Background:
Rheumatoid arthritis (RA) treatment can be grouped into two different classes; traditional non-biologic disease modifying antirheumatic drugs (DMARDs) and biologic DMARDs which comprise both the tumor necrosis factor (TNF) inhibitors and miscellaneous non-TNF biologic DMARDs including the Janus Kinase (JAK) inhibitors. The purpose of this Formulary Brief is to summarize the clinical findings from the miscellaneous non-TNF biologic DMARDs review, which consisted of abatacept, anakinra, rituximab, tocilizumab and tofacitinib. As a result of this pharmacotherapeutic analysis and IHS usage and procurement trends review, no modifications were made to the IHS National Core Formulary (NCF).

Discussion:
The American College of Rheumatology (ACR) published RA guidelines in 2015 with a treat to target goal and recommends that patients who have established moderate-to-severe RA and have failed non-biologic DMARDs be treated with any of the following; combination non-biologic DMARDs, TNF inhibitors, or non-TNF biologics (specifically excludes anakinra) or Janus Kinase (JAK) inhibitors.

Abatacept (Orencia®) is a soluble fusion protein, inhibiting T-cell activation by binding to CD80 and CD86 on antigen presenting cells, reducing autoantibody formation and pro-inflammatory cytokines. Abatacept is indicated for moderate-to-severe RA in adults either as monotherapy or in combination with methotrexate (MTX) or other non-biologic DMARDs. It can be administered as an IV infusion or subcutaneously. Common adverse drug reactions (ADRs) include nasopharyngitis, URI, cough, back pain, dyspepsia, UTI, rash and infusion-related reactions including headaches, dizziness and hypertension. Abatacept can increase the risk of serious and potentially fatal infections, lymphoma, lung cancer, and COPD exacerbations.

Anakinra (Kineret®) is a recombinant human interleukin-1 receptor antagonist that prevents degradation of cartilage and bone resorption. It is indicated in adults with moderate-to-severe RA who fail one or more DMARDs and is given as a daily SC injection with MTX or other non-TNF biologic DMARDs. Common ADRs are headaches, infections, injection site reactions, arthralgias and nasopharyngitis. Serious infections include pneumonia, osteomyelitis, cellulitis, bursitis, herpes zoster and neutropenia. Patients with asthma are at an increased risk of infections.

Rituximab (Rituxan®) is a chimeric and human monoclonal CD20 antibody causing B-lymphocyte depletion reducing progression of RA and structural damage. It is approved for moderate-to-severe RA in adults and is used in combination with MTX in those who fail TNF inhibitors. Rituximab is given as an IV infusion and has a Black Box warning for fatal infusion reactions, which happen most frequently with the first infusion. Other Black Box Warnings include mucocutaneous reactions, progressive multifactorial leukoencephalopathy and Hepatitis B reactivation. The most common ADRs with rituximab are peripheral edema, hypertension, fever, fatigue, chills, headaches and neuropathy.

Tocilizumab (Actemra®) is a humanized recombinant IgG1k monoclonal antibody inhibiting IL-6 receptors thus leading to a reduction of cytokines and acute phase reactant production. Tocilizumab is indicated in adults with moderate-to-severe RA who fail one or more DMARDs and is given IV every 4 weeks or SC weekly. Tocilizumab carries a Black Box Warning for fatal infections including tuberculosis, invasive, fungal, bacterial, viral and protozoal infections. Common serious infections are pneumonia, cellulitis, UTI, diverticulitis, herpes zoster, upper respiratory infections and nasopharyngitis. Other serious ADRs include neutropenia, thrombocytopenia, increased ALT and hyperlipidemia.

Tofacitinib (Xeljanz®) prevents cytokine growth factor mediated gene expression and intracellular activity of immune cells and B cells by inhibiting JAK enzymes. It is an oral, twice-daily formulation approved for adults with moderate-to-severe RA as either monotherapy or in combination with non-biologic DMARDs.
It carries a Black Box Warning for increased risk of fatal infections (tuberculosis, invasive, fungal, bacterial, viral and protozoal) and malignancy. Other serious ADRs include lymphocytopenia, neutropenia, lipid abnormalities, increase in PR interval and decrease in heart rate. Use caution in patients with cardiovascular disease, diverticulitis and interstitial lung disease.

Numerous Cochrane Library reviews performed between 2009-2015 evaluated the miscellaneous non-TNF biologic DMARDs and concluded that they were safe and efficacious. Anakinra was shown to be relatively safe and modestly effective but less efficacious than etanercept and adalimumab. Etanercept had fewer withdrawals due to ADRs than adalimumab, anakinra and infliximab. Abatacept was modestly efficacious and safe but should not be used in combination with other biologic DMARDs. Tocilizumab was beneficial in decreasing RA disease activity and improving function, however, it significantly increased cholesterol levels. Rituximab with MTX was significantly more efficacious than MTX alone for improving the symptoms of RA and preventing disease progression. Overall, biologic DMARDs had statistically significantly higher rates of serious infections, tuberculosis reactivation, total ADRs and withdrawals due to ADRs.

A 2014 meta-analysis showed tocilizumab to be superior to TNF inhibitors and comparable to MTX in reduction of pain, and anakinra to be less effective to other biologic DMARDs. Additionally, tocilizumab was superior to rituximab and abatacept in a 2014 retrospective review by Pascat et al. A 2015 review of 54 trials comparing the effects of biologic DMARDs showed that all were effective compared to placebo. When combined with a non-biologic DMARD, certolizumab had the greatest efficacy followed by tocilizumab then anakinra. When used alone, TNF inhibitors (certolizumab, etanercept) were reported to be the most efficacious, followed by tocilizumab/abatacept.

Findings:
The miscellaneous biologic DMARDs are safe and effective and are indicated in treating adults with moderate-to-severe RA who fail initial non-biologic DMARD therapy. All of these therapies can be used as monotherapy or in combination with MTX (or other non-biologic DMARDs) except rituximab which should be used only in combination with MTX. There are several Black Box Warnings and disease-specific concerns that should be addressed prior to selecting a miscellaneous biologic DMARD. Non-biologic DMARDs remain the standard initial treatment for RA according to recent ACR guidelines. The IHS National Pharmacy & Therapeutics Committee concluded that miscellaneous non-TNF biologic DMARDs have a role in treating RA however declined to name a specific agent to the NCF.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

References: