GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

1. Does the patient have a diagnosis of moderate to severe rheumatoid arthritis (RA) and meets all of the following criteria?
   - therapy initiated by or in consultation with a rheumatologist
   - previous trial with at least one of the following DMARDs (disease-modifying antirheumatic drug) agents such as methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
   - 18 years of age or older
   - previous trial with the preferred formulary TNF (tumor necrosis factor) inhibitors: Enbrel and Humira

If yes, approve for 4 months by HICL with a quantity limit of 2 tablets per day.

APPROVAL TEXT: Renewal requires that the patient has experienced or maintained a 20% or greater improvement in tender joint count or swollen joint count while on therapy. If no, do not approve.

DENIAL TEXT: Our guideline for TOFACITINIB requires a diagnosis of moderate to severe rheumatoid arthritis. Additional guideline requirements apply.

For patients with moderate to severe rheumatoid arthritis requires all of the following:
   - therapy initiated by or in consultation with a rheumatologist
   - previous trial with at least one of the following DMARDs (disease-modifying antirheumatic drug) agents such as methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
   - 18 years of age or older
   - previous trial with the preferred formulary TNF (tumor necrosis factor) inhibitors: Enbrel and Humira

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TOFACITINIB

RENEWAL CRITERIA

1. Does the patient have a diagnosis of moderate to severe rheumatoid arthritis (RA) and meets the following criteria?
   - documentation that the patient has experienced or maintained a 20% or greater improvement in tender or swollen joint count while on therapy

   If yes, approve for 12 months by HICL with a quantity limit of #2 tablets per day. If no, do not approve.

   **DENIAL TEXT:** Our guideline for TOFACITINIB renewal requires a diagnosis of moderate to severe rheumatoid arthritis. Additional guideline requirements apply. Renewal for the diagnosis of moderate to severe rheumatoid arthritis requires:
   - documentation that the patient has experienced or maintained a 20% or greater improvement in tender or swollen joint count while on therapy.

RATIONALE
To ensure appropriate use of Xeljanz consistent with FDA approved indication.

The recommended dose of Xeljanz is 5 mg orally twice daily with or without food. Dosage modifications are needed for patients with moderate hepatic impairment, moderate to severe renal impairment, concomitant use of potent inhibitors of CYP2C19, concomitant use of moderate/potent inhibitors/inducers of CYP3A4, lymphopenia, neutropenia and anemia.

Xeljanz, an oral agent, is the first selective inhibitor of Janus kinase (JAK) 1 and JAK3 available for the treatment of RA. JAKs are intracellular kinases which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence intracellular immune processes. Xeljanz inhibits the signaling of several cytokine members simultaneously and is therefore being studied for use in the treatment of other autoimmune disorders including ulcerative colitis. While Xeljanz is FDA approved as first line therapy following failure of a DMARD, initially its utilization is expected to be limited to those patients who have failed or are not candidates for injectable biologic therapy (i.e., TNF inhibitors).

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RATIONALE (CONTINUED)
The American College of Rheumatology RA treatment guidelines recommend DMARDs (i.e. MTX, hydroxychloroquine, leflunomide, minocycline and sulfasalazine) as first line pharmacological treatment. Failure with a DMARD is followed by a trial of one or more TNF inhibitors (Humira, Cimzia, Enbrel, Simponi, and Remicade) followed by a non-TNF biologic such as abatacept (T-cell costimulation modulator), Rituximab (B-cell CD20 antagonist) and tocilizumab (IL-6 receptor antagonist). The TNF and non-TNF inhibitor biologics currently on the market today are administered via subcutaneous (SC) injection or intravenous (IV) infusion.

The safety and efficacy of Xeljanz was studied in five phase 3, double-blind, controlled, multicenter trials, in adult patients with moderate to severe active RA who had an inadequate response (IR) to previous DMARD treatment. Studies included IR to MTX, IR to TNF inhibitors and IR to any DMARD (biologic and nonbiologic). The trials ranged from 6 months to an ongoing 2-year trial and totaled 3,315 patients. The primary endpoints for all of the studies were proportion of patients who achieved an ACR 20 response, change in Health Assessment Questionnaire-Disability Index (HAQ-DI), and rates of Disease Activity Score DAS28-4 (ESR) less than 2.6. One study also included mean change from baseline in van der Heijde-modified total Sharp Score (mTSS) as another co-primary endpoint. All of the studies had different time points for primary endpoints ranging from 3 months to 6 months.

In all trials, patients treated with 5 mg twice daily Xeljanz had higher ACR20, ACR50, and ACR70 response rates versus placebo, with or without background non-biologic DMARD treatment, at Month 3 and Month 6. Higher ACR20 response rates were observed within 2 weeks compared to placebo. In the 12-month trials, ACR response rates in Xeljanz-treated patients were consistent at 6 and 12 months.

Study III, known in the literature as the Oral Standard trial, was the only trial to have an active comparator arm (Humira). Study duration was 12 months. Patients (N=792) were on stable doses of MTX and were randomly assigned to receive Xeljanz 5 mg or 10 mg twice daily, Humira 40 mg once every two weeks, or placebo. The ACR20 response rates for Xeljanz 5 mg, Humira and placebo were 51.5%, 47.2% and 28.3% respectively (p<0.001 for all comparison groups vs. placebo). The mean change from baseline in the HAQ-DI score at month 3 and percentage of patients with a DAS28-4 (ESR) below 2.6 at month 6 were also significantly greater with the active treatment versus placebo. The study was not designed or powered to directly compare the efficacy of Xeljanz versus Humira.

Xeljanz has black box warnings of serious infections and malignancies. Prior to starting Xeljanz patients should be tested for latent tuberculosis (TB) and all patients should be monitored for active TB during treatment even if the initial TB test was negative. Other warnings and precautions include gastrointestinal perforations, hepatic impairment, concurrent use of live vaccines, and the necessity to monitor specific laboratory parameters including lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids. The most common adverse reactions reported in >2% of patients treated with Xeljanz monotherapy or in combination with DMARDs were upper respiratory tract infections, headache, diarrhea and nasopharyngitis.

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RATIONALE (CONTINUED)
As Xeljanz undergoes hepatic metabolism via the Cytochrome P450 enzymes CYP3A4 and CYP2C19, drug-drug interactions with inhibitors/inducers of those enzymes can occur. Xeljanz is pregnancy category C.

FDA APPROVED INDICATIONS
Xeljanz is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).

Xeljanz should not be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine.

REFERENCES
• FDA News Release. US Food and Drug Administration. Available at
  http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm327152.htm
[Accessed 11/12/12].

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