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Abbreviated Class Update: Targeted Immune Modulators (TIMS)
New Drug Evaluation: Tofacitinib (Xeljanz)

Month/Year of Review: March 2013
End date of literature search: February 2013
New drug(s): Tofacitinib (Xeljanz®)
Manufacturer: Pfizer (Dossier Received)

Current Status of PDL Class:

- Preferred Agents: ADALIMUMAB (HUMIRA), ETANERCEPT (ENBREL),
- Non Preferred Agents: ABATACEPT (ORENCIA), ALEFACEPT (AMEVIVE), ANAKINRA (KINERET), CERTOLIZUMAB (CIMZIA), EFALIZUMAB (RAPTIVA), GOLIMUMAB (SIMPONI), INFLIXIMAB (REMICADE), NATALIZUMAB (TYSABRI), RITUXIMAB (RITUXAN), TOCLIZUMAB (ACTEMRA), USTEKINUMAB (STELARA)

Research Questions:

- Is tofacitinib more effective than currently available agents for the treatment of rheumatoid arthritis?
- Is tofacitinib safer than currently available agents for the treatment of rheumatoid arthritis?
- Are there specific subpopulations for which tofacitinib is better tolerated or more effective than other available agents?
- Is there any new evidence since the last class review resulting in necessary changes to the current preferred drug list (PDL) class?

Conclusions:

- There is low quality evidence of no conclusive differences in disease activity (ACR 50) efficacy between TIMS for treatment of RA.
- There is moderate quality evidence of improvements in disease activity (ACR 50) from combination therapy of TIMS plus methotrexate than from monotherapy with TIMS for treatment of RA.
- There is still insufficient evidence comparing individual TIMS to make conclusions for the treatment of chronic plaque psoriasis. Adalimumab, infliximab, ustekinumab, and etanercept are FDA approved for the treatment of plaque psoriasis.
- There is low strength evidence favoring individual TIMS versus non-biologic agents (methotrexate) in the treatment of plaque psoriasis.
- At this time, there is insufficient direct evidence to make conclusive statements on how tofacitinib compares with other proven agents used to treat RA. Tofacitinib was studied in patients who had failed trials with methotrexate or DMARDs and against placebo.
- There is moderate quality evidence that tofacitinib decreases symptoms compared to placebo, as measured by the ACR20 response (RR 0.45; 95% CI 0.33-0.62, NNT 3) and increases physical function at 3 months in patients with active RA who had prior inadequate response or intolerance to non-biologic or biologic DMARDs.

- There is moderate quality evidence that the addition of tofacitinib (RR 0.56; 95% CI 0.40-0.78, NNT 4) or adalimumab (RR 0.60; 95% CI 0.44-0.85, NNT 5) to methotrexate may decrease symptoms compared to placebo and increase physical function in patients with RA who have had an inadequate response to methotrexate monotherapy at 6 months.
- There is moderate quality evidence that the addition of tofacitinib to methotrexate improves symptoms compared to placebo (RR 0.58; 95%CI 0.4-0.8, NNT 5), as measured by the ACR20 response at month 6 and improves function in patients with RA and inadequate response to TNF inhibitors.
- Clinical trials showed an increase in discontinuations due to adverse events, serious adverse events, infections, and malignancies with tofacitinib compared to placebo. Due to limited evidence based on short term trials, there remain unanswered safety questions
- Adalimumab was recently approved for the treatment of ulcerative colitis. There is moderate quality evidence that adalimumab induces clinical remission at week 8 in patients with moderately to severely active ulcerative colitis who were not responding to, or intolerant to conventional therapies. However, the absolute differences in remission rates between adalimumab and placebo remained small (7-9%).
- There is low quality evidence that adalimumab it may reduce relapse rates and maintain clinical remission in patients with moderate to severe UC over 52 weeks who did not respond to conventional therapy with oral corticosteroids or immunosuppressive agents.
- There is moderate quality evidence that the FDA approved dose of tofacitinib monotherapy (5 mg twice daily) decreases symptoms compared to placebo, as measured by the ACR20 response (RR 0.45; 95% CI 0.33-0.62, NNT 3) and increases physical function at 3 months in patients with active RA who had prior inadequate response or intolerance to non-biologic or biologic DMARDs.
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- There is moderate quality evidence that the addition of tofacitinib to methotrexate improves symptoms compared to placebo (RR 0.58; 95%CI 0.4-0.8, NNT 5), as measured by the ACR20 response at month 6 and improves function in patients with RA and inadequate response to TNF inhibitors.

Recommendations:
- Update the PA criteria to include the new indication of ulcerative colitis for adalimumab and add the diagnosis of ulcerative colitis to #8 of PA Criteria (Appendix 1).
- Make tofacitinib non-preferred requiring an adequate trial of methotrexate or other oral DMARD and an approved TIM before approval.

Reason for Review:
In June of 2012, the Targeted Immune Modulators (TIMS) drug class review was updated by the Oregon Drug Effectiveness and Review Project (DERP) and subsequently reviewed by the Oregon Health Plan P&T Committee. At that time, prior authorization criteria was created and implemented for OHP patients, attempting to coordinate coverage between the medical and pharmacy plans (Appendix 2). Since then, tofacitinib was FDA approved as the first oral biologic agent for the treatment of rheumatoid arthritis (RA). In addition, there were two systematic reviews updated by the Agency for Healthcare Research and Quality (AHRQ). This new evidence will be reviewed for any necessary changes to the preferred drug list (PDL) or PA criteria.

Author: M. Herink, Pharm.D. Date: February 2013

Previous P&T Conclusions and Recommendations:

- Maintain the most recently approved TIMS, golimumab, tocilizumab, and ustekinumab as non-preferred TIMS due to limited comparative evidence and lack of clinical benefit compared to currently available TIMS.
- Approve proposed PA criteria for non-preferred TIMs requiring (Appendix 1):
    - Use in FDA-approved indications
    - A previous trial of DMARD therapy when appropriate
    - Dose limits to ensure maximum recommended doses
- Approve proposed PA criteria update to antipsoriatics to require trial of standard systemic therapies including cyclosporine, methotrexate, or acitretin if appropriate, before use of a non-preferred biologic agent
- Recommend coordinate coverage of this class in medical and pharmacy programs
- Make Remicade nonpreferred on PDL to coordinate coverage with medical program as it is IV med.

Background:

Rheumatoid arthritis (RA) is an autoimmune disease that involves inflammation of the synovium with progressive erosion to bone leading in most cases to misalignment of the joint, loss of function, and disability. RA does not have any racial predilections, can occur at any age with increasing prevalence up to the seventh decade of life, and is 3 times more common in women[1]. Treatment goals are to control pain and inflammation, and ultimately, remission or at least low disease activity. Therapies for RA include corticosteroids, oral disease-modifying antirheumatic drugs (DMARDS), and biologic DMARDs (anti-tumor necrosis factor drugs, or anti-TNF), such as adalimumab, etanercept, and infliximab. Methotrexate is the most commonly used DMARD because of its proven efficacy and well understood long-term effects. All of the previously biologic DMARDs approved for the treatment of RA are injectable agents that target extracellular cytokines. Tofacitinib is the first oral biologic DMARD that inhibits the intracellular tyrosine kinase called Janus kinase (JAK). The JAKs are critical to signal transduction of interleukins, and inhibition of these molecules has been shown to decrease inflammation and pain, and increase physical functioning.

Treatment of RA is typically initiated with NSAIDS and/or low-dose glucocorticoids, with the introduction of non-biologic DMARDs (usually methotrexate) quickly after diagnosis. If methotrexate or other non-biologic DMARD treatment does not control disease, a biologic agent (TNF inhibitor or TIM) is usually added to the regimen. If anti-TNF therapy does not produce a response, switching to another biologic DMARD is commonly practiced.

Primary endpoints used in the clinical trials are the American College of Rheumatology (ACR) response, the Health Assessment Questionnaire-Disability Index (HAQ-DI), and the Disease Activity Score 28 (DAS-28). The ACR response is a composite endpoint with seven components used to calculate the proportion of patients achieving a target percentage of improvement from baseline and is a considered a measure of efficacy and overall disease activity. Patients are said to meet ACR 20 criteria when they have at least 20% reductions in tender and swollen joint counts and in at least 3 of the domains. ACR 50 and ACR 70 criteria are similar, but with improvement of at least 50% and 70% in individual measures.[2] The FDA accepts ACR 20 response as an acceptable demonstration of efficacy supporting a clinical response claim, and ACR 70 response lasting for 6 months as supportive of a claim of a major clinical response.[3] ACR 50 and ACR 70 are considered more clinically significant than ACR 20. The HAQ-DI is a widely used self-report measure of functional capacity. Scores of 0 to 1 are generally considered to represent mild to moderate disability, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.[2] According to the FDA, the minimal clinically important difference is 0.25 units for a given patient or 0.22 units based on group means.[3] The DAS is another index of disease activity (similar

to the ACR response). A DAS-28 score >5.1 corresponds to high disease activity and <3.2 of low disease activity.[2,3] A score of 2.6 is considered to correspond to remission. The van der Heijde modified Total Sharp Score (mTSS0 is a radiographic scoring system for RA joint damage and a change in joint damage of 5.0 is considered minimally clinically important. [2,3]

Psoriasis is a chronic autoimmune skin disease which utilizes TIMs for the management of disease. Localized disease may be managed with topical agents, while patients with more widespread disease often require systemic treatment. The American Academy of Dermatology guidelines recommends the use of either biologic or nonbiologic systemic agents or phototherapy in patients with widespread disease, with no clear guidelines for selecting first-line therapy. Currently infliximab, etanercept, adalimumab, and ustekinumab are approved for the treatment of psoriasis.[4] Methotrexate is the most commonly prescribed nonbiologic systemic treatment for psoriasis worldwide.

Recently the U.S. Food and Drug Administration (FDA) expanded the approved use of adalimumab to include treatment of moderate-to-severe ulcerative colitis (UC) in adults. Previously, infliximab was the only TIM approved for this indication. The treatment goals in UC are to reduce and maintain remission of symptoms and inflammation and prevent complications.[5] Distal disease may be treated with topical agents and mild disease can be controlled with oral and/or topical 5-aminosalicylate drugs. The American College of Gastroenterologists recommends treatment with infliximab for moderate to severe UC for patients who are steroid refractory or steroid dependent. The Mayo Score is a disease activity index that includes endoscopy and one of the most widely used of the indices in clinical trials.[6] It takes into account sum of stool frequency, rectal bleeding, mucosal appearance, and physician's global assessment. The FDA has recognized a definition of remission as a Mayo Clinic Score ≤2.[7] This definition is considered less stringent than other endpoints used in clinical trials. [7]

Methods:

A Medline literature search ending February 2013 for new systematic reviews and clinical guidelines comparing targeted immune modulators was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

<u>Agency for Healthcare Research and Quality (AHRQ): Rheumatoid Arthritis</u>

A recent update to the comparative effectiveness report evaluating the benefits and harms of corticosteroids, oral and biologic DMARDs for adults with RA was published.[2] Two hundred and fifty eight published articles were included and most studies were of fair quality. This report demonstrated no clinically important differences in efficacy among oral DMARDs (methotrexate, sulfasalazine, leflunomide). There was limited direct evidence comparing biologic DMARDs. One head-to-head trial comparing abatacept and infliximab found no clinically important differences between the two. A meta-analysis found higher odds of

reaching ACR 50 response for etanercept compared with most other biologic DMARDs for methotrexate-resistant patients with active RA. Major conclusions were as followed:

- Low quality evidence that there are no differences in ACR 20 between leflunomide and methotrexate and moderate quality of no difference between sulfasalazine and methotrexate.
- Low quality evidence of greater improvement in health-related quality of life for leflunomide compared to methotrexate.
- Low quality evidence of no differences in tolerability and discontinuation rates between oral DMARDs.
- Low quality evidence of no difference in remission or functional capacity between abatacept and infliximab, with a slightly greater improvement in disease activity for abatacept.
- Low quality evidence that discontinuation rates and sever adverse events are higher with infliximab compared to abatacept.
- Insufficient evidence for any other comparisons of biologic DMARDs.
- Low quality evidence based on a meta-analysis of placebo-controlled trials with greater improvement in disease activity (ACR50 response) for etanercept compared with abatacept, adalimumab, anakinra, infliximab, rituximab and toclizumab.
- Low quality evidence that combining two biologic DMARDs does not add to improvement in disease activity, functional capacity, or symptoms response more than one biologic DMARD and increases the risk of serious adverse effects.
- Moderate quality evidence for better improvements in disease activity from combination therapy of biologic DMARDs plus methotrexate than from monotherapy with biologics.
- Low quality evidence that in patients who are resistant to methotrexate there may be clinically observable differences in the efficacy of the biologic DMARDs. However, evidence from head-to-head comparisons is too limited to provide guidance for clinical decisionmaking.
- Evidence was insufficient to assess comparative risk of serious adverse events among biologic DMARDs.
- Limited good or fair evidence for benefits or harms of subpopulations exists.

<u>Agency for Healthcare Research and Quality (AHRQ): Chronic Plaque Psoriasis (CPP)</u>

In November 2012, a review was completed to examine the comparative effectiveness of biologic systemic agents versus nonbiologic systemic agents or phototherapy for the treatment of CPP.[4] A total of 33 citations were included. Overall there was limited evidence directly comparing biologic agents and insufficient evidence to determine comparative effectiveness of individual therapies. Only five randomized controlled trials (RCTs) and four observational studies directly compared agents using an outcome of interest. No RCTs evaluated the comparative effectiveness of individual systemic biologic agents on outcomes. The following main conclusions were found. The literature found was most applicable to patients with more advanced CPP and is not applicable to milder forms.

- Low quality evidence that adalimumab and infliximab improved health related quality of life compared to methotrexate.
- Insufficient evidence to grade other final health outcomes comparing adalimumab or infliximab with methotrexate.
- There is insufficient evidence and no RCTs comparing ustekinumab with methotrexate.
- Based on one systematic review, infliximab, adalimumab, and etanercept had higher probabilities of achieving a given Psoriasis Area and Severity Index (PASI) than either of the nonbiologic systemic agents (methotrexate and cyclosporine).

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New Guidelines:

National Institute for Health and Clinical Excellence (NICE): Tocilizumab for the treatment of rheumatoid arthritis.

A guideline was updated in 2012 to evaluate the clinical effectiveness and cost-effectiveness of tocilizumab for the treatment of RA.[8] This guidance recommended tocilizumab, in combination with methotrexate, as a treatment option for RA in adults if:

- There was an inadequate response to DMARDs , or
- The disease has responded to DMARDs and a TNF inhibitor and the person cannot receive rituximab, or
- The disease has responded inadequately to one or more TNF inhibitor treatments and to rituximab

American College of Rheumatology recommendations for the use of DMARDs and biologic agents in the treatment of RA:

These 2008 guidelines were updated to provide clinicians choices for treatments of patients with active RA.[9] Evidence was rated as Level A (Data derived from multiple RCTs), Level B (Data derived from a single randomized trial, or nonrandomized studies, or Level C (only consensus opinion of experts, case studies, or standard-of-care). The following are main recommendations:

- In patients with early RA, recommend the use of DMARD monotherapy for low, moderate, or high disease activity (level of evidence A-C)
- In patients with early RA who have high disease activity with poor prognostic features, recommend the use of an anti-TNF biologic with or without methotrexate (level of evidence A and B). Infliximab is only recommended in combination with methotrexate; not as monotherapy.
- If a patient has moderate to high disease activity after 3 months of methotrexate monotherapy or DMARD combination therapy, recommends adding or switching to an anti-TNF biologic, abatacept, or rituximab (level of evidence A-C)
- If patient still has moderate or high disease activity after 3 months of anti-TNF biologic therapy and this is due to a lack of benefit, switching to another biologic is recommended (level of evidence B and C)
- The guidelines recommend that etancercept could potentially be used in RA patients with hepatitis C (level of evidence C)
- Recommends not using an anti-TNF biologic in RA patients with CHF that is New York Heart Association (NYHA) class III or IV and have an ejection fraction of 50% or less.

Canadian Rheumatology Association Recommendations for Pharmacological Management of RA:

A systematic search was performed to prepare the 2012 guidelines for the management of RA.[10] A custom system for assigning the level of evidence and strength of recommendations was utilized. Levels of evidence were described as Level I (Metaanalyses, systematic reviews, or individual RCT), Level II (Systematic reviews of observational studies, individual observational studies, or RCT subgroup or post hoc analyses), Level III (Nonanalytic studies), and Level IV (Expert Opinion). Strength of the recommendations were labeled as strong (A recommendation), moderate (B recommendation), C (weak recommendation), or D (consensus recommendation). Main recommendations are as followed:

- Methotrexate is the preferred DMARD with respect to efficacy and safety and should be the first DMARD used (Level I, Strength A)

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- In patients being considered for biologic therapy, an inadequate response to DMARD is defined as moderate to high disease activity despite treatment with at least 2 DMARD alone or combination therapy after 3 months at target dose (Level IV, Strength D).
- Methotrexate coprescription with biologics is recommended for improved efficacy (Level I, Strength A).
- Anti TNF therapy is recommended for the treatment of patients with RA after an inadequate response to DMARD (level I, strength A).
- Abatacept or tocilizumab is recommended after inadequate response to DMARD or anti TNF therapy (level I, strength A).
- Rituximab is recommended in RF positive RA after an inadequate response to DMARD or anti TNF therapy (level I, Strength A).

New Safety Alerts:
In January 2012, the FDA notified healthcare professionals of a new risk factor for progressive multifocal leukoencephalopahy (PML) associated with use of natalizumab for the treatment of multiple sclerosis or Crohn's disease.[11] Testing positive for anti-JC virus (JCV) antibodies was identified as a risk factor for PML. The risk factors for PML are the presence of anti-JCV antibodies, long duration of natalizumab, and prior treatment with an immunosuppressant medication. Patients with all three risk factors have an estimated risk of PML of 11/1,000 users and the risks and benefits of continuing treatment with natalizumab should be carefully considered in those found to be anti-JCV antibody positive or have more risk factors.

Indications:
In September, 2012 the FDA expanded the approved use of adalimumab (Humira) to include the treatment of moderate-to-severe ulcerative colitis in adults. Adalimumab is approved to control ulcerative colitis when immunosuppresants (corticosteroids, azathioprine, 6-mercaptopurine) have not worked. Its safety and effectiveness for ulcerative colitis were demonstrated in two clinical studies. The recommended dose for induction is 160 mg followed by 80 mg after 2 weeks. The recommended dose for maintenance is 40 mg every other week in responders to induction.

<u>ULTRA-1</u>
Adalimumab for induction of clinical remission in ulcerative colitis (ULTRA 1) was a fair quality 8-week, randomized, double blind, placebo-controlled study conducted in adult ambulatory patients with moderately to severely active ulcerative colitis, defined by a full Mayo score of 6-12, on concurrent and stable treatment with oral corticosteroids and/or immunomodulators.[12] The objective was to assess the efficacy and safety of two dosing regimens of adalimumab for the induction of clinical remission. Patients were excluded for previous use of any anti-TNF agent or any biological agent. Patients were randomized to adalimumab induction (adalimumab 160/80 or adalimumab 80/40) or placebo using a central randomization scheme. Patients and investigators were blinded to treatment assignment. The primary efficacy endpoint was the proportion of patients in each treatment group in remission at week 8 (defined as Mayo score ≤2 with no individual subscore >1). Overall, attrition was low (10%) and similar between treatment groups. The most common reasons for discontinuations were adverse events and lack of efficacy. Overall, 62.3% of patients were male and the median age was 37.8 years.

Of those receiving placebo, 9.2% reached clinical remission, compared to 10% in the adalimumab 80/40 group (p=0.833) and 18.5% in the adalimumab 160/80 group (p=0.031). The absolute differences in remission rates remain modest (9%). Treatment effect was more pronounced in more severe and extensive disease. There was no statistically significant difference in the percentage of patients achieving clinical response or mucosal healing between either group and placebo, and higher than expected response rates were seen in placebo patients. A significant difference between adalimumab and placebo was only seen for 2

of the secondary end points at week 8 (rectal bleeding and Physician's Global Assessment subscores). The proportion of patients who discontinued the study because of adverse events was similar between groups. Ulcerative colitis was the most common event leading to discontinuation (4% of placebo, 3.8% of 80/40 dose group, and 3.6% of 160/80 dose group). There was no statistically significant difference in the incidence of serious adverse events, although almost double the incidence was observed in the adalimumab 160/80 group.

ULTRA-2

Ulcerative colitis long-term remission and maintenance with adalimumab 2 (ULTRA 2) was a fair-good quality 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of adalimumab in induction and maintenance of clinical remission in patients with moderate-to-severe UC (n=494) who received concurrent treatment with oral corticosteroids or immunosuppressants.[13] Patients were adults with moderately-to -severely active UC for at least 3 months with a Mayo score of 6-12 points, despite therapy with steroids and/or azathioprine or 6-mercaptopurine. Patients were also included who failed to respond to or could not tolerate previous corticosteroid or immunomodulator treatment. Patients with a history of infliximab use, recent infection, HIV, and history of malignancy were excluded. Patients were randomized to receive adalimuamb 160 mg at week 0, 80 mg at week 2, and then 40 mg every other week beginning at week 4, or matching placebo. Patients with an inadequate response could switch to open-label adalimumab at week 12. The co-primary efficacy end points were: 1) proportion of patients achieving clinical remission at week 8 and 2) proportion of patients achieving clinical remission at week 52. Clinical remission was defined as Mayo score ≤2 with no subscore >1, similar to ULTRA 1. There were multiple secondary end points. Clinical response was defined as a decrease from baseline in the total Mayo score by at least 3 points and at least 30% with an accompanying decrease in rectal bleeding subscore of at least 1 point or absolute rectal bleeding subscore of 0 to 1.

Baseline characteristics were similar between groups. Of the randomized patients, 75% were currently on treatment with steroids and/or azathioprine or 6-mercaptopurine. Twenty five percent of patients had previously failed and discontinued one of both of these agents. Forty percent had previously received and discontinued an anti-TNF agent. At week 8, 16.5% of patients receiving adalimumab achieved clinical remission compared to 9.3% on placebo (p=0.019; absolute difference 7.2%, 95% CI 1.2-12.9). At week 52, it was 17.3% vs. 8.5%, respectively (p=0.004; absolute difference 8.8%, 95% CI 2.8-14.5). These absolute differences are relatively small. There was also a statistically significant difference in clinical response at week 8 in those on adalimumab compared to placebo (50.4% vs. 34.6%; p<0.001) and at week 52 (30.2% vs. 18.3%; p=0.002). The proportion of patients achieving clinical remission favored adalimumab over placebo for those who were among the anti-TNF experienced patients, but the results were not statistically significant at week 8 (9.2% vs. 6.9%; p=0.559). However, it was statistically significant at week 52 (10.2% vs. 3%; p=0.039). There was also no statistically significant difference in those receiving prior anti-TNF therapy in clinical response at week 8 (28.7 vs. 36.7%; p=0.228). When stratified for no prior anti-TNF treatment, results were statistically significant for clinical remission and clinical response at both week 8 and 52. However, the study was not powered to address the efficacy of adalimumab in this subgroup of patients.

Overall, treatment emergent adverse events were similar between the adalimumab and placebo groups. A statistically significant difference was seen in the proportion of patients reporting injection site related (12.1% vs. 3.8%; p<0.001) and hematologic-related adverse events (1.9% vs. 0%; p=0.030) in those receiving adalimumab compared to placebo, respectively. The increase in injection site adverse events is a potential limitation of the study; allowing the possibility of unblinding both patients and providers to the treatment group. There was no statistically significant difference in any other of the adverse events of interest. Two adalimumab patients experienced malignancies and there were no deaths reported.

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New Drug Evaluation: Tofacitinib

FDA approved indications: Tofacitinib is an inhibitor of Janus kinases and is indicated for the treatment of adult patients with moderately to severe active rheumatoid arthritis 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). Tofacitinib should not be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine.[14]

Potential Off-label Use: Tofacitinib is also being evaluated for the treatment of psoriasis, inflammatory bowel disease, and psoriatic arthritis.

Clinical Efficacy Data:
Evidence for tofacitinib comes from 5 randomized, double-blind, phase 3 studies as well as two ongoing, open-label extension studies. These evaluated a variety of patients, including methotrexate-naïve patients and those who have failed non-biologic or biologic DMARD therapies, including anti-TNF agents. Primary endpoints for all of the phase 3 studies included: proportion of patients achieving ACR20 response, change from baseline in modified Total Sharp Score, Change from baseline in HAQ-DI Score, and Proportion of patients achieving DAS28-4 <2.6. Other important clinical outcomes include proportion of patients achieving ACR50 or ACR70 response and will be reported on when available. Three of these studies have been completed and published (ORAL Solo, ORAL Standard, and ORAL Step) have been published and will further be appraised and evaluated (see evidence table). Most of the patients in the clinical trials were white women with a relatively younger average age, limiting the generalizability to the overall population. There were stringent exclusion criteria that included specific ranges of laboratory values due to the potential increased risk of infections and malignancies.

The ORAL Solo trial was a 6-month, randomized, phase III, placebo-controlled study (n=610) which evaluated the efficacy and safety of tofacitinib monotherapy in adults with active RA who had an inadequate response or intolerance to at least one non-biologic or biologic DMARDs.[15] Patients were randomized to receive tofacitinib 5 mg or 10 mg twice daily or placebo. After 3 months, patients in the placebo group were advanced blindly to one of the tofacitinib groups to minimize the risk of patients receiving inadequate treatment and primary endpoints were measured at month 3. Efficacy and safety analysis included data from all patients who underwent randomization and who received at least one dose of study medication (modified intention-to-treat or mITT). All patients had received at least 1 non-biologic or biologic DMARD prior to the study. In total, 84.9% of patients had received previous methotrexate, 66.4% had received a different non-biologic DMARD, and 6.7% had received prior biologic DMARDs.

Solo demonstrated a statistically significant improvement in both the 5 mg and 10 mg groups versus placebo in the proportion of patients achieving ACR20 response (59.8%, 65.7%, and 26.7%, respectively; $p<0.0001$) and achieving the minimally clinical important difference in HAQ-DI score of at least 0.22 (52.9%, 55.7%, and 31.7%, respectively; $p<0.001$). There was no significant difference in the proportion of patients achieving DAS28 score < 2.6. A post-hoc subgroup analyses demonstrated that age, sex, geographic region and seropositivity status were not associated with meaningful differences in the ACR 20 results. Among patients who had previously had an inadequate response to TNF inhibitors, 42.9% in the 5-mg group ($p=0.06$) and 62.5% in the 10-mg group ($p<0.001$), compared to 17.7% of those receiving placebo achieved an ACR20 response, which was slightly lower than the overall study population. The proportion of patients who achieved an ACR50 response at month 3 was also statistically significantly improved for the 5 mg and 10 mg group compared to placebo (31.1%, 36.8%, and 12.5%, respectively; $p<0.001$) as well as for those achieving an ACR70 response (15.4%, 20.3%, and 5.8%, respectively; $p<0.03$ 5 mg vs. placebo, $p<0.001$ 10 mg vs. placebo).

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ORAL Standard assessed the efficacy of tofacitinib in combination with methotrexate in patients with inadequate response to previous methotrexate treatment over 12 months.[16] Patients were randomized in a 4:4:1:1;4: ratio to receive tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo advanced to tofacitinib 5 mg after 3 or 6 months, placebo advanced to tofacitinib 10 mg after 3 or 6 months, or an active-control group of adalimumab 40 mg subcutaneously every two weeks. The trial was not designed to assess noninferiority or superiority of tofacitinib to adalimumab. Patients in placebo were advanced blindly at 3 months if they were nonresponders or after 6 months regardless of response. Patients continued on their background methotrexate therapy. In addition to prior methotrexate, 7.1% had received prior anti-TNF therapies, and 2.1% received other biologics. Overall attrition was slightly higher than previous trials (22.5%).

ORAL Standard results demonstrated a statistically significant greater percentage of patients on tofacitinib 5 mg (51.5%) or 10 mg (52.6%) achieved an AC20 response at month 6 compared to placebo (28.3%; $p<0.001$). Significantly more patients on adalimumab also achieved an ACR20 response compared to placebo (47.2%, $p<0.001$). In addition, the percentage of patients who achieved an ACR50 response (36.7%, 34.7%, 27.6%, 12.3% for patients on tofacitinib 5 mg, tofacitinib 10 mg, adalimumab, and placebo, respectively; $p<0.001$, all groups vs. placebo) and ACR70 response (19.9%, 21.9%, 9.1%, 1.9%, respectively; $p<0.0001$, tofacitinib vs. placebo; $p<0.05$ for adalimumab vs. placebo) at month 6 was statistically significantly greater among all active treatment groups compared to placebo. Statistically significant improvements in physical functioning (HAQ-DI score) was seen in treatment groups compared to placebo and the percentage of patients achieving the minimally clinically important difference was significantly greater at month 3, although these absolute values were not provided.

ORAL step was a 6-month trial (n=399) evaluating tofacitinib in combination with methotrexate in patients with inadequate response or intolerance to at least one previous anti-TNF biologic therapy.[17] Patients were randomized to receive tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo advanced to tofacitinib 5 mg after 3 months, or placebo advanced to tofacitinib 10 mg after 3 months, all with methotrexate. The top three TNF inhibitors previously used were adalimumab, etanercept, and infliximab. A total of 30.8% of patients had received a previous non-biologic DMARD other than methotrexate, and 11.5% had received biologic DMARDs other than anti-TNF therapies. The majority of patients were female (84%) and white (83%). The mean age of patient was 55 years. Overall attrition was 22.1%, with more discontinuations due to adverse events in the tofacitinib groups.

At month 3, 41.7% of patients receiving tofacitinib 5 mg and 48.1% of those receiving 10 mg achieved an ACR20r response, compared to 24.4% in the placebo group ($P<0.05$ and $p<0.0001$, respectively). Results were also statistically significant for tofacitinib 5 mg and 10 mg compared to placebo for achieving an ACR50 response (26.5%, 27.8%, and 8.4%, respectively; $p<0.0001$ for both) and an ACR70 response (13.6%, 10.5%, and 1.5%, respectively; $p<0.0001$ for 5 mg vs. placebo and $p\leq0.05$ for 10mg vs. placebo). [17] Responses were seen as early as week 2 in patients on tofacitinib. Statistically significant improvements were also seen in physical functioning (HAQ-DI score) and disease activity (DAS28-4 <2.6) in patients on both doses of tofacitinib compared to placebo.

ORAL Scan is a 24-month phase III, double-blind, parallel-group placebo-controlled study which compared tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo followed by tofacitinib 5 mg twice daily, and placebo followed by tofacitinib twice daily (4:4:1:1) in patients on background methotrexate therapy who had a previous inadequate response to methotrexate (n=797). The study includes radiographic endpoints to evaluate the preservation or joint structure. The interim 12-month analysis has been published.[18] The majority of patients were female (85.2%) and the most common reported race was white (46.3%). The mean age was 52 years. Overall attrition was 19.3% and more patients in both tofacitinib groups discontinued due to adverse events. The ACR20 response rates

at month 6 were 51.5% for tofacitinib 5mg, 61.8% for tofacitinib 10%, and 25.3% for placebo ($p<0.0001$) for both doses. In addition the ACR50 response rates (32.4%, 43.7%, and 8.4%, respectively; $p<0.0001$ for both vs. placebo) and ACR70 rates (14.6%, 22.3%, and 1.3%, respectively; $p<0.0001$ for both groups vs. placebo) were statistically significantly greater for patients receiving tofacitinib 5 mg, 10mg, compared to those on placebo. Inhibition of progression of structural damage (as measured by the mean change from baseline in mTSS score at month 6) was statistically significant for the tofacitinib 10 mg group compared to placebo (0.06 vs. 0.47, $p=0.038$) but did not reach statistical significance for tofacitinib 5 mg compared to placebo (0.12 vs. 0.47; $p=0.079$). The proportion of patients with no radiographic progression at months 6 and 12 were significantly greater for both tofacitinib groups compared to placebo ($p\leq0.05$). Rates of remission and physical functioning were statistically significantly greater for tofacitinib 10 mg compared to placebo. However, since tofacitinib 5 mg failed to reach significance for radiographic progression, significance was not declared for these endpoints for the 5 mg dose. Six patients treated with tofacitinib experienced 6 nonfatal cardiovascular events that met adjudication event criteria. Nine patients were diagnosed as having carcinoma.

One additional study, ORAL Sync, is unpublished and cannot be fully evaluated for quality and risk of bias. Therefore it will not be included in the analysis for conclusions and recommendations. Inclusion/exclusion criteria and primary endpoints are similar to the other clinical trials. ORAL Sync is a phase 3 trial assessing two doses of tofacitinib in combination with non-biologic DMARDs in patients with inadequate response or intolerance to at least one previous non-biologic or biologic DMARD over 12 months (n=792). [19] Both doses were statistically significant compared to placebo for percentage of patients achieving ACR20 response at month 6, mean change from baseline in HAQ-DI score at month 3, and percentage of patients achieving a DAS28-4 score <2.6 at month 6.

Lastly, ORAL Start is an ongoing, 24-month, trial designed to evaluate two doses of tofacitinib as monotherapy compared to methotrexate in patients with moderate to severe RA.[19] A 12-month interim analysis shows a statistically significantly greater percentage of patients on tofacitinib 5 mg twice daily and tofacitinib 10 mg achieved an ACR70 response at Month 6 compared to methotrexate (25.5%, 37.7%, 12%, respectively; $p<0.001$ for both comparisons). [19]

Clinical Safety:
Overall, the most common adverse events seen in clinical trials were upper respiratory tract infection, headache, and diarrhea. The most common serious adverse reactions seen in clinical trials were serious infections. The most common included pneumonia, cellulitis, herpes zoster, and urinary tract infection. Several opportunistic infections were also reported in clinical trials. There were seven events involving serious infections in six patients in Oral SOLO. In ORAL SYNC, serious infections were experienced by 3 patients who received tofacitinib 5 mg twice daily, 8 patients who received tofacitinib 10 mg twice daily, compared to no patients on placebo.

Changes in laboratory test results also occurred more frequently with tofacitinib compared to placebo and appeared to be dose dependent. In Oral SOLO, mean low-density lipoprotein (LDL) cholesterol levels increased by 3.5% with placebo, compared with 13.6% with the 5-mg dose and 19.5% with the 10-mg dose. Neutrophil counts declined in the tofacitinib groups, and neutropenia occurred more frequently. Changes in hemoglobin, liver enzymes, and small increases in serum creatinine levels were also observed. There were limited patients older than 75 years old in clinical trials and tofacitinib was not evaluated ih those with a baseline creatinine clearance of less than 40 ml/min.

Malignancies associated with a cause of death were seen. In the clinical studies, 11 solid cancers and one lymphoma were diagnosed in 3328 patients receiving tofacitinib, compared to 0 solid cancers and 0 lymphomas in 809 patients in the placebo group. In all clinical studies, discontinuations due to adverse effects were more common in tofacitinib groups compared to placebo.

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COMPARATIVE CLINICAL EFFICACY: Evidence Table

Ref./Study Design	Drug Regimens/ Duration	Patient Population (R1/R2/P)	N	Outcomes/ Efficacy Results (CI, p-values)	NNT	Safety Results (CI, p-values)	NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
ORAL Solo[15] DB, PC, PG, R	1.Tofacitinib (TFB) 5 mg BID 2. TFB 10 mg BID 3. Placebo: a. Placebo x 3 mo, TFB 5 mg BID, b.Placebo x 3 mo, TFB 10 mg BID Randomized 4:4:1:1 X 6 months	Active RA who had an inadequate response or intolerance to non-biologic or biologic Mean age 51.8, 86.6% female, 67% white Inclusion Criteria, ≥18y/o, active RA, had an inadequate response to at least one nonbiologic or biologic DMARD due to lack of efficacy or the occurrence of toxic effects, and had D/C'd all DMARds. Exclusion criteria: HG<9.0 g/dl, HCT<30%, WBC <3.0x10^9/L, ANC <1.2, PLT<100, GFR <40ml/min, LFT's >1.5x upper limit of normal, recent, current, or chronic infection including HBV, HCV, HIV, h/o cancer	N=243 N=245 N=61 N=61	≥20% improvement in ACR20 at 3 months: 1)145 (59.8%) 2) 161 (65.7%) 3) 33 (26.7%) P<0.001 for both comparisons vs. placebo TFB 5mg vs. PLA: RR 0.45; 95% CI 0.33-0.62 TFB 10mg vs. PLA: RR 0.40; 95% CI 0.3-0.60 ≥0.22 improvement in HAQ-DI Score 1)129 (52.9%) 2) 136 (55.7%) 3) 39 (31.7%) P<0.001 for both comparisons vs. placebo TFB 5mg vs. PLA: RR 0.60; 95% CI 0.45-0.8 TFB 10mg vs. PLA: RR 0.57; 95% CI 0.43-0.76 Disease Remission (Acitivity Score <2.6) at month 3 1) 5.6% 2) 8.7% 3) 4.4% P=0.62 P=0.10 *Comparisons with placebo for the first 3 months were performed with combined data from the two placebo groups	ARR 32.6% NNT 3 ARR 38.7% NNT 2 ARR 21.1% NNT 4 ARR 23.5% NNT 4 NS	Discontinued due to Adverse events: 1) 3 (1.2%) 2) 11 (4.5%) 3) 5 (4.1%) TFB 5mg vs. PLA: RR 0.30; 95% CI 0.073-1.24 TFB 10mg vs. PLA: RR 1.1; 95% CI 0.39-3.1 Serious Infections: 1) 1 (0.4%) 2) 5 (2.0%) 3) 2 (1.6%)* TFB 5mg vs. PLA: RR 0.25; 95% CI 0.023-2.7 TFB 10mg vs. PLA: RR 1.2 ; 95% CI 0.3-6.3 *occurred after the switch from placebo to tofacitinib 5 mg.	NS NS	**Quality Rating:** Fair-Good **Internal Validity:** Selection: Randomization performed using an automated Web-based or telephone-based system. Appropriate allocation concealment. Longer mean duration of RA in TBF groups vs. placebo (8.6 years vs. 7.7 years). Statistically significant difference between TFB 10mg group and placebo on age (P=0.05). Performance: Patient and Investigators blinded. Detection: Unclear blinding of evaluators Attrition: Overall attrition of 9% (14% PLA, 4.5% TFB 5mg BIC, 11% TFB 10mg BID). Higher in 10mg BID group due to AE's and protocol violations or no longer willing that were not further explained. Higher in PLA groups due to lack of efficacy. **External Validity:** Patient Characteristics: Excluded common comorbidities and strict on lab value criteria which decreases generalizability to population. Average age younger than likely. Narrow ethnic and geographic diversity. Setting: Multinational - in 16 countries throughout North America, Latin America, Europe, and Asia. Sponsored by Pfizer Outcomes: Commonly used RA outcomes used.

ORAL Standard[10] RCT, DB, PC	1.TFB 5mg BID 2. TFB 10 mg BID 3. Placebo: a. Placebo x 3 or 6 mo→ TFB 5 mg BID, b.Placebo x 3 or 6 mo→, TFB 10 mg BID 4. Adalimumab(ADB) 4(mg SUBQ every 2 week Randomized 4:4:1:1 X 12 months	In combination with methotrexate in patients with previous inadequate response to methotrexate 81.7% female, 72.1% white, mean age 52.9 Inclusion Criteria: Received stable methotrexate for at least 4 mo, receive folic aci for at least 4 weeks, Exclusion criteria: prior treatment with adalimumab, lack of response o prior anti-TNF treatment, HG<9.0 g/dl, HCT<30%, WBC <3.0x10^9/L, ANC <1.2, PLT<100, GFR <40ml/min, LFT's >1.5x upper limit of normal, recent, current, or chronic infection including HBV, HCV, HIV, h/o cancer	N=204 N=201 N=56 N=52 N=204	≥20% improvement in ACR2(at 6 months: 1) 105 (51.5%) 2)105 (52.6%) 3) 31 (28.3%) 4) 96 (47.2%) P<0.001 for both comparisons vs. placebo TFB 5 mg vs. PLA: RR 0.56; 95% CI 0.40-0.78 TFB 10mg vs. PLA: RR 0.55; 95% CI 0.40-0.77 ADB vs. PLA: RR 0.60; 95%CI 0.44-0.85 Disease activity Score <2.6 1) 13 (6.2%) 2) 25 (12.5%) 3) 1 (1.1%) 4)14 (6.7%) P<0.005 TFB 5 mg vs. PLA RR 0.15; 95% CI 0.02-1.1 P<0.001 TFB 10 mg vs. PLA RR 0.07; 95% CI 0.01-0.54 P<0.001 ADB vs. PLA RR 0.14; 95% CI 0.02-1.0	 ARR 22.8% NNT 4 ARR 23.5% NNT 4 ARR 18.4% NNT 5 ARR 5.3% NNT 19 ARR 11.5% NNT 8 ARR 5.9% NNT 16	Discontinued due to Adverse events: 1) 24 (11.8%) 2) 24 (11.9%) 3) 5 (6.5%) 4) 22 (10.8%) TFB 5 mg vs. PLA: RR 2.5; 95% CI 0.99-6.5 TFB 10mg vs. PLA: RR 2.6; 95% CI 1.01-6.6 ADB vs. PLA: RR 2.3; 95%CI 0.9-6.0 Serious Infections: 1) 7 (3.4%) 2) 8 (3.9%) 3) 2 (1.9%) 4) 3 (1.5%) TFB 5 mg vs. PLA: RR 1.9; 95% CI 0.4-8.8 TFB 10mg vs. PLA: RR2.1 ; 95% CI 0.5-9.9 ADB vs. PLA: RR0.8 ; 95%CI 0.14-4.7	 NS ARI 7.3% NNH 14 NS NS	**Quality Rating:** Fair **Internal Validity:** Selection: Randomized with an interactive voice-response system Performance: All patients self-administered injections of either adalimumab or placebo and took placebo or tofacitinib pills twice daily. Patients and investigators blinded. Potential for unblinding due to increased injection site reactions with adalimumab. Detection: Unclear of evaluator blinding. Attrition: Overall attrition of 22.5% (21.4% TFB 10mg, 26.5% TFB 5mg, 20.4% PLA, 20.6% ADB) **External Validity:** Patient Characteristics: Excluded common comorbidities and strict on lab value criteria which decreases generalizability to population. Average age younger than likely. Narrow ethnic and geographic diversity. Recruitment: Unclear Setting: In 21 countries throughout North America, Latin America, Europe, Asia and Australia Outcomes: Commonly used RA Outcomes reported

ORAL Step[17] RCT, DB, PC, PG	1.TFB 5mg BID 2. TFB 10 mg BID 3. Placebo: a. Placebo x 3 mo→ TFB 5 mg BID, b.Placebo x 3 mo→, TFB 10 mg BID Randomized 2:2:1:1 X 6 months All with methotrexate	In combination with methotrexate with previous inadequate response to a TNF inhibitor 84% female, 83.2% white, mean age 55 Inclusion Criteria: Adults with active moderate-to severe RA, previous inadequate response to TNF, on stable methotrexate Exclusion criteria: , HG<9.0 g/dl, HCT<30%, WBC <3.0x10^9/L, ANC <1.2, PLT<100, GFR <40ml/min, LFT's >1.5x upper limit of normal, recent, current, or chronic infection including HBV, HCV, HIV, h/o cancer	N=133 N=134 N=66 N=66	≥20% improvement in ACR20 at 3 months: 1)55 (41.7%) 2) 64 (48.1%) 3) 32 (24.4%) TFB 5 mg vs. PLA: P=0.0024 RR 0.58; 95%CI 0.4-0.8 TFB10mg vs PLA: P=<0.0001 RR 0.5; 95% CI 0.4-0.72 ≥0.22 improvement in HAQ-DI Score at month 3 1) 71 (54.2%) 2) 78 (58.7%) 3) 53 (40.5%) TFB 5mg vs. PLA:P=0.0245 RR 0.75; 95% CI 0.60-0.98 TFB 10mg vs. PLA: P=0.0026 RR 0.70; 95% CI 0.5-0.9 Disease Activity Score <2.6 at 3 months: 1) 8 (6.7%) 2) 11 (8.8%) 3) 2 (1.7%) TFB 5mg vs. PLA :P=0.0496 RR 0.25; 95%CI 0.05-1.2 TFB 10mg vs PLA :P=00105 RR 0.19; 95%CI 0.042-0.8	 ARR 17.1% NNT 5 ARR 23.5% NNT 4 ARR 13.2% NNT 7 ARR 18% NNT 5 ARR 4.55% NNT 22 ARR 6.7% NNT 14	Discontinued due to Adverse events: 1) 12 (9%) 2) 13 (9.1%) 3) 4 (6%) 4) 4 (6%) TFB 5 mg vs. PLA RR 1.4; 95%CI 0.6-3.3 TFB10mg vs PLA RR 1.4; 95% CI 0.6-3.5 Serious Infections: 1) 2 (1.5%) 2) 2 (1.5%) 3) 1 (1.5%) 4) 0 (0%) TFB 5 mg vs. PLA RR 1.8; 95%CI 0.2-20.0 TFB10mg vs. PLA RR 1.8; 95% CI 0.2-19.8	 NS NS	**Quality Rating:** Fair **Internal Validity:** Selection: Randomized with an automated internet or telephone randomization system. Baseline characteristics similar between groups. Performance: Patients, investigators, and sponsor were masked to treatment assignment. Detection: No intention to treat analysis done. Unclear blinding of evaluators Attrition: Overall attrition of 22.4% (23.5% placebo, 19.5% TFB 5 mg BID, and 23.1% TFB 10 mg BID). More discontinuations due to adverse events in TFB groups compared to placebo. **External Validity:** Patient Characteristics: Excluded common comorbidities and strict on lab value criteria which decreases generalizability to population. Average age younger than likely. Narrow ethnic and geographic diversity. Setting: In 82 centers in 13 countries worldwide Recruitment: Unclear Outcomes: Commonly used efficacy outcomes were reported. Not a true effectiveness trial.

Study design abbreviations: DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel-group, MC=multi-center.
Results abbreviations: OR= Odds Ratio, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
Quality Rating: Good- likely valid; Fair- likely valid/possibly valid; Poor- fatal flaw-not valid

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Author: M. Herink, Pharm.D. Date: February 2013

Appendix 1: Prior Authorization Criteria

Targeted Immune Modulators (TIMS)

Goal(s):

- *Cover TIMs according to OHP list guidelines.*
- *Promote use that is consistent with National Guidelines and medical evidence.*
- *Promote use of high value products.*

Requires PA: Non-preferred products

Preferred Products: Adalimumab (Humira®), Etanercept (Enbrel®)

Length of Authorization: 12 months

Generic Name	Trade Name	Indication
Abatacept	Orencia	RA, Juvenile RA, Juvenile idiopathic arthritis
Adalimumab	Humira	RA, Psoriatic arthritis, ankylosing spondylitis, Juvenile idiopathic arthritis, Crohn's disease, Plaque psoriasis, ulcerative colitis
Anakinra	Kineret	RA
Certolizumab	Cimzia	RA, Crohn's disease
Etanercept	Enbrel	RA, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, plaque psoriasis
Golimumab	Simponi	RA, psoriatic arthritis, ankylosing spondylitis
Infliximab*	Remicade	RA, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, plaque psoriasis
Natalizumab*	Tysabri	Crohn's disease
Rituximab*	Rituxan	RA
Tocilizumab*	Actemra	RA, juvenile idiopathic arthritis
Ustekinumab	Stelara	Plaque psoriasiss
Tofacitinib	Xeljanz	RA

Abbreviations: RA, rheumatoid arthritis
* Must be billed via J-code and payment requires trial of preferred self-administered drug first.

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Approval Criteria : Targeted Immune Modulators (TIMS)		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis covered by OHP?	**Yes:** Go to #3	**No:** Pass to RPH; Deny (medical appropriateness)
3. Will the provider change to a preferred product?	**Yes:** Inform provider of covered alternatives in class..	**No:** Go to #4
4. Is the diagnosis psoriasis (ICD-9: 696.1-696.2, 696.8) and the product requested FDA approved for psoriasis (see table above)? * Moderate/Severe psoriasis treatments are covered on the OHP.	**Yes:** Refer to anti-psoriatics PA criteria at http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/OR%20Medicaid%20PA%20Criteria/PA%200711.pdf	**No:** Go to #5
5. Is the diagnosis ankylosing spondylitis (ICD-9 720) and the product requested is FDA approved for ankylosing spondylitis?	**Yes:** Approve treatment for up to 1 year	**No:** Go to #6
6. Is the diagnosis rheumatoid arthritis (ICD-9 714.xx) or psoriatic arthropathy (ICD-9 696.0) and the product requested FDA approved for rheumatoid arthritis (see table above)?	**Yes:** Go to #7	**No:** Go to #10
7. Has the patient had a trial and inadequate response to methotrexate or other first line DMARDs (leflunomide, sulfasalazine, hydroxychloroquine, penicillamine) and a disease duration of ≥6 months? Or, An intolerance or contraindication to oral DMARDs?	**Yes:** Go to #8	**No:** Pass to RPH; Deny (medical appropriateness)
8. Is the request for tofacitinib?	**Yes:** Go to #9	**No:** Approve treatment for up to 1 year
9. Has the patient had an inadequate response or interolerance to 1 or more biologic TIM (Humira, Enbrel, Cimzia, Simponi, Orencia)?	**Yes:** Approve treatment for up to 1 year	**No:** Pass to RPH: Deny (medical appropriateness)
10. Is the diagnosis Crohn's disease (ICD-9 555) or ulcerative colitis (ICD-9 556.0-556.9) and the product requested FDA approved for the indication (see table above)?	**Yes:** Go to #11	**No:** Pass to RPH; Deny (medical appropriateness)
11. Has the patient had a trial and inadequate response to conventional therapy including immunosuppressive therapy (mercaptopurine, azathioprine) and/or corticosteroid treatments? Or, Has an intolerance or contraindications to conventional therapy?	**Yes:** Approve treatment for up to 1 year	**No:** Pass to RPH; Deny (medical appropriateness)

P&T Action: 8-30-12 (MH)
Revision(s): 3-28-13 (MH)
Initiated:

Author: M. Herink, Pharm.D. Date: February 2013

Appendix 2: Specific Drug Information

CLINICAL PHARMACOLOGY: Tofacitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	74%
Protein Binding	40%
Elimination	70% hepatic metabolism and 30% renal excretion of the parent drug
Half-Life	3 hours
Metabolism	CYP3A4 with minor contribution from CYP2C19

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
5 mg	PO	BID	Immediate-release tablets	Should be reduced to 5 mg once daily in moderate or severe renal insufficiency	Should be reduced to 5 mg once daily in moderate hepatic impairment	Has not been established	As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.	Should be reduced to 5 mg once daily in patients: • Receiving potent inhibitors of CYP3A4 • Receiving one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 • It is recommended that XELJANZ not be initiated in patients with a lymphocyte count less than 500 cells/mm3, an absolute neutrophil count (ANC) less than 1000 cells/mm3, or who have hemoglobin levels less than 9 g/dL

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications):

- No Contraindications
- Boxed warnings related to Infections, Malignancy, and Tuberculosis

Warnings and Precautions:

- Serious Infections – Serious and sometimes fatal infections due to bacterial mycobacterial, invasive fungal, viral or other opportunistic pathogens have been reported. Tofacitinib should not be initiated in patients with an active infection, including localized infections. Patients should be monitored closely for signs and symptoms of infection and should be interrupted in patient develops a serious infection. Patients should be evaluated and tested for latent or active tuberculosis prior to treatment.
- Malignancy and lymphomas have been reported in patients taking tofacitinib.
- Gastrointestinal Perforation – use with caution in patients at an increased risk.
- Laboratory values – Increases in lipid parameters, neutropenia, and anemia have been observed with tofacitinib therapy.
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Table 4: Adverse Reactions Occurring in at Least 2% or More of Patients[14]

	Tofacitinib 5mg Twice Daily	**Tofacitinib 10 mg Twice Daily**	**Placebo**
Preferred Term	**N = 1336 (%)**	**N = 1349 (%)**	**N = 809 (%)**
Diarrhea	4.0	2.9	2.3
Nasopharyngitis	3.8	2.8	2.8
Upper respiratory tract infection	4.5	3.8	3.3
Headache	4.3	3.4	2.1
Hypertension	1.6	2.3	1.1
N reflects randomized and treated patients from the seven clinical trial			