CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211675Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211675
PDUFA Goal Date	August 16, 2019
OSE RCM #	2018-2753
Reviewer Name(s)	Bob Pratt, Pharm.D.
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Division Director	Jamie Wilkins, Pharm.D.
Review Completion Date	August 15, 2019
Subject	Evaluation of need for a REMS
Established Name	Upadacitinib
Trade Name	Rinvoq
Name of applicant	AbbVie Inc.
Therapeutic Class	Janus kinase (JAK) inhibitor
Formulation(s)	Extended-release oral tablets 15 mg
Dosing Regimen	15 mg once daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Rinvoq (upadacitinib) is necessary to ensure the benefits of the drug outweigh its risks. AbbVie Inc. (AbbVie) submitted a New Drug Application (NDA 211675) on December 18, 2018 for upadacitinib, a disease-modifying antirheumatic drug that belongs to the class of Janus kinase inhibitors. The applicant's proposed indication is (b) (4) The serious risks associated with the use of upadacitinib include infections, malignancies, gastrointestinal perforations, thrombosis, and laboratory abnormalities. A REMS was not included in the application.

DRISK and the Division of Pulmonary, Allergy, and Rheumatology Products agree that a REMS is not needed to ensure the benefits of upadacitinib outweigh its risks. The efficacy of upadacitinib has been established based on significant improvements in the primary endpoint and key secondary endpoints compared with placebo or methotrexate in the pivotal studies. There have been several communication plan REMS required, completed, and released for disease-modifying antirheumatic drugs (including the Janus kinase inhibitor tofacitinib) for the treatment of rheumatoid arthritis that addressed serious risks similar to those of upadacitinib. We therefore expect that healthcare providers who treat rheumatoid arthritis to be familiar with the risks associated with upadacitinib for the proposed indication.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Rinvoq (upadacitinib) is necessary to ensure the benefits of this drug outweigh its risks. AbbVie submitted a New Drug Application (NDA 211675) for upadacitinib on December 18, 2018. The applicant's proposed indication is (b) (4) This application is under review in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). The applicant did not submit a REMS with this application.

2 Background

2.1 PRODUCT INFORMATION

Rinvoq (upadacitinib), a new molecular entity[a], is a Janus kinase (JAK) inhibitor proposed for (b) (4) Janus kinases are a family of four tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) that phosphorylate and activate cytokine receptors as well as the JAKs themselves, triggering cytokine signaling. Upadacitinib has higher selectively to inhibit JAK1 over JAK2 and JAK3.[1] The JAKs have multiple effects on hematopoiesis, T cell proliferation and function, B cell function, lymphocyte effector function, macrophage activation, airway reactivity, acute phase responses, lipid metabolism, anti-inflammatory effects, antiviral responses, and other effects. In the setting of immune-mediated disorders, JAK inhibitors prevent JAKs from activating highly complex signal transduction and activation of transcription (STAT) pathways that are implicated in the pathogenesis of rheumatoid arthritis and other autoimmune and inflammatory diseases.[2]

[a] FDAAA factor (F): Whether the drug is a new molecular entity.

The class of currently approved Janus kinase inhibitors includes ruxolitinib (Jakafi), tofacitinib (Xeljanz), and baricitinib (Olumiant), each of which is a non-selective JAK inhibitor. Ruxolitinib was approved in November 2011 for the treatment of intermediate or high-risk myelofibrosis and polycythemia vera. There were no REMS considerations at the time of ruxolitinib's approval.[3] Tofacitinib was approved in November 2012 with a REMS consisting of a communication plan for the treatment of moderate to severe rheumatoid arthritis (RA) in adult patients who have had an inadequate response or intolerance to methotrexate. The goal of the tofacitinib REMS was to mitigate the risk of serious infections, malignancies, lympho-proliferative disorders, increased cholesterol, and low blood cell counts by informing healthcare prescribers and pharmacists about these risks. The REMS was eliminated in February 2016 after the Agency determined the communication plan was no longer necessary because it had been completed and the most recent REMS assessment demonstrated the communication plan had met its goals. Baricitinib was approved in May 2018 for the treatment of adult patients with moderate to severe rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies. A REMS was not required for the approval of baricitinib because the likely prescribers were expected to be familiar with the risks of JAK inhibitors due to the knowledge demonstrated by prescribers of tofacitinib, which has similar risks. Although baricitinib is associated with an increased risk of thrombosis, the risk is currently addressed using a Boxed Warning.

Upadacitinib is supplied as an extended-release oral tablet and is to be administered as a chronic therapy[b] in a single daily dose of 15 mg. As an oral therapy, the drug will typically be self-administered in the outpatient setting. Upadacitinib is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 211675 relevant to this review:

- 12/18/2018: NDA 211675 submission (b) (4) received.
- 04/02/2019: A mid-cycle communication meeting was held between the Agency and the applicant via teleconference. There was no discussion related to the need for a REMS. The Agency noted that the inclusion of the risks of malignancy, hepatitis B reactivation, venous thromboembolism, and embryo-fetal toxicity in the Boxed Warning and/or Warnings and Precautions sections of the label are review issues under consideration.
- 6/11/2019: A late-cycle meeting was held between the Agency and the applicant. There was no discussion related to the need for a REMS. The Agency noted that the risks of malignancy will be included in a Boxed Warning and the risks of hepatitis B reactivation, gastrointestinal perforations, and embryo-fetal toxicity will be included in the Warnings and Precautions sections of the label. The risk of thromboembolism remained under review.

[b] FDAAA factor (D): The expected or actual duration of treatment with the drug.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

RA is a chronic, systemic, inflammatory disorder of unknown etiology that primarily involves synovial joints. The annual incidence of RA has been reported to be approximately 40 per 100,000.[c] The disease prevalence is about 1 percent in Caucasians but varies between 0.1 percent in rural Africans to 5 percent in certain Native American tribes. Women are affected two to three times more often than men. The peak onset of RA is between the ages of 50 and 75, and because of the consistently higher rates in females, the prevalence in females over age 65 is as high as 5 percent.[4]

The onset of RA is usually insidious, with the predominant symptoms being pain, stiffness, and swelling of many joints. The arthritis is typically symmetrical and usually leads, if uncontrolled, to destruction of joints due to erosion of cartilage and bone, causing joint deformities. However, the disease shows varied clinical expression in individual patients, including the number of involved joints and pattern of joint involvement; fluctuations in the disease activity and ability to achieve remission; and the rate of progression and extent of structural damage. RA usually progresses from the periphery to more proximal joints and results in significant disability within 10 to 20 years in patients who do not fully respond to treatment. In patients with severe joint disease, non-articular organs can become involved.[5] Involvement of the musculoskeletal system (other than joints) and of organs not considered part of the musculoskeletal system (e.g., skin, eye, lung, heart, kidney, blood vessels) occurs in about 40 percent of patients with RA over a lifetime of disease and is associated with increased disease severity, morbidity, and premature mortality.[6,d]

3.2 Description of Current Treatment Options

Pharmaceutical treatment options in RA include nonsteroidal anti-inflammatory drugs (NSAIDs), selective NSAID COX-2 inhibitors, corticosteroids, conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate; other small-molecule DMARDS that target and inhibit Janus kinase; and biologic DMARDs such as tumor necrosis factor [TNF] inhibitors, interleukin (IL) inhibitors, T-cell co-stimulation modulators, and B-cell depletion therapies. Anti-inflammatory drugs, including NSAIDs and corticosteroids, are used primarily as adjuncts for temporary control of disease activity. The DMARDs are a diverse group of therapeutic agents that reduce signs and symptoms of RA as well as slow disease progression.[7]

Table 1 below shows a list of the DMARDs approved in the U.S. since 1998. Of this group of products, the TNF inhibitors, the IL-6 inhibitor tocilizumab, and the Janus kinase inhibitor tofacitinib all required communication plan REMS that were approved during the period from 2008 to 2012. All these REMS have been released because the communication plans had been completed and the REMS assessments showed that each REMS had met its goals. Although several of the REMS included a Medication Guide as a required element, it was subsequently determined that maintaining the Medication Guide as part of the labeling under CFR 208 is sufficient to address the risks.

Table 1: DMARDs approved in the U.S. for adult rheumatoid arthritis since 1998

Product Name (Trade Name) Year of Approval	Mechanism of action	Indications	REMS History	• Boxed Warnings *Risks addressed by REMS*

Leflunomide (Arava) 1998	Anti-metabolite	• Rheumatoid arthritis	No REMS	• Embryo-fetal toxicity • Hepatic toxicity
Etanercept (Enbrel) 1998	TNF inhibitor	• Rheumatoid arthritis • Polyarticular juvenile idiopathic arthritis • Psoriatic arthritis • Ankylosing spondylitis • Plaque psoriasis	(REMS Approved 2008) Medication Guide Communication Plan REMS Released August 2011	• Serious infections • Malignancies *Serious bacterial and fungal infections*
Infliximab (Remicade) 1999	TNF inhibitor	• Crohn's disease • Pediatric Crohn's disease • Ulcerative colitis • Pediatric ulcerative colitis • Rheumatoid arthritis • Ankylosing spondylitis • Psoriatic arthritis • Plaque psoriasis	(REMS Approved 2009) Medication Guide Communication Plan REMS Released August 2011	• Serious infections • Malignancy *Serious fungal infections*
Anakinra (Kineret) 2001	IL-1 inhibitor	• Rheumatoid arthritis • Cryopyrin-associated periodic syndromes	No REMS	
Adalimumab (Humira) 2002	TNF inhibitor	• Rheumatoid arthritis • Juvenile idiopathic arthritis • Psoriatic arthritis • Ankylosing spondylitis • Adult Crohn's disease • Pediatric Crohn's disease • Ulcerative colitis • Plaque psoriasis • Hidradenitis suppurativa • Uveitis	(REMS Approved 2010) Communication Plan REMS Released December 2011	• Serious infections • Malignancy *Serious fungal infections*
Abatacept (Orencia) 2005	T cell activation inhibitor	• Rheumatoid arthritis • Juvenile idiopathic arthritis • Psoriatic arthritis	No REMS	
Rituximab (Rituxan) 2006	Anti-CD 20 B-cell depletion	• Non-hodgkin's lymphoma • Chronic lymphocytic leukemia • Rheumatoid arthritis • Granulomatosis with polyangiitis and microscopic polyangiitis • Pemphigus vulgaris	No REMS	• Fatal infusion reactions • Severe mucocutaneous reactions • Hepatitis B reactivation • Progressive multifocal leukoencephalopathy
Golimumab (Simponi) 2009	TNF inhibitor	• Rheumatoid arthritis • Psoriatic arthritis • Ankylosing spondylitis • Ulcerative colitis	Medication Guide Communication Plan REMS Released March 2011	• Serious infections • Malignancy *Serious infections, malignancies, congestive heart failure, demyelinating disorders*
Certolizumab Pegol (Cimzia) 2008	TNF inhibitor	• Crohn's disease • Rheumatoid arthritis • Psoriatic arthritis • Ankylosing spondylitis • Non-radiographic axial spondyloarthritis • Plaque Psoriasis	Medication Guide Communication Plan REMS released July 2011	• Serious infections • Malignancy *Serious fungal infections, malignancies, psoriasis-like lesions*
Product Name (Trade Name) Year of Approval	Mechanism of action	Indications	REMS History	• Boxed Warnings *Risks addressed by REMS*

Tocilizumab (Actemra) 2010	IL-6 inhibitor	• Rheumatoid arthritis • Giant cell arteritis • Polyarticular juvenile idiopathic arthritis • Systemic juvenile idiopathic arthritis • Cytokine release syndrome	Communication Plan REMS released August 2015	• Serious infections *Serious infections, gastrointestinal perforations, hepatic effects, decreased neutrophil or platelet counts, elevations in lipid parameters, demyelinating disorders, malignancies*
Tofacitinib (Xeljanz) 2012	Janus kinase inhibitor	• Rheumatoid arthritis • Psoriatic arthritis • Ulcerative colitis	Communication Plan REMS released February 2016	• Serious infections • Malignancies *Serious infections, malignancy, increase in cholesterol, and decrease in blood counts*
Sarilumab (Kevzara) 2017	IL-6 inhibitor	• Rheumatoid arthritis	No REMS	• Serious infections
Baricitinib (Olumiant) 2018	Janus kinase inhibitor	• Rheumatoid arthritis	No REMS	• Serious infections • Malignancies • Thrombosis

4 Benefit Assessment

The clinical development program for upadacitinib included five multicenter, double-blind, parallel-group, randomized, placebo- or active-controlled Phase 3 studies of patients with moderate to severe RA. Each study had a randomized controlled period and a long-term extension period. The studies evaluated patients who were naïve to methotrexate (MTX); patients who had an inadequate response to methotrexate and/or other conventional DMARDs; and patients who were refractory or intolerant to treatment with biological DMARDs.

- Study M13-545 evaluated 947 patients who were naïve to MTX. Patients were randomized to receive treatment with either MTX, upadacitinib 15 mg daily, or upadacitinib 30 mg daily. The primary efficacy endpoint was ACR50[e] response at Week 12.
- Study M15-555 evaluated 648 patients who were inadequate responders to MTX. Patients received treatment with either MTX, upadacitinib 15 mg daily, or upadacitinib 30 mg daily. The primary efficacy endpoint was ACR20[f] at Week 14. Patients initially randomized to MTX crossed over to upadacitinib 15 mg or 30 mg at Week 14.
- Study M13-542 assessed 499 patients with inadequate response to biological DMARD therapy. Patients were randomized to receive treatment with upadacitinib 15 mg daily, upadacitinib 30 mg daily, or placebo. Background conventional DMARD therapy was continued. The primary efficacy endpoint was ACR20 at Week 12. Patients initially randomized to placebo crossed over to upadacitinib 15 mg or 30 mg at Week 12.
- Study M13-549 evaluated 661 patients who were inadequate responders to conventional DMARDs. Patients were randomized to receive treatment with upadacitinib 15 mg daily, upadacitinib 30 mg daily, or placebo. Background conventional DMARD therapy was continued. The primary efficacy endpoint

[e] The American College of Rheumatology's 50% response in RA (ACR50) is a composite measure calculated as a ≥50% improvement in tender joint count and swollen joint count as well as a ≥50% improvement in three of the following five criteria: patient global assessment, physician global assessment, functional ability measure [most often Health Assessment Questionnaire (HAQ)], visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein (CRP).

[f] ACR20 is calculated using the same instruments as ACR50 but with improvement levels defined as a 20% response.

was ACR20 at Week 12. Patients initially randomized to placebo crossed over to upadacitinib 15 mg or 30 mg at Week 12.

- Study M14-465 evaluate 1629 patients who had an inadequate response to MTX. The study randomized patients 2:2:1 to upadacitinib 15 mg daily versus placebo (through Week 26) and versus adalimumab 40 mg every other week (through Week 48). Patients could cross-over between the adalimumab and upadacitinib arms as early as Week 14. All patients were on background MTX therapy. The primary efficacy endpoint was ACR20 at Week 12.

Multiple ranked secondary endpoints were also evaluated in the studies, including the change from baseline in DAS28-hsCRP[g], HAQ-DI[h], modified Total Sharp Score (mTSS)[i], SF-36-PCS[j], and several other endpoints. Table 2 below shows the efficacy results for the primary endpoint and the first three ranked secondary endpoints from the five Phase 3 studies.[8]

Table 2. Efficacy results from the Phase 3 studies of upadacitinib for the treatment of moderate to severe RA.

Study	M13-545	M15-555	M13-542	M13-549	M14-465
Patient Population	MTX naïve	MTX-IR	bDMARD-IR	cDMARD-IR	MTX-IR
Treatment Arms	MTX (n=315) UPA15 (n=317) UPA30 (n=315)	MTX (n=216) UPA15 (n=217) UPA30 (n=215)	Placebo (n=169) UPA15 (n=165) UPA30 (n=165)	Placebo (n=221) UPA15 (n=221) UPA30 (n=219)	Placebo (n=651) UPA15 (n=651) Adalimumab (n=327)
Primary Endpoint Response Rate	ACR50 Week 12 MTX 28% UPA15 52%* UPA30 56%*	ACR20 Week 14 MTX 41% UPA15 68%* UPA30 71%*	ACR20 Week 12 Placebo 28% UPA15 65%* UPA30 56%*	ACR20 Week 12 Placebo 36% UPA15 64%* UPA30 66%*	ACR20 Week 12 Placebo 36% UPA15 71%* Adalimumab 63%
Secondary Endpoints[§]	ΔDAS28-hsCRP (W 12) MTX -1.85 UPA15 -2.73† UPA30 -2.85†	ΔDAS28-hsCRP (W14) MTX -1.20 UPA15 -2.29† UPA30 -2.61†	ΔDAS28-hsCRP (W 12) Placebo -1.02 UPA15 -2.31† UPA30 -2.29†	ΔDAS28-hsCRP (W 12) Placebo -1.02 UPA15 -2.20† UPA30 -2.34†	ΔDAS28-hsCRP (W12) Placebo -1.15 UPA 15 -2.48*
	ΔHAQ-DI (W 12) MTX -0.49 UPA15 -0.83† UPA30 -0.86†	ΔHAQ-DI (W 14) MTX -0.32 UPA15 -0.65† UPA30 -0.73†	ACR50 (W 12) Placebo 12% UPA15 34%† UPA30 36%†	ΔHAQ-DI (W 12) Placebo -0.25 UPA15 -0.59† UPA30 -0.54†	ΔmTSS (W 26) Placebo 0.92 UPA15 0.24*
	ΔmTSS (W 24) MTX 0.67 UPA15 0.14‡ UPA30 0.07†	ΔSF-36 PCS (W 14) MTX 4.32 UPA15 8.28† UPA30 10.19†	ΔHAQ-DI (W 12) Placebo -0.17 UPA15 -0.39† UPA30 -0.42†	ΔSF-36 PCS (W 12) Placebo 3.03 UPA15 7.58† UPA30 8.01†	ΔHAQ-DI (W 12) Placebo-0.28 UPA15 -0.60*

§=Secondary endpoints ranked in descending order per study; MTX=methotrexate; IR=inadequate responders; bDMARD=biologic disease-modifying antirheumatic drugs; cDMARD=conventional disease-modifying antirheumatic drugs; UPA15=upadacitinib 15mg; UPA30=upadacitinib 30mg; Δ=change from baseline; W=Week; * p<0.001 vs. MTX or Placebo; † nominal p<0.001; ‡ nominal p=0.001

The clinical-statistical team concluded the primary efficacy endpoint was met, as ACR50 or ACR20 were significantly greater at Week 12 or 14 for upadacitinib compared with placebo or methotrexate in each study.

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[g] Disease Activity Score in 28 joints calculated with the value of high sensitivity C-reactive protein. Higher scores indicate more active disease.

[h] Health Assessment Questionnaire-Disability Index. Higher scores indicate greater disability.

[i] The mTSS is a scoring system used to quantity the radiological signs of bone erosions and joint space narrowing in patients with rheumatoid arthritis. Higher scores indicate more radiographic damage.

[j] SF-36 assesses the general health-related quality of life of subjects and produces a physical component summary (PCS) score based on physical functioning, role-physical, bodily pain, general health, and vitality. Higher scores indicate better outcomes.

Key secondary endpoints including the change from baseline in HAQ-DI, DAS28-hsCRP and SF-36 PCS were also significantly improved comparing upadacitinib versus placebo or methotrexate. The clinical and statistical reviewers concluded that substantial evidence of clinical efficacy has been established for the use of upadacitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis who had an inadequate response or intolerance to methotrexate.[k,9,10]

However, based on the efficacy results for the 15 mg and 30 mg doses, AbbVie concluded there is a lack of meaningful incremental efficacy of the 30 mg dose, and therefore they requested approval of the 15 mg dose only.[2] In addition, a dose-dependent increase in serious adverse events (SAEs) was observed during the controlled and long-term study periods with a greater percentage of patients receiving the 30 mg dose reporting an SAE compared with the 15 mg-treated patients (see Section 5 below for further information).

5 Risk Assessment & Safe-Use Conditions

4443 patients were exposed to at least one dose of upadacitinib in the Phase 2 and Phase 3 RA studies. This group of patients is referred to as the Any RA UPA safety set. For the Any RA UPA analysis, patients who received 6 mg twice daily (in earlier studies) were grouped with those who received upadacitinib 15 mg once daily; in the same way, patients who received 12 mg twice daily were grouped with those who received 30 mg once daily.[l] Various other combinations of the Phase 3 clinical studies were pooled to evaluate short-term (through Week 12 or 14) and long-term[m] safety.[n] Treatment-emergent adverse events (TEAEs) for upadacitinib were defined as events with an onset date that is on or after the first dose and no more than 30 days after the last dose of upadacitinib.

5.1 SERIOUS ADVERSE EVENTS [o,p]

Patients in the upadacitinib dose groups had a higher incidence rate of SAEs in the short-term study period compared with the placebo groups or the methotrexate groups, though the difference in rate was significant only versus placebo. The incidence of SAEs was also higher in patients treated with upadacitinib 30 mg compared with upadacitinib 15 mg in the short-term study period as well as with cumulative exposure in the long-term study period. Long-term exposure showed a similar incidence rate to that for short-term exposure

[k] FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.
[l] Upadacitinib doses of 15 mg daily and 30 mg daily using the extended release formulation provide comparable systemic exposure to the 6 mg twice daily and 12 mg twice daily immediate release formulations, respectively. (He L. Division of Clinical Pharmacology 2, Clinical Pharmacology Integrated Review, NDA 211675, May 17, 2019.)
[m] Long-term integrated safety analyses described in this review include cumulative exposure in the Phase 3 studies with the exception of data from Study M14-465.
[n] The presence of double-crossing over between the upadacitinib and adalimumab arms as early as Week 14 in Study M14-465 limited the ability to draw active- and placebo-controlled safety comparisons for that study beyond Week 14.
[o] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
[p] FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

for each of the upadacitinib dose groups. Table 3 below shows the incidence rate data for several pooled analysis sets.

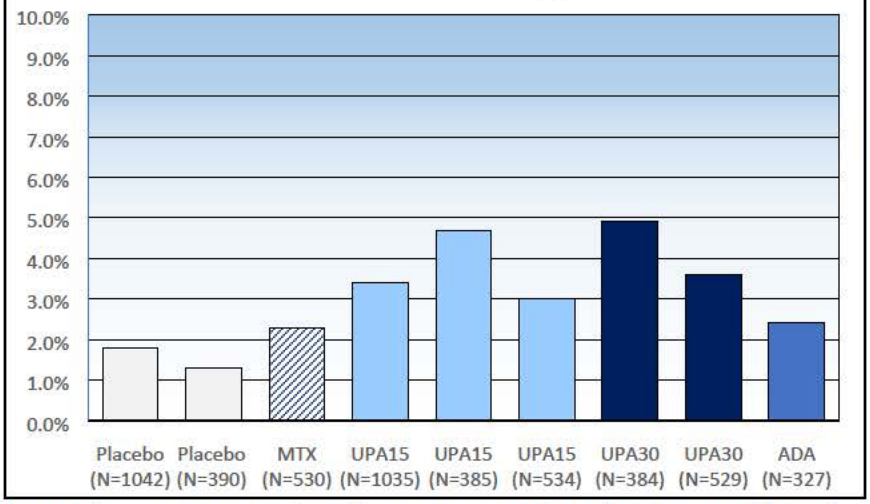
Table 3. Incidence of serious adverse events through 3 months and long-term cumulative exposure

Pooled Studies	M13-542 M13-549 M14-465		M13-542 M13-549			M13-545 M15-555			M13-542 M13-549 M13-545 M15-555	
Treatment	Placebo	UPA15	Placebo	UPA15	UPA30	MTX	UPA15	UPA30	UPA15	UPA30
Short-term Study Period 3 Months Exposure									Long-term Study Period Cumulative Exposure	
Patients (N)	1042	1035	390	385	384	530	534	529	1213	1204
Total exposure (PY)	255	256.4	85.1	85.5	84.2	120.7	125.9	125.6	1338.2	1280.6
Patients with ≥ 1 SAE (n)	19	35	5	18	19	12	16	19	159	193
Incidence rate (n/100 PY)	7.4	13.7	5.9	21.1	22.6	9.9	12.7	15.1	11.9	15.1
Incidence rate difference (95% CI)	6.2 (0.6,11.8)*		UPA15 vs. PBO: 15.2 (4.2,26.2)* UPA30 vs. PBO: 16.7 (5.3,28.0)*			UPA15 vs. MTX: 2.8 (-5.6,11.2) UPA30 vs. MTX: 5.2 (-3.7,14.0)				

UPA15=Upadacitinib 15 mg; UPA30=Upadacitinib 30 mg; PBO=Placebo; MTX=Methotrexate; PY=Patient-Years; SAE=Serious Adverse Event; N=Number of patients; *95% CI excludes 0. Source: ISS. Table 2.4 1.1.1.3; Table 2.4 2.1.1.3; Table 2.4 3.1.1.3; Table 2.4 5.1.1.3.1

In the controlled short-term study period of the Phase 3 studies, the proportion of patients experiencing an SAE in the combined methotrexate group was 2.3%. In the placebo groups the proportion ranged from 1.3%–1.8%, and 2.4% of patients in the adalimumab group experienced an SAE. The proportion of patients who had an SAE in the upadacitinib 15 mg groups ranged from 3.0%–4.7% compared with 3.6%–4.9% in the upadacitinib 30 mg groups. See Figure 1 below for a comparison of the percentage of SAEs reported in various groups pooled from the Phase 3 studies.

Figure 1. Percentage of patients with serious adverse events in controlled short-term study period



MTX=Methotrexate; UPA15=Upadacitinib 15 mg; UPA30=Upadacitinib 30 mg; ADA=Adalimumab; N=Number of patients

Source: Integrated Summary of Safety (ISS). Table 2.4 1.1.1.1; Table 2.4 2.1.1.1; Table 2.4 3.1.1.1; Table 14.3 1.1.1.1.1

Deaths

During the placebo- and active-controlled portions of the Phase 3 studies (prior to treatment switching), there were 4 deaths in the combined placebo, MTX monotherapy and adalimumab arms (n=1899 patients) compared with 5 deaths in patients who received upadacitinib (n=2482 patients). In the Phase 2 and 3 RA studies, there were 25 treatment-emergent deaths and 9 non-treatment emergent deaths reported in the upadacitinib groups. The causes of death in patients treated with upadacitinib included cardiovascular (n=23), malignancy (n=6), respiratory (n=3), and infection (n=2). Cardiovascular-related causes included sudden death, myocardial infarction, congestive heart failure, pulmonary embolism, hemorrhagic stroke, and death for reason not specified.[11] The clinical reviewer noted that all the adjudicated cardiovascular deaths[q] occurred in patients with underlying cardiovascular risk factors. There were 5 additional treatment-emergent deaths and 5 non-treatment emergent deaths reported in the 120-day safety update. The causes of death included infection (n=4), malignancy (n=4), respiratory failure (n=1), and decline in health (n=1). The clinical reviewer had no concerns regarding the additional deaths, which were assessed as due to infections/complications and malignancies, for which the drug will be clearly labeled.[r]

5.2 ADVERSE EVENTS OF SPECIAL INTEREST

5.2.1 Infections

Serious infections

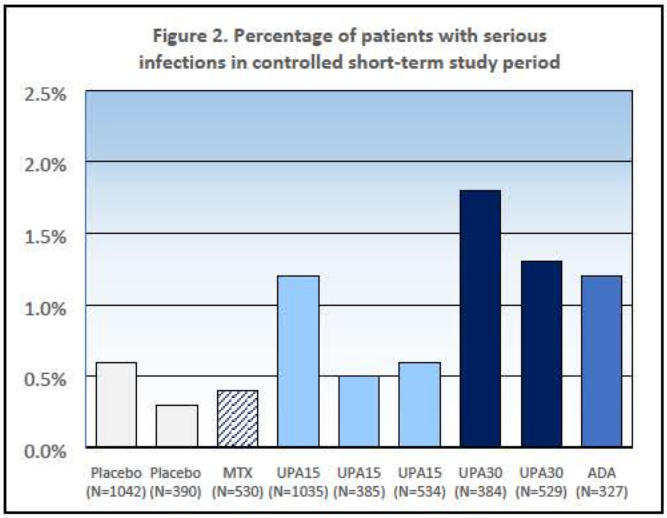
As shown in Figure 2 below, the proportion of patients with serious infections in the controlled short-term study period was higher in the upadacitinib 30 mg groups (1.3%–1.8%) than in the 15 mg groups (0.5%–1.2%). Serious infections were reported in 0.3%–0.6% in patients who received placebo, 0.4% of patients in the methotrexate group, and 1.2% of patients in the adalimumab group. The long-term study period found the event rate of serious infections was higher in the upadacitinib 30 mg group (6.2/100 patient-years) than the 15 mg group (3.6/100 patient-years). Of the 134 serious infections reported during long-term exposure, the three most common infections associated with upadacitinib were pneumonia (n=38), sepsis (n=10), and urinary tract infection (N=6).

Herpes zoster

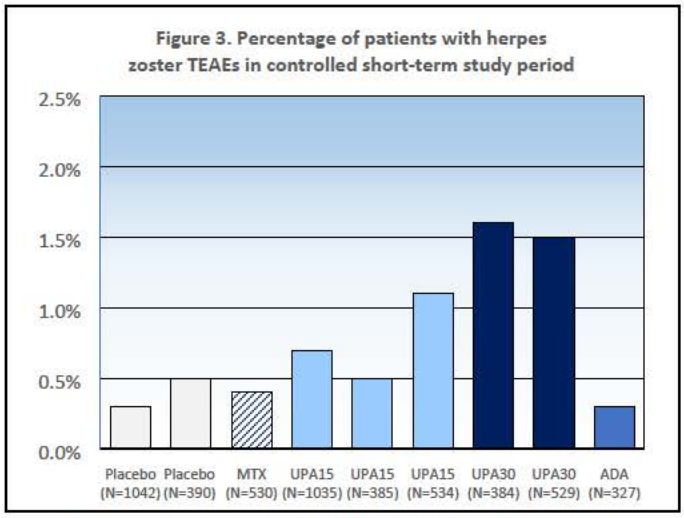
Upadacitinib was associated with a higher percentage of herpes zoster TEAEs in upadacitinib-treated patients compared with the other treatment groups, as shown in Figure 3 below. In the controlled short-term study period, there were 29 patients in the upadacitinib groups with treatment-emergent herpes zoster (2 serious cases) compared with 2 patients in the methotrexate group, 5 patients in the placebo groups, and one patient in the adalimumab group. The long-term period of the Phase 3 studies of 15 mg and 30 mg found an increased event rate of herpes zoster in the 30 mg group (6.3/100 patient-years) compared to the 15 mg group (4.0/100 patient-years). There were 86 herpes zoster adverse events in the 30 mg group and 57 in the 15 mg group. Seven of the adverse events in the 30 mg group were serious compared with none of the adverse events in the 15 mg group.

[q] All deaths in the upadacitinib clinical development program were adjudicated to assess for a cardiovascular or non-cardiovascular cause of death.

[r] Hull K. Division of Pulmonary, Allergy, and Rheumatology Products. Personal email communication, July 29, 2019.



Source: ISS. Table 2.4_3.3 5; Table 2.4_1.3.1.5; Table 2.4_2.3.1 5; Table 2.4_7.1 2



Source: ISS. Table 2.4_3.3.17; Table 2.4_1.3.1.17; Table 2.4_2.3.1.17; Table 2.4_7.1.2

Tuberculosis

Patients were screened for tuberculosis infection at study entry. Patients with latent tuberculosis could enroll in the study after documented initiation or prior completion of prophylactic treatment. In the Any RA UPA safety set, five nonfatal cases of active tuberculosis were reported in patients receiving upadacitinib. Each of the five cases occurred outside the US. Three of the five patients were diagnosed with latent tuberculosis at screening. Two patients developed serious extra-pulmonary tuberculosis infections.

Hepatitis B reactivation

Approximately 9% (395/4443) of patients in the Phase 2 and Phase 3 studies had a positive hepatitis B core antibody test at screening. Four patients experienced hepatitis B virus (HBV) reactivation. The HBV reactivation event was serious in two patients, who required treatment and discontinued the study.

5.2.2 Malignancies

Malignancies were observed in the clinical studies. The clinical reviewer noted the number of malignancies reported during the placebo- or active-controlled periods of the phase 3 studies were small and definitive conclusions could not be drawn regarding the rates of malignancies during this short time period. In the Any RA UPA safety set, there were a total of 71 (1.6%) patients who developed treatment-emergent malignancies associated with upadacitinib. Of the 71 patients, 24 experienced nonmelanoma skin cancers (NMSC) such as basal cell or squamous cell carcinomas. There was otherwise no clear pattern of malignancies, which included 10 cases of breast cancer, 8 cases of colorectal cancer, 6 cases of metastatic melanoma, 5 cases of prostate cancer, and 4 cases of lung cancer. Other malignancies were reported one or two times. Excluding NMSC, the treatment-emergent event rate associated with all exposure was slightly higher in the upadacitinib 30 mg group (1.4/100 patient-years) than in the 15 mg group (1.3/100 patient-years).

5.2.3 Major Adverse Cardiovascular Events

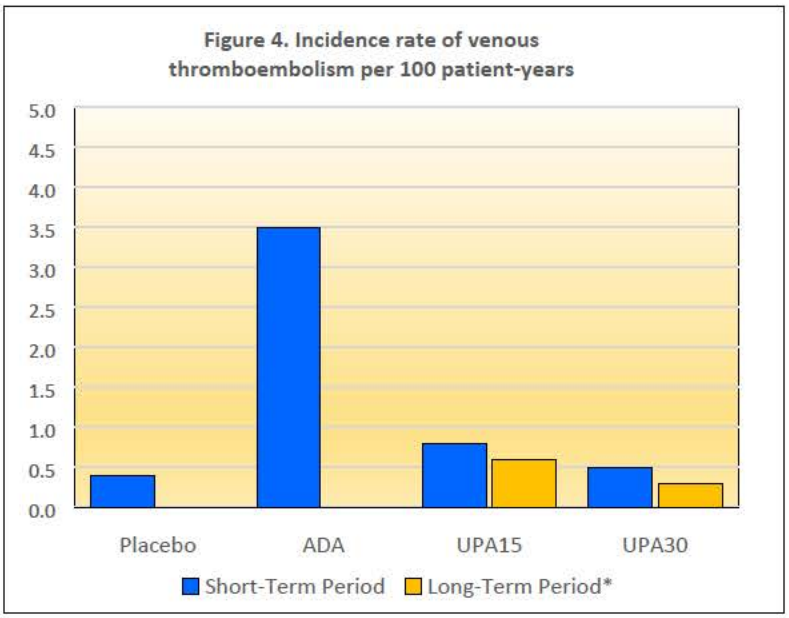
In the Phase 2 and 3 studies, potential cases of cardiovascular events were adjudicated by a cardiac adjudication committee. Major adverse cardiovascular events (MACE) were defined as cardiovascular (CV) death, non-fatal myocardial infarction, and non-fatal stroke. The incidence rate of MACE during the controlled short-term period per 100 patient-years was highest for patients who received upadacitinib 30 mg (1.9/100 patient-years) in

comparison with upadacitinib 15 mg (0.8/100 patient-years), methotrexate (0.8/100 patient-years) or placebo (1.2/100 patient-years). In the long-term study period associated with all exposure, the incidence rate of MACE was similar between the upadacitinib 30 mg group (1.0/100 patient-years) and the upadacitinib 15 mg group (0.8/100 patient-years).

5.2.4 Thrombosis

Suspected venous and arterial thrombotic events in the Phase 3 studies were adjudicated by a thrombotic adjudication committee. The incidence rate of venous thromboembolic events (VTE) during the controlled short-term study period was 0.8/100 patient-years in the upadacitinib 15 mg group and 0.5/100 patient-years in the upadacitinib 30 mg group. The rates in the adalimumab (ADA) and placebo groups were 3.5/100 patient-years and 0.4/100 patient-years, respectively. There were no VTE events in the methotrexate group during the short-term period. In the long-term study period associated with all exposure, the incidence rate of VTE was slightly lower in the upadacitinib 15 mg group (0.6/100 patient-years) and the upadacitinib 30 mg group (0.3/100 patient-years) compared with the short-term period, as shown in Figure 4 below.

In the Any RA UPA analysis set, there were 3 upadacitinib patients who experienced peripheral arterial thromboembolic events. Each of the three patients had a history of either venous thrombosis, femoral artery stents, or peripheral vascular disease.



*Long-term period shows results for UPA15 and UPA30 only.
Methotrexate is not shown because the short-term period incidence rate = 0.
Source: Summary of clinical safety. Table 117; Table 118.

5.2.5 Gastrointestinal Perforations

In the Any RA UPA analysis set, there were 9 patients who experienced a gastrointestinal perforation TEAE. Three of the 9 events had alternative explanations and were likely not related to upadacitinib treatment. Five of the remaining 6 events were serious and included intestinal perforation (n=3), anal fistula, and peritonitis. There were no events of GI perforation identified in patients receiving placebo, MTX, or adalimumab in the other analysis sets.

5.2.6 Hepatic Laboratory Test Elevations

During the controlled short-term period of the Phase 3 studies, there were variable increases observed in alanine transaminase (ALT) values in the upadacitinib, methotrexate, and placebo groups. The proportion of patients who experienced an increase in ALT ≥ 3x the upper limit of normal (ULN) ranged from 0.8%–2.1% in the upadacitinib 15 mg pooled groups compared with 1.0%–1.7% in the upadacitinib 30 mg groups, 1.3%–1.5% in the placebo groups, and 1.9% in the methotrexate groups. The pattern of increases observed in aspartate transaminase (AST) values ≥ 3x ULN was similar to that seen with ALT. In the long-term study period associated with all exposure, the proportion of patients experiencing an increase in ALT ≥ 3x ULN or AST ≥ 3x ULN in the upadacitinib 15 mg pooled groups was 3.0% and 1.9%, respectively, compared with 3.8% and 2.0% in the upadacitinib 30 mg pooled groups.

Four cases in the Any RA UPA analysis set met the biochemical criteria for Hy's Law. However, the clinical reviewer noted there were alternative etiologies associated with each of these cases and none were definitively assessed as drug-induced liver injury.

5.2.7 Other Laboratory Abnormalities

There was a greater mean decrease from baseline to Week-12 in neutrophil count in the upadacitinib 15 mg and 30 mg groups compared with placebo. The mean decreases in the upadacitinib 15 mg and 30 mg groups at 12 weeks were approximately 900 and 1000 cells/mm^3 respectively, whereas the mean neutrophil count in the placebo group was stable. In the placebo-controlled period of the Phase 3 studies, Grade 3 and Grade 4 decreases in neutrophil count were observed more frequently in the upadacitinib groups compared to placebo. In the Any RA UPA analysis set, 13 (0.3%) patients experienced Grade 4 decreases in the neutrophil count (ANC < 500/mm^3). Of the 13 patients, 10 were without associated infections. Three patients experienced infections, including a nonserious tooth abscess; urinary tract infection and serious urosepsis; and serious infections of pneumonia and sepsis that resulted in the patient's death.

In the placebo-controlled studies, the mean lymphocyte counts slightly increased from baseline to Week 12 in the upadacitinib 15 mg group and 30 mg group. Although the mean lymphocyte counts increased, some patients across groups experienced decreases in the count. The proportion of patients who experienced a decrease in count to < 500/mm^3 in the placebo, upadacitinib 15 mg, and upadacitinib 30 mg groups was 0.5%, 0.5-0.9%, and 2.4%, respectively. In the Any RA UPA analysis set, 91 patients (2.1%) experienced a decreased lymphocyte count to < 500/mm^3. There were no SAEs of lymphopenia reported.

Upadacitinib was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. In the placebo-controlled period, treatment-emergent hypercholesterolemia or hyperlipidemia adverse events were reported in approximately 0.3% of patients who received placebo, compared with 0.3-1.1% of patients treated with upadacitinib 15 mg and 0.5-1.0% of patients who received upadacitinib 30 mg. There were no SAEs of hypercholesterolemia or hyperlipidemia reported in the placebo-controlled studies or in the Any RA UPA analysis set.

5.2.8 Non-Clinical Toxicity

The pharmacology-toxicology review noted upadacitinib is associated with skeletal malformations in rats in the absence of maternal toxicity, as well as cardiac and skeletal malformations in rabbits concurrent with maternal toxicity. The finding of teratogenicity in rats and rabbits at clinically relevant exposures indicates a serious risk for human fetal toxicity. This finding was considered more concerning for upadacitinib than previously approved JAK

inhibitor products (e.g., tofacitinib, baricitinib) based on the observed lower exposure margins to proposed clinical dose levels.[12]

6 Expected Postmarket Use

We expect the prescribing community for upadacitinib to be similar to that for tofacitinib and baricitinib. In the FDAAA Section 915 New Molecular Entity (NME) Postmarket Safety Summary for tofacitinib NDA 203214, dated December 4, 2014, a review of prescription claims data found that rheumatologists comprised approximately 80% of tofacitinib prescribers, followed by primary care physicians, and to a small extent, other specialties. Upadacitinib is likely to be prescribed by a similar provider profile. As an orally administered drug, upadacitinib will primarily be self-administered by patients in the outpatient setting as a chronic therapy.

7 Risk Management Activities Proposed by the applicant

The applicant did not submit a REMS with the application but included a pharmacovigilance plan that describes the use of routine pharmacovigilance activities as well as ongoing long-term extension studies and other postmarketing studies.

8 Discussion of Need for a REMS

The clinical and statistical reviewers concluded that substantial evidence of clinical efficacy has been established for the use of upadacitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis who had an inadequate response or intolerance to methotrexate.

Rheumatoid arthritis is a chronic, systemic, inflammatory disorder of unknown etiology that primarily involves synovial joints. If uncontrolled, the disease can lead to joint destruction due to erosion of cartilage and bone, causing deformities and significant disability. In patients with severe joint disease, non-articular organs can also become involved, including the skin, eye, lung, heart, kidney, and other organ systems. This is associated with increased disease severity, morbidity, and premature mortality.

Five double-blind, randomized, placebo- or active-controlled Phase 3 studies of patients with moderately to severely active RA demonstrate effectiveness of upadacitinib for the treatment of patients with moderately to severely active rheumatoid arthritis who had an inadequate response to methotrexate. Studies M13-542 and M15-555, which evaluated patients with insufficient response to treatment with MTX or biologic DMARDs, showed significant effects for upadacitinib 15 mg and 30 mg therapy compared to placebo or methotrexate based on the ACR20 response. Study M13-545 evaluated patients who were MTX-naïve to treatment with upadacitinib 15 mg or 30 mg or MTX. Significant improvements in the ACR50 response were observed for the upadacitinib groups compared to MTX. Study M13-549 evaluated treatment with upadacitinib 15 mg or 30 mg compared with placebo and found significant improvements in ACR20 in patients who were inadequate responders to conventional DMARDs. And Study M14-465 found significant improvements in ACR20 in patients with a history of inadequate response to MTX who received treatment with upadacitinib 15 mg compared with placebo.

Based on the efficacy results for the 15 mg and 30 mg doses, the Applicant concluded there is a lack of meaningful incremental efficacy of the 30 mg dose; in addition, a dose-dependent increase in serious adverse events was

observed during the controlled and long-term study periods with a greater percentage of patients receiving the 30 mg dose reporting an SAE compared with the 15 mg-treated patients. Therefore, they requested approval of the 15 mg dose only.

As with other Janus kinase inhibitors currently approved for the treatment of RA, the most serious risks associated with upadacitinib include serious infections, malignancies, and thrombosis. The proposed prescribing information for upadacitinib includes a Boxed Warning for these risks. Additional serious risks observed in the upadacitinib studies include gastrointestinal perforations and laboratory abnormalities, which are also associated with the other members of the JAK-inhibitor class; the clinical reviewer recommends describing these risks as well as respective laboratory monitoring recommendations in the Warnings and Precautions section of the upadacitinib label. The risk of embryo-fetal toxicity identified in non-clinical studies will also be addressed by a Warning and Precaution.

Upadacitinib is in the class of Janus kinase inhibitors that include tofacitinib and baricitinib. Tofacitinib was approved with a communication plan REMS in November 2012 to address the risk of serious infections, malignancies, lympho-proliferative disorders, increased cholesterol, and low blood cell counts by informing healthcare prescribers and pharmacists about these risks, which are similar to the risks of other immunosuppressive DMARDs that required a REMS. The tofacitinib REMS was eliminated in February 2016 after the Agency determined the communication plan was no longer necessary because it had been completed and the most recent REMS assessment demonstrated the communication plan had met its goals. The tofacitinib label also includes new safety information related to the risk of thrombosis, which was approved as an addition to the Boxed Warnings on July 25, 2019. The serious risks of baricitinib are similar to those for tofacitinib. The Agency determined a REMS was not required for the serious risks associated with baricitinib, and that the risks would be communicated by the label.

Based on the data available, the prescribing community is expected to be familiar with the risks associated with upadacitinib, which do not pose unique REMS considerations compared with the risks associated with tofacitinib or other DMARDs approved with REMS that were subsequently released. At this time, this reviewer is not recommending a REMS for the management of the risks of upadacitinib therapy.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks of upadacitinib therapy for the treatment of rheumatoid arthritis. In general, healthcare providers who treat moderate to severe rheumatoid arthritis are already familiar with the risks and need for patient monitoring associated with Janus kinase inhibitors as well as other DMARDs.

Should DPARP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 REFERENCES

[1] AbbVie. Clinical overview for upadacitinib, NDA 211675, December 18, 2018.
[2] Schwartz DM, et al. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. Nat Rev Drug Discov 2017; 16:843-862.
[3] Kaminskas E. Summary Review for Regulatory Action, NDA 202192, November 15, 2011.
[4] Crowson CS. Epidemiology of, risk factors for, and possible causes of rheumatoid arthritis. In:UpToDate, O'Dell JR, Romain PL (Eds), Waltham, MA 2019.
[5] Venables PJW. Clinical manifestations of rheumatoid arthritis. In:UpToDate, O'Dell JR, Romain PL (Eds), Waltham, MA 2019.
[6] Matteson EL and Davis JM. Overview of the systemic and nonarticular manifestations of rheumatoid arthritis. In:UpToDate, O'Dell JR, Romain PL (Eds), Waltham, MA 2019.
[7] Moreland LW and Cannella A. General principles of management of rheumatoid arthritis in adults. In:UpToDate, O'Dell JR, Romain PL (Eds), Waltham, MA 2019.
[8] AbbVie. Clinical summary of efficacy, NDA 211675, December 18, 2018.
[9] Hull K. Division of Pulmonary, Allergy, and Rheumatology Products. Clinical Review, NDA 211675, August 14, 2019.
[10] Koh W. Division of Biometrics 2, Statistical Review, NDA 211675, August 13, 2019.
[11] AbbVie. Clinical summary of safety, NDA 211675, December 18, 2018.
[12] Jones B. Division of Pulmonary, Allergy, and Rheumatology Products. Pharmacology/Toxicology NDA Review and Evaluation, NDA 211675, May 21, 2019.

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/s/

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