PDL DRUG REVIEW

Proprietary Name: Rinvoq®
Common Name: upadacitinib, extended-release
PDL Category: Anti-Inflammatories, Non-NSAID

Comparable Products	Preferred Drug List Status
Humira	Preferred with Conditions
Olumiant	Non-Preferred with Conditions
Xeljanz	Non-Preferred with Conditions

Summary

Pharmacology/Usage: Upadacitinib, the active ingredient of Rinvoq®, 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 pathways, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs), which modulate intracellular activity including gene expression. Upadacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs.

Indication: For the treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. Use of Rinvoq® in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine, is not recommended.

There is no pregnancy category for this medication; however, the risk summary indicates the limited human data on use in pregnant women are not sufficient to assess a drug-associated risk for major birth defects or miscarriage. Based on animal studies, upadacitinib has the potential to adversely affect a developing fetus. Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis. Adverse pregnancy outcomes include preterm delivery, low birth weight infants, and small for gestational age at birth. Pregnancy status should be verified prior to starting treatment in females of reproductive potential. In addition, advise females of reproductive potential to use effective contraception during treatment and for 4 weeks after the final dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Extended-Release Tablets: 15mg. Swallow tablets whole, do not split, crush, or chew.

Recommended Dosage: Rinvoq® may be used as monotherapy or in combination with methotrexate or other non-biologic DMARDs. Take 15mg PO QD, with or without food. Rinvoq® initiation is not recommended in patients with an absolute lymphocyte count (ALC) <500 cells/mm^3, absolute neutrophil count (ANC) <1000 cells/mm^3, or hemoglobin level <8g/dL. Rinvoq® treatment should be interrupted if a patient develops a serious infection until the infection is controlled. Refer to the prescribing information for additional information.

Dose adjustments are not required with renal impairment; however, use has not been studied in subjects with end-stage renal disease. In addition, dose adjustments are not required with mild or moderate hepatic impairment; however, use is not recommended in patients with severe hepatic impairment.

Drug Interactions: Rinvoq® should be used with caution in patients receiving chronic treatment with strong CYPA34 inhibitors. In addition, the coadministration of Rinvoq® with strong CYP3A4 inducers is not recommended.

Use of live, attenuated vaccines during, or immediately prior to, Rinvoq® treatment is not recommended. Prior to starting Rinvoq®, it is recommended that patients be brought up to date with all immunizations, including prophylactic zoster vaccinations, in agreement with current immunization guidelines.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Rinvoq®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included upper respiratory tract infection (4%), nausea (1.3%), cough (1.2%), and pyrexia (1.2%). Other adverse reactions reported in less than 1% of patients in the Rinvoq® group and at a higher rate than in the placebo group included pneumonia, herpes zoster, herpes simplex (including oral herpes) and oral candidiasis.

Rinvoq® has a box warning regarding the increased risk of serious infections, malignancy, and thrombosis. Patients treated with Rinvoq® are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt Rinvoq® until the infection is controlled. Reported infections included active tuberculosis (TB; patients should be tested for latent TB prior to use and during therapy; treatment for latent infection should be considered prior to Rinvoq® use); invasive fungal infections (including cryptococcosis and pneumocystosis); and bacterial, viral (including herpes zoster), and other infections due to opportunistic pathogens. The risks/benefits of treatment with Rinvoq® should be considered prior to starting therapy in patients with chronic or recurrent infection. In addition, patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Rinvoq®, including the development of TB in patients who tested negative for latent TB infection prior to starting treatment.

The box warning also adds that lymphoma and other malignancies have been observed in patients treated with Rinvoq®. Furthermore, a warning adds that non-melanoma skin cancer (NMSCs) have been reported in patients treated with Rinvoq®. Periodic skin exams are recommended for patients who are at increased risk for skin cancer.

The box warning includes thrombosis, including DVT, PE, and arterial thrombosis that have occurred in patients treated with JAK inhibitors used to treat inflammatory conditions. Many of the adverse events were serious and some resulted in death. Consider the risks/benefits prior to treating patients who may be at increased risk. Patients with symptoms of thrombosis should be assessed and treated appropriately.

Rinvoq® should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g. patients with a history of diverticulitis or taking NSAIDs). Patients presenting with new onset abdominal symptoms should be assessed for early identification of GI perforation.

There were numerous laboratory abnormalities with use. Treatment with Rinvoq® was associated with an increased incidence of neutropenia (ANC <1000 cells/mm^3). Assess neutrophil counts at baseline and thereafter per routine patient management. Lymphopenia was reported, with ALC <500 cells/mm^3 reported in Rinvoq® clinical trials. Assess lymphocyte count at baseline and thereafter per routine patient management. Anemia was reported, with decreases in hemoglobin levels to <8g/dL reported in Rinvoq® clinical trials. Assess hemoglobin at baseline and thereafter per routine patient management.

Treatment with Rinvoq® was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Patients should be monitored 12 weeks after starting treatment and thereafter per clinical guidelines for hyperlipidemia.

Treatment with Rinvoq® was associated with increased incidence of liver enzyme elevation compared to placebo. Assess at baseline and thereafter per routine patient management. If increases in ALT or AST are seen during routine patient management and drug-induced liver injury is suspected, interrupt treatment until this diagnosis is excluded.

Contraindications: There are currently no contraindications listed with this product.

Manufacturer: Abbvie

Analysis: The safety and efficacy of Rinvoq® were assessed in 5 phase 3, multicenter, double-blind, randomized studies that included adults 18 years of age and older with moderately to severely active RA with the presence of at least 6 tender and 6 swollen joints and evidence of systemic inflammation based on elevation of hsCRP at baseline. Note that in the information below, upadacitinib 30mg was utilized in some studies but is not an FDA approved dose.

Study 1 (RA-1) was a 24-week monotherapy study that included adults who were naïve to methotrexate (N=947) and received Rinvoq® 15mg, upadacitinib 30mg or methotrexate as monotherapy. The primary endpoint was the proportion who achieved an ACR50 response at week 12. Key secondary endpoints included disease activity score (DAS28-CRP) ≤3.2 at week 12, DAS28-CRP <2.6 at week 24, change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) at week 12, and change from baseline in van der Heijde-modified total Sharp Score (mTSS) at week 24.

Study 2 (RA-II) was a 14-week monotherapy study that included adults who had an inadequate response to methotrexate (N=648), and patients received Rinvoq® 15mg, upadacitinib 30mg or continued their stable dose of methotrexate. The primary endpoint was the proportion who achieved an ACR20 response at week 14.

Study 3 (RA-III) was a 12-week study that included adults who had an inadequate response to conventional disease modifying anti-rheumatic drugs (cDMARDs; N=661), and patients received Rinvoq® 15mg, upadacitinib 30mg or placebo added to background cDMARD therapy. The primary endpoint was the proportion who achieved an ACR20 response at week 12.

Study 4 (RA-IV) was a 48-week study that included adults who had an inadequate response to methotrexate (N=1,629), and patients received Rinvoq® 15mg, active comparator, or placebo added to background methotrexate. At week 26, all patients randomized to placebo were switched to Rinvoq® 15mg in a blinded manner. The primary endpoint was the proportion who achieved an ACR20 response at week 12 versus placebo.

Study 5 (RA-V) was a 12-week study that included adults who had an inadequate response or intolerance to biologic DMARDs (N=499), and patients received Rinvoq® 15mg, upadacitinib 30mg or placebo added to background cDMARD treatment. The primary endpoint was the proportion who achieved an ACR20 response at week 12.

The percentages of Rinvoq®-treated patients achieving ACR20, ACR50, and ACR70 responses, as well as DAS28-CRP <2.6 in all studies can be seen in the table below. Patients treated with Rinvoq® 15mg, alone or in combination with cDMARDs, achieved higher ACR response rates compared to methotrexate or placebo at the primary efficacy timepoint.

	Study 1- monotherapy		Study 2- monotherapy		Study 3- background cDMARDs		Study 4- background MTX		Study 5- background cDMARDs	
	MTX (N=314)	Rinvoq® (N=317)	MTX (N=216)	Rinvoq® (N=217)	Placebo (N=221)	Rinvoq® (N=221)	Placebo (N=651)	Rinvoq® (N=651)	Placebo (N=169)	Rinvoq® (N=164)
ACR20										
Week 12*/14**	54%	76%	41%	68%	36%	64%	36%	71%	28%	65%
Week 24^/26#	59%	79%					36%	67%		
ACR50										
Week 12*/14**	28%	52%	15%	42%	15%	38%	15%	45%	12%	34%
Week 24^/26#	33%	60%					21%	54%		
ACR70										
Week 12*/14**	14%	32%	3%	23%	6%	21%	5%	25%	7%	12%
Week 24^/26#	18%	44%					10%	35%		
DAS28-CRP <2.6										
Week 12*/14**	14%	36%	8%	28%	10%	31%	6%	29%	9%	29%
Week 24^/26#	18%	48%					9%	41%		

*Study RA-1, Study RA-3, Study RA-4, Study RA-5 ** Study RA-2 ^ Study RA-1 # Study RA-4

Treatment with Rinvoq® 15mg, alone or in combination with cDMARDs, resulted in greater improvements in the ACR components compared to methotrexate or placebo at the primary efficacy timepoint.

The prescribing information did not have any of the active comparator data included. Study 4 included the active comparator adalimumab. Per the full-text study by Fleischmann et al[2], there were 2 separate primary endpoints, including ACR20% improvement response criteria and the proportion who achieved a DAS28-CRP of <2.6 at week 12. An ACR20 improvement response was achieved by significantly larger number in the upadacitinib 15mg group (71%) compared with the placebo group (36%; p≤0.001), added to background methotrexate. In addition, 63% of the adalimumab group achieved a response (adalimumab-adjusted difference 7.5%; nominal p≤0.05). A DAS28-CRP score of <2.6 was seen in 29% of the upadacitinib group vs 6% of the placebo group, which was significantly different in favor of upadacitinib (p≤0.001). In addition, 18% of the adalimumab group achieved DAS28-CRP score of <2.6 at week 12 (adalimumab-adjusted difference 10.7%; nominal p≤0.001).

The study reports that upadacitinib was significantly better than placebo or adalimumab based on the ACR50 and ACR70 response rates and met the multiplicity-controlled superiority comparison to adalimumab for the ACR50 response rate, which was 45% in the upadacitinib group vs 15% with placebo (placebo-adjusted difference 30.3%) and 29% in the adalimumab group (adalimumab-adjusted difference 16.1%; p≤0.001 for both). Upadacitinib also met multiplicity-controlled superiority comparisons to adalimumab regarding improvements from baseline to week 12 in the pain severity score (mean change -32.1 with upadacitinib vs -25.6 with adalimumab; p≤0.001) and the HAQ DI score (mean change -0.6 with upadacitinib vs -0.49 with adalimumab; p≤0.01). Improvements were maintained through 26 weeks. Compared to placebo and adalimumab groups, patients receiving upadacitinib had significantly greater improvements in quality of life, fatigue, and duration of morning stiffness by week 12 (p≤0.001 for each). Improvements in these measures continued to be seen through week 26. The authors of this study concluded that upadacitinib was superior to both placebo and adalimumab for improving signs, symptoms, and physical function in RA patients who were receiving background methotrexate. The overall safety profile of upadacitinib was similar to adalimumab except that upadacitinib had higher rates of herpes zoster and creatine phosphokinase elevations.

Place in Therapy: Rinvoq® is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. Use of Rinvoq® in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine, is not recommended. Rinvoq® does have a box warning regarding increased risk of serious infections, malignancy, and thrombosis. In clinical trials compared with placebo, it was found to be more effective for ACR response.

A 2019 Bayesian network meta-analysis by Song et al[3] included 9 randomized controlled trials (N=5794) to assess the safety and efficacy of tofacitinib and upadacitinib in patients with RA with an inadequate response to conventional synthetic (cs) or biologic (b) disease-modifying anti-rheumatic drugs (DMARDs). Ranking probability based on the surface under the cumulative ranking curve (SUCRA) was performed. Results suggested that upadacitinib 15mg plus methotrexate (MTX) and upadacitinib 30mg (this dose is not FDA approved) plus MTX were associated with the most favorable SUCRA for the ACR20 response rate while placebo plus MTX was associated with the least favorable results (OR 4.90, OR 4.69). All of the intervention achieved a significant ACR20 response rate compared with placebo plus MTX. A greater efficacy was noted with upadacitinib 15mg plus MTX, upadacitinib 30mg plus MTX, tofacitinib 10mg plus MTX and tofacitinib 5mg plus MTX than with adalimumab plus MTX. The rankings probability per SUCRA for efficacy were as follows: upadacitinib 15mg plus MTX (SUCRA 0.820), followed by upadacitinib 30mg plus MTX (SUCRA 0.762), tofacitinib 10mg plus MTX (SUCRA 0.623), tofacitinib 5mg plus MTX (SUCRA 0.424), adalimumab plus MTX (SUCRA 0.371), and placebo plus MTX (SUCRA 0.001). The rankings probability per SUCRA for safety were as follows: placebo plus MTX (SUCRA 0.865), adalimumab plus MTX (SUCRA 0.658), tofacitinib 10mg plus MTX (SUCRA 0.480) and tofacitinib 5mg plus MTX (SUCRA 0.464) had the higher probabilities of being the safest treatment, followed by upadacitinib 15mg plus MTX (SUCRA 0.343) and upadacitinib 30mg plus MTX (SUCRA 0.190). The authors concluded that upadacitinib 15mg plus MTX and

upadacitinib 30mg plus MTX were the most efficacious interventions and not associated with significant risks of serious adverse events. Long-term studies are warranted.

There is some evidence in a phase 3 study to suggest that Rinvoq® may be more effective than adalimumab in RA patients when added to methotrexate; however, there is no evidence that Rinvoq® is safer or more effective than other currently available, less costly treatment options. It is therefore recommended that Rinvoq® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Rinvoq [package insert]. North Chicago, IL: AbbVie; 2019.
[2] Fleischmann R, Pangan AL, Song IH, et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: Results of a phase III, double-blind, randomized controlled trial. *Arthritis Rheumatol*. 2019. [Epub ahead of print].
[3] Song GG, Choi SJ, Lee YH. Comparison of the efficacy and safety of tofacitinib and upadacitinib in patients with active rheumatoid arthritis: A Bayesian network meta-analysis of randomized controlled trials. *Int J Rheum Dis*. 2019; 22(8): 1563-1571.