Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: *JAK & Interleukin 12/23 Inhibitors*
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Background:

JAK inhibitors represent a novel class of oral targeted therapies for a growing number of autoimmune/ inflammatory conditions. They exert their effect by interfering with intracellular transcription of inflammatory cytokines. Available JAK inhibitors are tofacitinib (indicated for rheumatoid arthritis, psoriatic arthritis, ulcerative colitis), upadacitinib (rheumatoid arthritis) and baricitinib (rheumatoid arthritis).

Interleukin (IL) 12/23 inhibitors are parenteral biologic monoclonal antibodies that bind the p40 subunit shared by IL 12 and IL 23 and include the agents, ustekinumab and guselkumab. Ustekinumab is currently the only such agent available and is approved for use in psoriasis, psoriatic arthritis and inflammatory bowel disease.

Following clinical and pharmacoeconomic review of the JAK and IL 12/23 inhibitors, the **NPTC made no modifications to the IHS National Core Formulary** at this time. Tofacitinib has advantages over other JAK inhibitors through approval for both rheumatoid arthritis and psoriatic arthritis. However, upadacitinib may have fewer side effects.

Discussion:

Rheumatoid arthritis is a chronic autoimmune disease affecting the joints and other organ systems that, if untreated, can cause substantial pain, deformity, loss of function and deterioration of quality of life. Rheumatoid arthritis and, to a lesser extent, psoriatic arthritis, are more common in American Indian/Alaskan Native (AI/AN) populations than in the general population, with approximately 1% of the world-wide population affected but up to 8% of AI/AN populations[1,2]. Inflammatory bowel disease is less common in the general population than either rheumatoid arthritis or psoriatic arthritis and appears to affect the AI/AN population to the lesser extent[3].

Available medications for treating rheumatoid arthritis include the conventional synthetic DMARDs methotrexate, sulfasalazine, hydroxychloroquine and leflunomide, which are available on the IHS National Core Formulary. In spite of the efficacy of these therapies, there remain up to 30% of patients whose disease is not adequately controlled with either single or combination therapy. Targeted biologic treatments became available in 1995, with the FDA approval of etanercept, a TNF (tumor necrosis factor) inhibitor. Since that time, multiple additional targeted therapies have been developed. In 2016, the NPTC added TNF inhibitors (either etanercept or adalimumab) to the National Core Formulary. The advent of JAK inhibitors presents an opportunity to address rheumatoid arthritis in patients who have failed, or are unable to take, conventional DMARDs or anti-TNF therapy. The advantages of JAK inhibitors include oral administration, tolerability and rapid onset of action. They may also provide benefits for reducing pain, beyond their effects on controlling inflammation[4].

JAK inhibitors are associated with an increased risk of infection compared with placebo, but similar or reduced rates compared with biologic DMARDs[5]. Herpes zoster risk is increased compared with both placebo and biologic DMARDs. Cytopenias and increased LDL cholesterol levels can be seen with JAK inhibitors[6]. Post-marketing safety data has revealed an increased risk of thromboembolic disease, primarily with the higher dose of tofacitinib (for use in ulcerative colitis). The understanding of the risk of VTE with these therapies continues to evolve. The use of JAK inhibitors in pregnancy is not yet studied.

Psoriasis affects approximately 2-3% of the world wide population. Up to 42% percent of people with psoriasis have features of psoriatic arthritis (though some studies cite much lower rates). Psoriatic arthritis is associated with the HLA B27 antigen. Although epidemiological data on psoriatic arthritis in AI/AN populations is not well-defined, a high rate of HLA B27 positivity in some populations has been documented[7]. HLA B27 is also associated with peripheral spondyloarthropathies and ankylosing spondylitis. Anecdotal experience among rheumatologists who care for AI/AN populations support a higher prevalence of these conditions than in the general population.

Available treatments on the IHS National Core Formulary for psoriatic arthritis include the conventional DMARDs methotrexate and, to a lesser extent, sulfasalazine; as well as TNF inhibitors. The JAK inhibitors provide an alternative for those who fail these therapies. Although rheumatologists have been slower to adapt JAK inhibitor treatment for psoriatic arthritis, it is anticipated that these will become more important therapies over time, and that indications will expand to other spondyloarthropathies.

The IL 12/23 inhibitors are safe and effective therapies but have a more important role in the treatment of inflammatory bowel disease than in either rheumatoid arthritis or psoriatic arthritis. Inflammatory bowel disease appears to be uncommon among AI/AN populations.

Findings:

Rheumatoid arthritis and psoriatic arthritis are seen in AI/AN populations at a higher rate than in the general population. Both conditions can cause substantial pain and disability. Optimal treatment includes providing options for therapies beyond conventional disease modifying agents. Anti TNF agents became available on the National Core Formulary in 2016. In spite of this availability, there remains a cohort of patients with suboptimal control, or loss of efficacy over time. Standard of care according to national and international groups involves switching therapy, without specifying "next best" targeted therapy. In addition to providing an alternative medication for patients needing a change in therapy.

JAK inhibitors have advantages over other biologic DMARDs. Side effect profiles and risk of infection are not substantially different from TNF inhibitors. The risk of VTE continues to be evaluated. A major limiting factor in the expansion of the formulary for these conditions continues to be cost.

IL 12/23 inhibitors do not add substantially to the armamentarium for treating psoriasis or psoriatic arthritis. Although ustekinumab would provide an alternative for poorly controlled psoriatic arthritis, JAK inhibitors are a superior choice.

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.

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