable to be treated for LTBI, e.g., due to poor compliance or medication intolerance.
- If active TB develops during biologic therapy, the biologic agent should be discontinued. The optimal time to resume biologic therapy after completion of adequate anti-TB treatment is undetermined; consulting an infectious disease / TB management expert is recommended.
- If a patient develops a serious infection during biologic therapy, it is advisable to hold the biologic until the infection has resolved.
- Use caution and weigh risks and benefits when considering biologic therapy if the patient has chronic or

recurrent infection; has been exposed to tuberculosis; has resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidiomycosis, or blastomycosis; has a history of opportunistic infection; has a condition that may predispose to infection; has a household contact who is administered a live vaccine (because of the potential risk for transmission – applies to ustekinumab); is elderly because of increased risk of infections; is a carrier of hepatitis B virus; has been treated for hepatitis B reactivation and resumption of TNFI therapy is being considered.

- Consider the following therapy or tests:
  - Empiric antifungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.
  - For ustekinumab – Appropriate diagnostic testing, e.g., tissue culture, stool culture, as dictated by clinical circumstances; theoretically, patients with pharmacologic blockade of IL-12/23 may have increased risk for vulnerability to disseminated infections from mycobacteria, salmonella, and BCG vaccination

### Vaccinations

- If indicated, vaccination of patients is preferred before starting biologic therapy.
- During biologic therapy, consider routine influenza and pneumococcus vaccination and need for other killed virus vaccinations after weighing their potential risks and benefits. Use only killed virus vaccines. With TNFIs, immune response to pneumococcal or influenza vaccination has been attenuated but adequate in most studies. For ustekinumab, the product information warns that non-live vaccines may not elicit an adequate immune response.
- *Avoid live virus vaccines (including varicella, mumps, measles, rubella, oral typhoid, and yellow fever) and live-attenuated virus vaccines (including BCG, herpes zoster and inhaled / intranasal influenza) at any time during biologic therapy.* There are no CDC or other standardized recommendations for timing of administration of live vaccines *before* biologic therapy other than giving zoster vaccine at least 2 weeks before starting immunosuppressive therapy, and some experts advise waiting 4 weeks.<sup>1</sup> The CDC recommends avoiding administration of live vaccines for at least a month *following* immune modulator therapy.<sup>2</sup> When live vaccination is required, some experts consider giving live vaccine at least 3 to 4 weeks before starting biologic therapy, or at least 5 half-lives after discontinuation of biologic therapy and at least 6 months after infliximab therapy.<sup>3</sup>
- Use caution when live vaccines are to be given to household contacts of patients receiving ustekinumab because of the potential risk for shedding from the household contact and transmission to the patient.
- Ustekinumab should not be started in patients who have received BCG vaccine within the past year. BCG vaccine should not be given for at least one year following discontinuation of ustekinumab.

### Concurrent Antipsoriatic Therapies

- Ultraviolet therapy with or without oral retinoids is considered by experts to be safe to use with biologic agents, although published reports of such combination therapy are lacking.
- For plaque psoriasis, DMARDs (disease-modifying antirheumatic drugs) are approved for use with adalimumab, and methotrexate is approved for concurrent use with etanercept and infliximab.
- Clinicians should weigh the potential risks and benefits before deciding to use concurrent ultraviolet, systemic, or other immunosuppressive therapy with biologics. Justification for any concurrent use of systemic or other immunosuppressive antipsoriatic therapy with biologic agents (such as for transitioning or potential additive effects in partial responders) should be clearly documented.
- When biologics are used in combination therapy with another systemic agent, the contribution each agent is providing to patient response should be considered periodically. If continued use of one agent cannot be justified against potential adverse effects and overall cost, the agent should be discontinued.

### Drug-drug Interactions

- Upon initiation of ustekinumab concurrently with CYP450 substrates, particularly those with narrow therapeutic index, consider closely monitoring therapeutic effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and adjusting the dose of the affected drug as needed.

### Pregnancy

- All five biologics are Pregnancy Category B and are preferable over conventional systemic agents (e.g.,

<sup>1</sup> Prevention of Herpes Zoster Recommendations of the Advisory Committee on Immunization Practices (ACIP). June 6, 2008

<sup>2</sup> <http://www.cdc.gov/vaccines/pubs/pinkbook/genrec.html>

<sup>3</sup> Duchet-Niedziolka P, et al. Vaccine. 2009 Mar 4;27(10):1523-9

methotrexate, leflunomide, acitretin) with contraindications or warnings against use in pregnancy or in women or men of childbearing potential who are planning conception or not using effective contraception. However, there is limited information from human experience on the use of the biologics in pregnancy.

### Methotrexate Contraindications and Risk Factors for Serious Adverse Effects

#### **A Trial of Methotrexate Should Not Be Required Before Biologics in the Presence of Any of the Following Conditions:**

##### Contraindications:

- Renal insufficiency (CrCl  $\leq$  60 ml/min)<sup>†</sup>
- Persistently abnormal liver function or enzyme tests and, if available, other markers of hepatic damage such as procollagen type III n-terminal peptide (PIIINP) levels
- Liver disease, including active or recurrent hepatitis and hepatic fibrosis or cirrhosis on liver biopsy (biologics may also not be advisable in this situation)
- Active infectious disease, including active untreated tuberculosis or advanced HIV infection; excludes acute infections for which methotrexate may be temporarily withheld
- Immunodeficiency (does not apply to treatment with other immunosuppressives such as biologic agents)
- Blood dyscrasias or cytopenias (contraindication for methotrexate; requires caution and risk-benefit evaluation for biologics)
- Conception in men or women; patients planning conception or patients of childbearing potential and not using adequate contraceptive method (conception should be avoided during methotrexate therapy and for at least 3 months after stopping therapy in males or at least one ovulatory cycle in females)
- Pregnant or nursing women
- Pneumonitis or significant pulmonary disease that may interfere with diagnosis or monitoring for methotrexate-induced lung disease / pulmonary fibrosis
- Recent vaccination, especially with live vaccine (also refer to live vaccine and BCG vaccination restrictions for biologics)
- Third-compartment spacing, such as persistent pleural effusion and ascites
- Malignant lymphoma (biologic therapy is also not advisable in this situation)
- Hypersensitivity

##### Relative Risk Factors (Methotrexate May Be Used, But Not Required)

- Lifetime cumulative dose of methotrexate is 3 grams or greater. Consider alternative systemic therapies at these cumulative doses, given the limitations of existing data to support or refute lifetime dose of methotrexate as a risk factor.
- Significant lifetime alcohol consumption (e.g., past or current use of >1–2 drinks per day). Methotrexate toxicity is associated with a history of total lifetime alcohol intake before methotrexate therapy. The exact amount of alcohol that confers risk is unknown and differs among persons.
- Chronic hepatitis C without evidence of significant liver disease (contraindicated in patients with HCV and cirrhosis).
- Family history of inheritable liver disease
- Obesity (body mass index greater than 30)
- Diabetes mellitus
- History of significant exposure to hepatotoxic drugs (e.g., azathioprine, retinoids, sulfasalazine) or chemicals
- Hyperlipidemia
- Lack of folate supplementation (i.e., folic acid 1 or 5 mg daily or folinic acid 5 mg every 12 h for 3 doses then once every week, with the first dose given 12 hours after the methotrexate dose)

<sup>†</sup>References: Methotrexate Product Monograph, Pfizer Canada, last updated April 21<sup>st</sup>, 2011. Available at: [http://www.pfizer.ca/en/our\\_products/products/monograph280](http://www.pfizer.ca/en/our_products/products/monograph280) (No CrCl cutoff is recommended in U.S. product information for methotrexate.) Kalb, et al. Methotrexate and Psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol 2009;60:824–37. Methotrexate Tablets, USP product information (online). DAVA Pharmaceuticals, Inc. Rev. 4/09.

### Quantity Limits

Initial prescription: up to 3 months' supply

### Renewal Criteria

More than minimal objective improvement over pre-biologic baseline after the first 3 months of biologic therapy and clinical benefits outweigh potential risks.

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