Tofacitinib (Xeljanz®)

National Drug Monograph

April 2014

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

Tofacitinib is a new oral therapy for the treatment of rheumatoid arthritis that provides a novel mechanistic approach via JAK intracellular pathways. Tofacitinib is a Janus kinase (JAK) inhibitor. The efficacy of tofacitinib was evaluated under the oral rheumatoid arthritis trials program (ORAL).

Efficacy:

- Tofacitinib is FDA-approved for the treatment of adult patients with moderate 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 non-biologic DMARDs (e.g. hydroxychloroquine, leflunomide, minocycline, sulfasalazine).
- Tofacitinib is dosed as 5 mg orally, twice daily, with or without food.
- Among the phase 3 trials, a statistically higher percentage of patients receiving tofacitinib achieved the primary endpoint of ACR20 at the pre-defined time point (month 3 vs. 6) compared to placebo.
- In five of the phase 3 trials, where tofacitinib was initiated after inadequate response to either biologic or non-biologic DMARD, tofacitinib, in combination with non-biologic DMARD therapy, was more effective than placebo.
- Adding the comparator, adalimumab 40mg every other week, showed that all three treatment arms (tofacitinib 5mg, 10mg and adalimumab) achieved a greater ACR20 response at month 6 compared to placebo, with tofacitinib and adalimumab responses being numerically similar.
- The higher tofacitinib dose (10mg twice daily) was associated with a statistically significant improvement in radiographic progression, but not the approved dose of 5 mg twice daily.
- Remission rates, evaluated as the DAS-28[ESR] endpoint were somewhat variable among the trials.
- Improvements in physical function were noted with tofacitinib treatment at the 3 months assessment point, compared to baseline HAQ-DI values.

Safety:

- Tofacitinib appears to be well-tolerated, but has a higher incidence of serious infections (including opportunistic infections and tuberculosis), malignancy, neutropenia and laboratory abnormalities (including LFTs and lipid profile).
- A boxed warning highlights the risk of serious infections and malignancy.
- The most common serious infections include pneumonia, cellulitis, herpes zoster and urinary tract infections.
- Tofacitinib's affect on the following laboratory parameters include: decreases in neutrophils and lymphocytes, elevations in LFTs, lipids and serum creatinine.
- Among the phase 3 trials, discontinuation rates of tofacitinib due to adverse events appears to be higher than the comparator arms.
- A REMS Medication Guide outlines the safety issues for patients.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating tofacitinib for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

Tofacitinib is a Janus kinase (JAK) inhibitor. The JAK family (JAK1, JAK2, JAK3 and TYK2) are tyrosine kinase proteins that play an important role in immune response. JAKs signal in pairs and facilitate the phosphorylation process of many proteins intracellularly. One such group of proteins is the signal transducers and activators of transcription (STATs). These proteins will regulate the transcription of genes that control inflammatory responses. Tofacitinib affects the signaling pathway at the point of the JAK family by preventing phosphorylation and activation of STATs.

Absorption: Oral administration of tofacitinib results in peak plasma concentrations that are attained within 0.5-1 hour with an elimination half-life ~ 3 hours. Steady state concentrations are achieved in 24-48 hours; accumulation is negligible after twice daily dosing. Oral bioavailability is 74%; co-administration with a high-fat meal resulted in no changes in AUC while Cmax was reduced by 32%. Tofacitinib was given without regard to meals in the clinical trial setting.
Distribution: After intravenous administration, the volume of distribution is 87L; protein binding ~ 40%, primarily to albumin (no binding to α1-acid glycoprotein). Distribution is equal between red blood cells and plasma.
Metabolism/Elimination: 70% hepatic metabolism and 30% renal excretion of parent drug; metabolism mediated primarily by CYP3A4 (minor CYP2C19 activity); human radiolabeled study identified more than 65% of circulating radioactivity was accounted for by unchanged tofacitinib while 35% was accounted for by 8 metabolites; the pharmacologic activity is attributed to the parent molecule.

FDA Approved Indication(s)

Tofacitinib is FDA-approved for the treatment of adult patients with moderate 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 non-biologic DMARDs (e.g. hydroxychloroquine, leflunomide, minocycline, sulfasalazine).

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

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Tofacitinib is currently being investigated for use in psoriasis, ulcerative colitis and renal transplantation.

Current Therapeutic Alternatives

Formulary options for patients with moderate to severe, active rheumatoid arthritis with intolerance or inadequate response to methotrexate include leflunomide, sulfasalazine, hydroxychloroquine or the combination of sulfasalazine and/or hydroxychloroquine with methotrexate (if able to tolerate).

Tumor necrosis factor inhibitors (e.g. adalimumab, etanercept, infliximab, certolizumab pegol, golimumab) are another therapeutic alternative. In addition, biologics that work via alternative mechanisms, such as tocilizumab, rituximab, abatacept and anakinra, may be therapeutic options in this setting.

Dosage and Administration

Tofacitinib is dosed as 5 mg orally, twice daily, with or without food. It may be used as monotherapy or in combination with non-biologic DMARDs (i.e. methotrexate).

Tofacitinib should not be used in patients with severe hepatic impairment
Therapy should not be initiated with the following laboratory parameters:

- Lymphocyte count < 500 cells/mm^3
- ANC < 1000 cells/mm^3
- Hemoglobin < 9 g/dL

Concomitant therapy with potent inducers of CYP3A4 (e.g. rifampin) may result in reduced clinical response to tofacitinib and should be avoided.

Dose Modifications

Interruptions in dosing are recommended to manage lymphopenia, neutropenia and anemia, as well as serious infections that occur during therapy.

Dose should be modified to 5 mg once daily in patients with the following:

- Moderate or severe renal insufficiency
- Moderate hepatic impairment
- Concomitant therapy with potential inhibitors of CYP3A4 (e.g. ketoconazole)
- Concomitant therapy with one or more drugs causing moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g. fluconazole)

Low Lymphocyte Count	
Lab value	Recommendation
Lymphocyte count ≥ 500 cells/mm^3	Maintain dose
Lymphocyte count < 500 cells/mm^3	Discontinue tofacitinib
Low ANC	
ANC > 1000 cells/mm^3	Maintain dose
ANC 500-1000 cells/mm^3	For persistent decreases in this range, interrupt dosing until ANC > 1000
ANC < 500 (confirm by repeat testing)	Discontinue tofacitinb
Low Hemoglobin Value	
≤ 2 g/dL decrease and greater than or equal to 9 g/dL	Maintain dose
> 2 g/dL decrease or Less than 8 g/dL	Interrupt therapy until hgb has normalized

Efficacy

Efficacy Measures

The primary measurement used to define efficacy in rheumatoid arthritis is the American College of Rheumatology (ACR) 20% improvement criteria. The ACR20 is defined as the following:

1. At least 20% improvement in tender joint count
2. At least 20% improvement in swollen joint count
3. At least 20% improvement in 3 of 5 ACR-core set measures:
   - Patient global assessment
   - Physician global assessment
   - Patient pain assessment
   - Patient self-assessed disability (disability index of the Health Assessment Questionnaire [HAQ-DI])
   - Acute phase reactant

Other measures used to define efficacy include:

- ACR50 (50% improvement in ACR criteria) and ACR70 (70% improvement in ACR criteria)
- Remission rate using the Disease Activity Score for 28 joint counts based on the erythrocyte sedimentation rate (DAS28-4[ESR]) of less than 2.6. Scores range from 0 to 9.4 and higher scores indicate more disease activity. This is a composite index of 4 weighted variables: (1) number of tender and swollen joints among 28 joints examined (2) ESR value (3) patient's global assessment of disease activity using VAS with range from 0 to 100. Disease activity is low if value $\leq$ 3.2; moderate if $\geq$ 3.2 and $\leq$ 5.1; high if > 5.1; remission if < 2.6.
- Physical function status as assessed with the use of the Health Assessment Questionnaire-Disability Index (HAQ-DI). Scores range from 0 to 3, with higher scores indicating greater disability.
- Modified Total Sharp Score (mTSS), which evaluates structural damage, as well as total modified Sharp/van der Heijde score (SHS)

Summary of efficacy findings

The efficacy of tofacitinib was evaluated in the following phase 3 trials under the oral rheumatoid arthritis trials program (ORAL). The ORAL Start trial evaluated use of tofacitinib in MTX-naïve patients. Data for this trial was only available in abstract form at the time of writing. The ORAL Step, Scan, Standard and Sync trials evaluated tofacitinib in conjunction with DMARD therapy after inadequate response to either biologic or non-biologic therapy. ORAL Solo evaluated tofacitinib while continuing therapy with an antimalarial agent.

The primary endpoints for all trials included the ACR response rate, HAQ-DI and DAS. Only the ORAL Scan and Start trials evaluated structural preservation with mTSS scores as a primary endpoint.

Table 2. Comparison of Primary Endpoint, ACR20

Phase 3 Trials	Study Population	Background therapy	Primary endpoint	ACR20 response rates (%)
ORAL Step Burmester 2013	Inadequate response to TNF-I	MTX	ACR20 (month 3) HAQ-DI (month 3) DAS-28 < 2.6 (month 3)	T 5mg + MTX: 41.7* T 10mg + MTX: 48.1*** P: 24.4
ORAL Scan Van der Heijde 2013	Inadequate response to MTX	MTX	ACR20 (month 6) DAS-28[ESR] < 2.6 (month 6) mTSS scores (month 6)	T 5mg + MTX: 51.5*** T 10mg + MTX: 61.8*** P + MTX: 25.3
ORAL Standard Van Vollenhoven 2012	Inadequate response to MTX	MTX	ACR20 (month 6) HAQ-DI (month 3) DAS-28 < 2.6 (month 6)	T 5mg + MTX: 51.5** T 10mg + MTX: 52.6** A 40mg + MTX: 47.2** P + MTX: 28.3
ORAL Solo Fleischmann 2012	Inadequate response to biologic or non-biologic	Stable antimalarial (AM)	ACR20 (month 3) HAQ-DI (month 3) DAS-28[ESR] < 2.6 (month 3)	T 5mg + AM: 59.8** T 10mg + AM: 65.7** P + AM: 26.7
ORAL Sync Kremer 2013	Inadequate response to biologic or non-biologic	1-2 non-biologic DMARDs	ACR20 (month 6) HAQ-DI (month 3) DAS-28[ESR] < 2.6 (month 6)	T 5mg + DMARD: 52.1** T 10mg + DMARD: 56.6** P + DMARD: 30.8
ORAL Start Lee 2012	MTX naïve	None	mTSS scores (month 6) ACR70 (month 6)	T 5mg 71*** T 10mg 75.8*** MTX 50.5

T tofacitinib, A adalimumab, AM antimalarial, MTX methotrexate P Placebo * P < 0.05; **P < 0.001; *** P < 0.0001

Among all of the phase 3 trials, a statistically higher percentage of patients receiving tofacitinib achieved the primary endpoint of ACR20 at the pre-defined time point (month 3 vs. 6) compared to placebo.

Adding the comparator group, adalimumab 40mg every other week, to the ORAL Standard trial showed that all three treatment arms (tofacitinib 5mg, 10mg and adalimumab) achieved a greater ACR20 response at month 6 compared to placebo. The tofacitinib and adalimumab responses were numerically similar.

In five of the phase 3 trials, where tofacitinib was initiated after inadequate response to either biologic or non-biologic DMARD, tofacitinib, in combination with non-biologic DMARD therapy, was more effective than placebo. Fleischmann et al. designed a trial in which tofacitinib was given as monotherapy in inadequate responders to prior DMARD therapy, although stable doses of antimalarial agents were allowed to continue.

Data from the ORAL Scan trial indicates that a higher tofacitinib dose (10mg twice daily) was associated with a statistically significant improvement in total SHS at month 12 compared to placebo. The approved dose of tofacitinib 5mg twice daily did not reach statistical significance. Data from the ORAL Start trial (abstract only, to date) is somewhat consistent with the ORAL Scan results. Although both tofacitinib 5 and 10mg arms showed less change from baseline mTSS scores and less radiographic progression compared to the MTX arm, the effect appeared to be greater in the 10mg arm.

Table 3. Comparison of Primary Endpoint, HAQ-DI

Phase 3 Trials	Study Population	Background therapy	Primary endpoint	Δ HAQ-DI (points)
ORAL Step Burmester 2013	Inadequate response to TNF-I	MTX	HAQ-DI (month 3)	T 5mg + MTX: -0.43*** T 10mg + MTX: -0.46*** P: -0.18
ORAL Standard Van Vollenhoven 2012	Inadequate response to MTX	MTX	HAQ-DI (month 3)	T 5mg + MTX: -0.55** T 10mg + MTX: -0.61** A 40mg + MTX: -0.49** P + MTX: -0.24
ORAL Solo Fleischmann 2012	Inadequate response to biologic or non-biologic	Stable antimalarial (AM)	HAQ-DI (month 3)	T 5mg + AM: -0.50** T 10mg + AM: -0.57** P + AM: -0.19**
ORAL Sync Kremer 2013	Inadequate response to biologic or non-biologic	1-2 non-biologic DMARDs	HAQ-DI (month 3)	T 5mg + DMARD: -0.44** T 10mg + DMARD: -0.53** P + DMARD: -0.15

T tofacitinib, A adalimumab, AM antimalarial, MTX methotrexate P Placebo * P < 0.05; **P < 0.001; *** P < 0.0001

Improvements from baseline HAQ-DI at month 3 were greater for all tofacitinib treatment arms, compared to placebo.

Table 4. Comparison of Primary Endpoint, DAS-28

Phase 3 Trials	Study Population	Background therapy	Primary endpoint	DAS-28[ESR]< 2.6 (%)
ORAL Step Burmester 2013	Inadequate response to TNF-I	MTX	DAS-28 < 2.6 (month 3)	T 5mg + MTX: 6.7 (p=0.049) T 10mg + MTX: 8.8 (p=0.01) P: 1.7
ORAL Scan Van der Heijde 2013	Inadequate response to MTX	MTX	DAS-28[ESR] < 2.6 (month 6)	T 5mg + MTX: 7.2 T 10mg + MTX: 16.0*** P + MTX: 1.6
ORAL Standard Van Vollenhoven 2012	Inadequate response to MTX	MTX	DAS-28[ESR] < 2.6 (month 6)	T 5mg + MTX: 6.2 T 10mg + MTX: 12.5 A 40mg + MTX: 6.7 P + MTX: 1.1
ORAL Solo Fleischmann 2012	Inadequate response to biologic or non-biologic	Stable antimalarial (AM)	DAS-28[ESR] < 2.6 (month 3)	T 5mg + AM: 5.6 T 10mg + AM: 8.7 P + AM: 4.4 (p NS)
ORAL Sync Kremer 2013	Inadequate response to biologic or non-biologic	1-2 non-biologic DMARDs	DAS-28[ESR] < 2.6 (month 6)	T 5mg + DMARD: 8.5^ T 10mg + DMARD: 12.5** P + DMARD: 2.6

T tofacitinib, A adalimumab, AM antimalarial, MTX methotrexate P Placebo **P < 0.001; *** P < 0.0001; ^ P=0.005

Remission rates, evaluated as the DAS-28[ESR] endpoint were somewhat variable among the trials. Both the ORAL Step and Solo trials evaluated the DAS-remission rate at month 3. Compared to placebo, statistical significance was shown in both tofacitinib 5 and 10 mg arms in the ORAL Step trial, while in the ORAL Solo trial, neither arm reached significance.

The results of ORAL Scan indicate that only the tofacitinib 10 mg arm reached statistical significance with respect to DAS-defined remission at month 6. Both ORAL Standard and Sync showed that all treatment arms fared better than the placebo arm.

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 16).

Adverse Events (Safety Data)

The adverse event profile is based on data compiled from two phase 2 and five phase 3 trials. Patients were randomized to either tofacitinib 5 mg twice daily or 10 mg twice daily as monotherapy, 5 mg or 10 mg twice daily in combination with DMARDs and placebo.

Deaths and Other Serious Adverse Events

A total of 12 deaths were reported from the phase 3 trials.

ORAL Scan: 6 deaths total; 4 attributed to study drug (pneumonia, ARDS, lung cancer, *pneumocystis jiroveci* pneumonia)
ORAL Standard: 2 deaths total; 1 attributed to study drug (*pseudomonas aeruginosa* pneumonia)
ORAL Step: 1 death; unrelated to drug (PE unrelated)
ORAL Sync: 4 deaths total: 3 attributed to study drug (acute HF, resp failure, traumatic brain injury)
ORAL Start: 2 deaths total: cause not stated
ORAL Solo: 1 death related to drug (CHF, renal failure)

Common Adverse Events

The most common adverse events were serious infections. Those commonly reported included upper respiratory tract infections (4%), nasopharyngitis (3%) and urinary tract infections (2%).

The most common serious infections included pneumonia, cellulitis, herpes zoster and urinary tract infections.

	0 to 3 months exposure		**0 to 12 months exposure**	
	Placebo	**Tofacitinib**	**Tofacitinib 5 mg**	**Tofacitinib 10 mg**
Serious infections	1 pt (0.5 events per 100 patient-yrs)	11 pts (1.7 events per 100 patient-yrs)	34 pts (2.7 events per 100 patient-yrs)	33 pts (2.7 events per 100 patient-yrs)
Tuberculosis Median exposure ~ 10 months	0	0	0	6 pts (0.5 events per 100 patient-yrs)
Opportunistic Infections Median exposure ~ 8 months	0	0	4 pts (0.3 events per 100 patient-yrs)	4 pts (0.3 events per 100 patient-yrs)

The most common types of malignancy reported were lung and breast cancer, then gastric, colorectal, renal cell, prostate cancer, lymphoma and malignant melanoma.

	0 to 3 months exposure		**0 to 12 months exposure**	
	Placebo	**Tofacitinib**	**Tofacitinib 5 mg**	**Tofacitinib 10 mg**
Malignancy	0	2 pts (0.3 events per 100 patient-yrs)	5 pts (0.4 events per 100 patient-yrs)	7 pts (0.6 events per 100 patient-yrs)

Other Adverse Events

Effect on Laboratory Tests

Lab parameter	Impact of tofacitinib on lab parameter
Lymphocytes	Counts < 500 cells/mm^3 in 0.04% during months 0 to 3 of tofacitinib exposure
Neutrophils	⇓ ANC < 1000 cells/mm^3 in 0.07% during months 0 to 3 of tofacitinib exposure
LFT's	⇑ LFT's 3x ULN observed in patients receiving tofacitinib; Monotherapy trials (0-3 months): no differences in AST/ALT between placebo or tofacitinib arms; DMARD trials (0-3 months): ALT ⇑ 3x ULN in placebo (1%), tofacitinib 5 mg (1.3%) and tofacitinib 10 mg (1.2%); AST ⇑ 3x ULN in placebo (0.6%), tofacitinib 5 mg (0.5%) and tofacitinib 10 mg (0.4%)
Lipids	Dose-related ⇑ in lipid parameters noted at one month, then remained stable; Mean LDL ⇑in tofacitinib 5 mg (15%) and tofacitinib 10 mg (19%) arms; Mean HDL ⇑ in tofacitinib 5 mg (10%) and tofacitinib 10 mg (12%) arms; Mean LDL/HDL ratios essentially unchanged in treated patients
Serum creatinine	Dose-related ⇑in serum creatinine observed; Mean ⇑ in serum creatinine < 0.1 mg/dL in 12-month pooled analysis; Increasing duration of exposure in long-term extensions, up to 2% discontinued tofacitinib due to creatinine ⇑ of > 50% of baseline

Other Adverse Reactions

Adverse Events occurring in ≥ 2% on tofacitinib 5 or 10 mg BID with or without DMARD (0-3 months) and at least 1% greater than that observed in patients on placebo

	Tofacitinib 5 mg BID N= 1336 (%)	Tofacitinib 10 mg BID N= 1349 (%)	Placebo N= 809 (%)
Diarrhea	4	2.9	2.3
Nasopharyngitis	3.8	2.8	2.8
Upper RTI	4.5	3.8	3.3
Headache	4.3	3.4	2.1
Hypertension	1.6	2.3	1.1

Tolerability

The following chart summarizes discontinuation from therapy due to adverse events.

Phase 3 Trials	DC due to AE (months)
ORAL Step Burmester 2013	T 5mg + MTX: 6% (0-3) T 10mg + MTX: 4.5% (0-3) P: 5.3% (0-3)
ORAL Scan Van der Heijde 2013	T 5mg + MTX: T 10mg + MTX: P + MTX:
ORAL Standard Van Vollenhoven 2012	T 5mg + MTX: 6.9% (0-3) T 10mg + MTX: 5% (0-3) A 40mg + MTX: 1.5% (0-3) P + MTX: 2.8% (0-3)
ORAL Solo Fleischmann 2012	T 5mg + AM: 0.8% (0-3) T 10mg + AM: 2.4% (0-3) P + AM: 4.1% (0-3)
ORAL Sync Kremer 2013	T 5mg + DMARD: 6.2# (0-12) T 10mg + DMARD: 9.7# (0-12) P + DMARD: 5.4# (0-12)

events per 100 patient-yrs of exposure

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 16).

Contraindications

No contraindications are listed within the Prescribing Information. Relative contraindications to tofacitinib therapy include the following:

- Severe hepatic impairment
- Lymphocyte count < 500 cells/mm^3
- ANC < 1000 cells/mm3
- Hemoglobin < 9 g/dL

Warnings and Precautions

Boxed Warning pertains to risk of Serious Infections and Malignancy

- Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral and other opportunistic infections, have occurred in patients receiving tofacitinib.
- If a serious infection develops, interrupt tofacitinib until the infection is controlled.
- Prior to starting tofacitinib, perform a test for latent tuberculosis; if positive, start treatment for tuberculosis prior to starting tofacitinib.
- Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative.
- Lymphoma and other malignancies have been observed in patients treated with tofacitinib. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with tofacitinib and concomitant immunosuppressive medications.

Serious Infections

Infections due to bacterial, mycobacterial, invasive fungal, viral or other opportunistic pathogens have been serious and at times, fatal. Most common infections include pneumonia, cellulitis, herpes zoster and urinary tract infections. Opportunistic infections, tuberculosis and other mycobacterial infections, including cryptococcus, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus

and BK virus have been reported with tofacitinib. Some presented with disseminated disease and were often taking concomitant immunomodulating agents (i.e. methotrexate, corticosteroids).

Tofacitinib should not be initiated in the setting of an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- With chronic or recurrent infection
- Who have been exposed to tuberculosis
- With a history of a serious or an opportunistic infection
- Who have resided or traveled in areas of endemic tuberculosis or endemic mycoses
- With underlying conditions that may predispose them to infection

Closely monitor patients for signs and symptoms of infection during and following treatment with tofacitinib. Interrupt therapy if a serious infection develops and initiate a prompt and complete diagnostic workup for an immunocompromised patient, including appropriate antimicrobial therapy and close monitoring.

Tuberculosis

Evaluate patients and test for latent/active infection prior to giving tofacitinib.

Consider anti-tuberculosis therapy prior to giving tofacitinib in patients with a past history of latent/active tuberculosis if an adequate treatment course cannot be confirmed. Also consider anti-tuberculosis therapy in those with a negative test for latent tuberculosis but who have risk factors for tuberculosis infection. When in doubt, consult with a physician with expertise in tuberculosis management.

Monitor patients closely for signs and symptoms of tuberculosis, even if they tested negative for latent disease prior to initiating therapy.

Those with latent tuberculosis should be treated with standard antimycobacterial therapy before administering tofacitinib.

Viral Reactivation

Viral reactivation was noted in the clinical studies with tofacitinib. The impact of tofacitinib on chronic viral hepatitis reactivation is unknown. Those who screened positive for hepatitis B or C were excluded from clinical trials.

Malignancy and Lymphoproliferative Disorder

Malignancies were observed in tofacitinib clinical trials. Consider the risks and benefits of tofacitinib prior to starting therapy in a patient with a known malignancy other than a successfully treated non-Melanoma skin cancer (NMSC). Also consider potential risks and benefits of tofacitinib therapy in a patient who develops a malignancy.

Among seven RA clinical trials that included 3328 patients receiving tofacitinib, 11 solid cancers and one case of lymphoma was diagnosed. This compares to 0 solid cancers and 0 lymphomas among 809 patients that received placebo during the first 12 months of exposure. Lymphomas and solid cancers have also been observed in the long-term extension studies in RA patients treated with tofacitinib.

Among *de-novo* renal transplant patients in the clinical trial setting who have received induction therapy with basiliximab, high dose corticosteroids and mycophenolic acid products, Epstein Barr Virus-associated post-transplant lymphoproliferative disorders was noted in 5 of 218 patients treated with tofacitinib (2.3%) compared to 0 of 111 treated with cyclosporine.

Gastrointestinal (GI) Perforation
GI perforation has been reported in RA patients treated with tofacitinib in the clinical trial setting. The role of JAK inhibition in this setting is not known.

Use caution when prescribing tofacitinib in patients who may be at increased risk of GI perforation. Those presenting with new onset abdominal symptoms should be evaluated promptly for GI perforation.

Impact on Laboratory Parameters

Lymphocytes
Tofacitinib therapy has been associated with an initial lymphocytosis following one month of exposure that has been followed by a subsequent decrease in mean lymphocyte counts to below baseline values of approximately 10% during 12 months of therapy. Lymphocyte counts less than 500 cells/mm^3 have been associated with an increased incidence of treated and serious infections.

Avoid starting tofacitinib in patients with a low lymphocyte count (less than 500 cells/mm^3). Tofacitinib is not recommended in those patients who develop an absolute lymphocyte count less than 500 cells/mm3.

Monitor lymphocyte counts at baseline and every 3 months thereafter. Refer to *Dosage and Administration* for recommended dose modifications.

Neutrophils
Avoid starting tofacitinib in patients with a low neutrophil count (i.e. ANC less than 1000 cells/mm^3) as tofacitinib therapy was associated with an increased incidence of neutropenia compared to placebo. For those who develop a persistent ANC of 500-1000 cells/mm^3, interrupt tofacitinib dosing until ANC is greater than or equal to 1000 cells/mm^3. Tofacitinib is not recommended in patients who develop an ANC less than 500 cells/mm^3.

Hemoglobin
Avoid starting tofacitinib in patients with a low hemoglobin level (i.e. less than 9 g/dl). Interrupt tofacitinib if patient develops a hemoglobin level less than 8 gm/dL or whose hemoglobin level drops greater than 2 g/dL on treatment.

Monitor hemoglobin at baseline and after 4-8 weeks of treatment, then every 3 months thereafter. Refer to *Dosage and Administration* for recommended dose modifications.

Lipids
Increases in total cholesterol, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol have been associated with tofacitinib therapy. Maximum effects have been noted within 6 weeks. The effect on cardiovascular morbidity and mortality has not been determined.

Assess lipid parameters 4-8 weeks following initiation of tofacitinib.

Liver Enzymes
Compared to placebo, patients receiving tofacitinib were noted to have increased incidence of liver enzyme elevations. Most of these enzyme elevations occurred with background DMARD (primarily MTX) therapy.

Monitor liver enzymes routinely and promptly investigate causes of enzyme elevations to identify potential cases of drug-induced liver injury. If drug-induced injury is suspected, interrupt tofacitinib until this diagnosis is excluded.

Vaccinations
Update immunizations per current guidelines prior to initating tofacitinib therapy. There are no data available on the response to vaccines or on the secondary transmission of infection by live vaccines to patients receiving tofacitinib. Live vaccines should not be given concurrently with tofacitinib.

Hepatic Impairment
Tofacitinib is not recommended in patients with severe hepatic impairment.

Special Populations

Pregnancy
Pregnancy Category C. *Teratogenic Effects*: Use tofacitinib in pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant women. The drug has fetocidal and teratogenic effects in rats and rabbits when given at exposure 146 times and 13 times, respectively, the maximum recommended human dose (MRHD).

Non-teratogenic effects: Reductions in live litter size, postnatal survival and pup body weight was noted in a rat study with exposures approximately 73 times the MRHD.

Pregnancy Registry: Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972, to monitor outcomes of pregnant women exposed to tofacitinib.

Nursing Mothers
Tofacitinib has been secreted in the milk of lactating rats. It is not known if the drug is excreted in human milk. Because of the potential risk to infants, a decision should be made whether to discontinue nursing or to discontinue the drug in nursing mothers, considering the importance of the drug to the mother.

Pediatric Use
Safety and efficacy of tofacitinib has not been established in the pediatric population.

Geriatric Use
Of 3315 patients enrolled in tofacitinib clinical trials, 505 patients with rheumatoid arthritis were 65 years of age and older, including 71 patients aged 75 years and older. The frequency of serious infections among patients 65 years and older was higher than those under the age of 65, therefore caution should be used when treating elderly patients.

Hepatic Impairment
In those with mild hepatic impairment, no dose adjustment of tofacitinib is needed. Tofacitinib should be reduced to 5 mg once daily in patients with moderate hepatic impairment. Safety and efficacy has not been studied in patients with severe hepatic impairment or positive hepatitis B or hepatitis C virus serology.

Renal Impairment
No dose adjustment is necessary in settings of mild renal impairment. Reduce tofacitinib dose to 5 mg once daily in moderate to severe renal impairment. Tofacitinib was not evaluated in patients with creatinine clearance values less than 40 ml/min.

Sentinel Events

None

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a Joint Commission standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

LA/SA for generic name 'tofacitinib': Trametinib, Tocilizumab, Trastuzumab
LA/SA for trade name 'Xeljanz': Xolegel, Xalatan, Zaltrap, Selzentry

Drug Interactions

Drug-Drug Interactions

Tofacitinib is metabolized by CYP3A4 therefore drugs that inhibit or induce CYP3A4 may affect its pharmacokinetics. Drugs that inhibit CYP2C19 alone or P-glycoprotein are unlikely to affect tofacitinib.

Drugs that may impact PK of tofacitinib	Recommended management strategy
CYP3A4 inhibitors (ketoconazole)	Reduce tofacitinib dose to 5 mg once daily
CYP3A & CYP2C19 inhibitors (fluconazole)	Reduce tofacitinib dose to 5 mg once daily
CYP inducer (rifampin)	May decrease efficacy of tofacitinib
Methotrexate	No dose adjustment
Tacrolimus	Risk of added immune suppression
Cyclosporine	Risk of added immune suppression

Acquisition Costs

Please refer to the last page for VA drug acquisition costs. Prices shown in this internal, draft document may include additional discounts available to VA. This information is considered strictly confidential and must not be shared outside of VA. All cost information will be removed from the document when posted to the PBM website.

Pharmacoeconomic Analysis

There are none available at the present time.

Conclusions

Tofacitinib is a new oral therapy for the treatment of rheumatoid arthritis that provides a novel mechanistic approach via JAK intracellular pathways. The efficacy of tofacitinib was evaluated in the following phase 3 trials under the oral rheumatoid arthritis trials program (ORAL).

Among the phase 3 trials, a statistically higher percentage of patients receiving tofacitinib achieved the primary endpoint of ACR20 at the pre-defined time point (month 3 vs. 6) compared to placebo.
In five of the phase 3 trials, where tofacitinib was initiated after inadequate response to either biologic or non-biologic DMARD, tofacitinib, in combination with non-biologic DMARD therapy, was more effective than placebo.

Adding the comparator, adalimumab 40mg every other week, showed that all three treatment arms (tofacitinib 5mg, 10mg and adalimumab) achieved a greater ACR20 response at month 6 compared to placebo, with tofacitinib and adalimumab responses being numerically similar.

The higher tofacitinib dose (10mg twice daily) was associated with a statistically significant improvement in radiographic progression, but not the approved dose of 5 mg twice daily. Remission rates, evaluated as the DAS-28[ESR] endpoint were somewhat variable among the trials. Improvements in physical function were noted with tofacitinib treatment at the 3 months assessment point, compared to baseline HAQ-DI values.

Tofacitinib appears to be well-tolerated, but has a higher incidence of serious infections (including opportunistic infections and tuberculosis), malignancy, neutropenia and laboratory abnormalities (including LFTs and lipid profile). A boxed warning highlights the risk of serious infections and malignancy. A REMS Medication Guide outlines the safety issues for patients.

Tofacitinib is a twice daily oral formulation that may provide a convenient option for patients. Yet the conveniences of the formulation need to be considered in light of the safety profile which requires that patients adhere to follow-up and monitoring schedules.

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Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to December 2013) using the search terms 'tofacitinib' and 'Xeljanz'. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Summary of Published Phase 3 Clinical Trials in the oral rheumatoid arthritis trials program (ORAL)

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results
Van Vollenhoven (2012) ORAL Standard R, Phase 3 12-month 115 centers Between 1/30/2009 – 2/10/2011	Inclusion: Adults with active RA; on MTX 7.5-25mg/wk with incomplete response	4:4:4:1:1 ratio 5 arms: 1) T 5mg BID; 2) T 10mg BID; 3) Adalimumab 40mg subQ q2 weeks; 4) Placebo x 3 or 6 mos, then T 5mg BID 5) Placebo x 3 or 6 mos, then T 10mg BID Primary endpoints: ACR20 at 6 mos; Change in HAQ-DI at 3 mos; DAS28 < 2.6 at 6 mos; safety Secondary endpoints: T 5mg, T 10mg vs. placebo in ACR20, ACR50, ACR70, HAQ-DI and DAS28-4[ESR]	N=717 Women 75-85% White 67-74% Mean duration RA 7-9 yrs 556 (77%) completed 12 mos of study	ACR20 at 6 months: T 5mg: 51.5% T 10mg: 52.6% A 40mg: 47.2% Placebo: 28.3% (p<0.001) ∆ HAQ-DI at 3 mos: T 5mg -0.55 T 10mg -0.61 A 40mg -0.49 Placebo -0.24 DAS28-4(ESR) < 2.6 @ 6 mos: T 5mg 6.2% T 10mg 13.1% A 40mg 7.3%	Initial ⇓ ANC @ 3 mos in all arms, then stable to 12 mos. Mild (ANC 1500-1999) @ mo 3: T 5mg 3% T 10mg 3% A 40mg 5% Placebo 2% Moderate (ANC 500-1499) @ mo 3: T 5mg 2% T 10mg 3% A 40mg 0 Placebo 0 ⇓ Hgb (-1 to -3g/dL) @ mo 3: T 5mg: 15% T 10mg: 15% A 40mg: 10% Placebo 9% ⇑ LDL, HDL: T 5mg: 3.9% T 10mg: 6.5% A 40mg: 0.1% Placebo: 0.9% SAE (infections): T 5mg 3.4% T 10mg 4% A 40mg 1.5% DC due to SAE (0-3): T 5mg 6.9% T 10mg 5% A 40mg 4.9% Placebo 2.8% 2 cases pulm TB (T 10mg)

Fleischmann (2012) ORAL Solo R, Phase 3, DB, PC, PG, 6-month study 94 centers Feb 2009-June 2010 Sponsored by Pfizer	Inclusion: RA & inadequate response ≥ 1 non-biologic or biologic DMARD NSAIDs, ≤ 10mg pred equiv allowed Exclusion: Hgb < 9g/dl Hct < 30% WBC < 3000 ANC < 1200 Plt < 100K Gfr < 40 ml/min LFT > 1.5x ULN	4:4:1:1 4 arms: 1) T 5mg BID x6 mos; 2) T 10mg BID x6 mos; 3) Placebo x 3 mos, then T 5mg BID x3 mos; 4) Placebo x3 mos then T 10mg BID x3 mos Primary endpoints, mo 3: ACR20 HAQ-DI DAS28-4[ESR]	N=611 Women 87% Caucasian 67% Duration RA ~ 8yrs Mean age 50-52 yrs Prior TNF-I: T 5mg: 14% T 10mg: 16.7% Placebo: 10.7% Prior other biologic: T 5mg: 4.9% T 10mg: 7.8% Placebo: 8.2% Prior MTX: T 5mg: 86% T 10mg: 84.5% Placebo: 83.6%	Primary endpoints, mo 3: ACR20 HAQ-DI DAS28-4[ESR] ACR20 at 3 mos: T 5mg 59.8%; T 10mg 65.7%; Placebo 26.7% (p<0.001) ACR50 at 3 mos: T 5mg 31.1%; T 10mg 36.8%; Placebo 12.5% (p,0.001) ACR70 at 3 mos: T 5mg 15.4% (p=0.003) T 10mg 20.3% (p<0.001) Placebo 5.8% ∆HAQ-DI scores, 3 mos: T 5mg -0.50 pts; T 10mg -0.57 pts; Placebo -0.19 pts (p<0.001) DAS28-4[ESR], 3 mos: T 5mg 5.6%; T 10mg 8.7%; Placebo 4.4% (p NS)	Common AEs: upper resp tract infection, headache Common AE, mo 0-3: T 5mg 51% T 10mg 56.7% Placebo 54.9% SAE T 5mg 0.4% T 10mg 2% Placebo 4.9% Serious infection T 5mg 0 T 10mg 0.4% Placebo 0 DC due to AE T 5mg 0.8% T 10mg 2.4% Placebo 4.1% ⇓ ANC from baseline T 5mg -0.83±11 T 10mg -1.35±0.12 Placebo -0.06±0.17 Primarily mild, ANC 1500-1999 ∆ LDL from baseline T 5mg 13.6±1.56 T 10mg 10.1±1.60 Placebo 3.5±2.28 ∆HDL from baseline T 5mg 12.24±1.31 T 10mg 14.98±1.34 Placebo -0.76±1.93

Burmester (2013) ORAL Step R, Phase 3, DB, PG 82 centers; 13 countries	Inclusion: Active, mod-severe RA & inadequate response to TNF-I Stable MTX & anti-malarial tx allowed NSAIDs, ≤ 10mg pred equiv allowed Exclusion: Hgb < 9g/dl Hct < 30% WBC < 3000 ANC < 1200 Plt < 100K Gfr < 40 ml/min LFT > 1.5x ULN	2:2:1:1 4 arms: 1) T 5mg BID + MTX 2) T 10mg BID + MTX 3) Placebo + MTX, then T 5mg BID 4) Placebo + MTX, then T10mg BID Primary endpoints, mo 3: ACR20 HAQ-DI DAS28-4[ESR] < 2.6	N=399 Women: T 5mg: 85% T 10mg 87% Placebo 80% Caucasian: T 5mg 81.2% T 10mg 83.6% Placebo 84.8% Mean age 55 yrs Duration RA, 12 yrs 1 prior TNF-I: T 5mg 63.2% T 10mg 67.2% Placebo 65.2% 2 prior TNF-I: T 5mg 27.8% T 10mg 22.4% Placebo 28% ≥ 3 prior TNF-I: T 5mg 8.3% T 10mg 9% Placebo 6.8%	Primary endpoints, mo 3: ACR20 HAQ-DI DAS28-4[ESR] < 2.6 ACR20 at 3 mos: T 5mg 41.7% T 10mg 48.1% Placebo 24.4% ∆ HAQ-DI scores, 3 mos: T 5mg -0.43 pts T 10mg -0.46 pts Placebo -0.18 pts DAS28-4[ESR], 3 mos: T 5mg 6.7% T 10mg 8.8% Placebo 1.7%	Common AEs, 0-3 mos: Diarrhea 4.9% Nasopharyngitis 4.1% Headache 4.1% UTI 3% SAEs: T groups: 1.5% Placebo: 4.5% DC due to AEs, 0-3 mos: T groups 5.2% Placebo: 5.3% Common AEs, 3-6 mos: Upper Resp Tract infection 3.3% Nasopharyngitis 2.8% Bronchitis 2.3% Serious AEs, 3-6 mos: T 5mg: panniculitiis (1), Bronchopneumonia (1) T 10mg: pyelonephritis (1), Diverticulitis (1), P → T 10mg: asp pna (1) DC due to AE, 3-6 mo: 3.5%

Van der Heijde (2013) ORAL Scan R, Phase 3, DB, PG, PC 111 centers	Inclusion: Active RA, joint erosion, on stable MTX NSAIDs, ≤ 10mg pred equiv allowed; prior biologic or nonbiologic DMARD allowed Stable MTX Exclusion: Hgb < 9g/dl Hct < 30% WBC < 3000 ANC < 1200 Plt < 100K Gfr < 40 ml/min LFT > 1.5x ULN	4:4:1:1 4 arms: 1) T 5mg BID; 2) T 10mg BID; 3) Placebo x 3 mos, then T 5mg BID; 4) Placebo x3 mos then T 10mg BID Primary endpoints, mo 6: ACR20 SHS score HAI-DQ score (mo 3) DAS28-4[ESR]	N=797 Mean age 53 yrs Female 85% Nonwhite 54% Mean duration RA 9 yrs	Primary endpoints, mo 6: ACR20 SHS score HAI-DQ score (mo 3) DAS28-4[ESR] ACR20, mo 6: T 5mg 51.5% T 10mg 61.8% Placebo 25.3% (p<0.0001) ∆ total SHS, mo 6: T 5mg 0.12 (p NS) T 10mg 0.06 (p ≤ 0.05) Placebo 0.47 ∆ HAI-DQ score, mo 3: T 5mg -0.40 T 10mg -0.54 (p<0.0001) Placebo/T 5mg -0.15 DAS28-ESR<2.6, mo 6: T 5mg 7.2% T 10mg 10% (p<0.0001) Placebo/T 5mg 1.6% DAS28-ESR<2.6, mo 12: T 5mg 10.6% T 10mg 15.2% ACR50, mo 6: T 5mg 32.4% T 10mg 43.7% Placebo 8.4% (p<0.0001) ACR70, mo 6: T 5mg 14.6% T 10mg 22.3% Placebo 1.3% (p<0.0001)	AEs, mo 6-12: T 5mg 51.7% T 10mg 55.1% P → T 5mg 42% P → T 10mg 44.3% Most common AEs: Infections, infestations, GI disorders, lab abnormalities Incidence rates serious infection per 100 patient-yrs to mo 12: T 5mg 4.17 T 10mg 2.32 Placebo 3.68 Six deaths T 5mg 4 deaths T 10mg 1 death Placebo 1 death Six CV events in T arms: angina pectoris (1), CAD (1), CA stenosis (1), cerebral infarct (1), lacular infarct (2) Nine carcinomas in T arms: Basal cell (3), stomach adeno (2), bone SCCa (1), breast (1), NHL (1), cervix SCCa (1) ⇓ ANC ⇑ LDL cholesterol ⇑ SCr

Kremer (2013) R,Phase 3, DB, PC, 1-year trial 114 centers; 19 countries; May 2009-Jan 2011 Sponsored by Pfizer	Inclusion: Active RA, inadequate response to ≥ 1 biologic or non-biologic DMARD before baseline and continue with ≥ 1 non-biologic DMARD at stable doses throughout the study At least 4 months of therapy w/stable dose of MTX; ≤ 10mg pred equiv allowed Exclusion: Hgb < 9g/dl Hct < 30% WBC < 3000 ANC < 1200 Plt < 100K Gfr < 40 ml/min LFT > 1.5x ULN	4:4:1:1 4 arms: 1) T 5mg BID; 2) T 10mg BID; 3) Placebo x3 mos, then T 5mg BID; 4) Placebo x3 mos then T10mg BID At month 3, P non-responders randomized to T 5mg or 10mg At month 6, all P patients randomized to T 5mg or 10mg Primary endpoints, Month 3: HAQ-DI Month 6: ACR20, DAS28-4[ESR] Safety over 12 mos	N=795 Mean age 50-53 yrs Female 75-84% Mean duration RA 8-10 yrs 62-73% continued to receive 1 DMARD; 25-37% continued to receive ≥ 2 DMARDs; 79% continued MTX	Primary endpoints, Month 3: HAQ-DI Month 6: ACR20, DAS28-4[ESR] Safety over 12 mos No ACR20, mo 3: T 5mg 25.4% T 10mg 18.2% Placebo 49.1% ACR20, mo 3: Placebo 27% ACR20, mo 6: T 5mg 21.2%; p<0.001 T 10mg 25.8%; p<0.001 ∆ HAI-DQ score, mo 3: T 5mg -0.44 (p<0.001) T 10mg -0.53 (p<0.001) Placebo -0.15 DAS28-4(ESR)<2.6, mo 6 T 5mg 8.5% (p=0.005) T 10mg 12.5% (p<0.001) Placebo 2.6%	AEs incidence rate, mo 0-12 (events per 100 pt-yrs) T 5mg 171.9 T 10mg 175.7 Placebo/T 342.3 SAEs incidence rate (events per 100 pt-yrs) T 5mg 6.9 T 10mg 7.3 Placebo/T 10.9 Most common AEs: Upper resp tract infections, Nasopharyngitis 4 cases of OI in T arms 4 deaths occurred: 2 T 10mg arm 2 T 5mg arm 3 CV events: T 5mg TIA, CVA T 10mg CHF -> died ⇓ ANC at month 3, stable to month 12 ⇑ LDL, HDL cholesterol at month 3, stable to month 12 ⇑ SCr

T Tofacitinib, R randomized, DB double-blind, PG parallel-group, PC placebo-controlled, RA rheumatoid arthritis, MTX methotrexate, NSAIDs non-steroidal anti-inflammatory drugs, hgb hemoglobin, hct hematocrit, WBC white blood cell, ANC absolute neutrophil count, plt platelet, GFR glomerular filtration rate, LFT liver function tests, SHS total modified Sharp/van der Heijde score, HAI-DQ Health Assessment Questionnaire disability index score, DAS28-4[ESR] Disease Activity Score in 28 joints using ESR, AEs adverse events, GI gastrointestinal, CV cardiovascular, CAD coronary artery disease, SCCa squamous cell carcinoma, NHL non-hodgkins lymphoma, LDL low density lipoprotein, adeno adenocarcinoma, N number