CLINICAL UPDATE

Brand Name	Rinvoq®
Generic Name	upadacitinib
Drug Manufacturer	AbbVie Inc.

Clinical Update

TYPE OF CLINICAL UPDATE

New indication and Strength

FDA APPROVAL DATE

January 14, 2022

LAUNCH DATE

January 20, 2022

REVIEW DESIGNATION

Priority

TYPE OF REVIEW

Type 1 - New Molecular Entity; New Drug Application (NDA): 211675

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Rheumatoid Arthritis- Indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers.
Limitations of Use: Use in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine, is not recommended.
Psoriatic Arthritis- Indicated for the treatment of adults with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers.
Limitations of Use: Use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine, is not recommended.
Atopic Dermatitis- Indicated for the treatment of adults and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable.
Limitations of Use: Not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants.

MECHANISMS OF ACTION

Upadacitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs) which modulate intracellular activity including gene expression.

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Upadacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. JAK enzymes transmit cytokine signaling through their pairing (e.g., JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/JAK2, JAK2/TYK2). In a cell-free isolated enzyme assay, upadacitinib had greater inhibitory potency at JAK1 and JAK2 relative to JAK3 and TYK2. In human leukocyte cellular assays, upadacitinib inhibited cytokine-induced STAT phosphorylation mediated by JAK1 and JAK1/JAK3 more potently than JAK2/JAK2 mediated STAT phosphorylation. However, the relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known.

DOSAGE FORM(S) AND STRENGTH(S)

Extended-release tablets: 15 mg and 30 mg.

DOSE & ADMINISTRATION

Rheumatoid Arthritis- 15 mg once daily.

Psoriatic Arthritis- 15 mg once daily.

Atopic Dermatitis (Adults 65 Years of Age and Older)- 15 mg once daily.

Pediatric Patients 12 Years of Age and Older Weighing at Least 40 kg and Adults Less Than 65 Years of Age- Initiate treatment with 15 mg once daily. If an adequate response is not achieved, consider increasing the dosage to 30 mg once daily. Discontinue if an adequate response is not achieved with the 30 mg dose. Use the lowest effective dose needed to maintain response.

EFFICACY

SELECT-COMPARE Results at 72 Weeks

Results of this Long-Term Extension (LTE) of the SELECT-COMPARE study show that Rinvoq® plus MTX maintained higher levels of clinical response, including remission compared to adalimumab plus MTX, through week 72.

SELECT-COMPARE Results* at 72 Weeks†,[1]

	RINVOQ 15 mg plus MTX (n=651)	Adalimumab plus MTX (n=327)
ACR20[a]	64%	53%
ACR50[a]	51%	38%
ACR70[a]	38%	25%
Clinical Remission[b]	41%	26%
Low Disease Activity[c]	49%	32%

* Efficacy data reported based on randomized treatment. For patients who were rescued, non-responder imputation (NRI) was used for binary endpoints. All reported endpoints achieved p-values of ≤0.001 for RINVOQ plus MTX versus adalimumab plus MTX through week 72, except for ACR20 at week 72 (p≤0.01).

† Patients who received adalimumab were switched to receive 15 mg of RINVOQ, and vice versa, if they did not achieve at least a 20 percent improvement in both tender and swollen joint count at weeks 14, 18 or 22, or if Clinical Disease Activity Index (CDAI) was greater than 10 at week 26. NRI was used for rescue prior to week 26 and last observation carried forward was used for rescue at week 26.

[a]ACR20/50/70 is defined as at least a 20 percent/50 percent/70 percent reduction from baseline in the number of both tender and swollen joint counts and equivalent improvement in three or more of the five remaining American College of Rheumatology core set measures: patient assessments of pain, global disease activity and physical function, physician global assessment of disease activity and acute phase reactant.

[b]Clinical remission is defined as Disease Activity Score with 28 joint counts C-reactive protein (DAS28-CRP) less than 2.6.

[c]Low disease activity (LDA) is defined as Disease Activity Score with 28 joint counts C-reactive protein (DAS28-CRP) less than or equal to 3.2.

SELECT-MONOTHERAPY Results at 84 Weeks

In this LTE of the SELECT-MONOTHERAPY study, patients who received continued MTX in the first phase of the study were switched to receive blinded upadacitinib (15 mg or 30 mg) at week 14 based on pre-specified assignment at baseline. Results of this LTE show that upadacitinib monotherapy resulted in continued improvements in rheumatoid arthritis signs and symptoms through 84 weeks.

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SELECT-MONOTHERAPY Results* at 84 weeks[†,2]				
	cMTX to upadacitinib 15 mg	cMTX to upadacitinib 30 mg	Continuous upadacitinib 15 mg	Continuous upadacitinib 30 mg
ACR20[a]	86%	90%	88%	96%
ACR50[a]	71%	68%	71%	78%
ACR70[a]	49%	50%	54%	66%
Clinical Remission[b]	56%	63%	60%	77%
Low Disease Activity[c]	80%	79%	76%	85%

*Results are based on as observed analyses.

†Upadacitinib 30 mg is not an approved dose.

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Radiographic Inhibition at Approximately Two Years: SELECT-EARLY and SELECT-COMPARE

Both SELECT-EARLY and SELECT-COMPARE enrolled rheumatoid arthritis patients at high risk for progressive structural damage with baseline erosive joint damage and/or seropositivity. Rinvoq® inhibited structural joint damage in MTX-naïve patients receiving Rinvoq® monotherapy and in patients with an inadequate response to MTX in combination with MTX

Radiographic Inhibition at Approximately 2 Years (96 weeks)*,[3]						
	SELECT-EARLY			SELECT-COMPARE		
	Upadacitinib 30 mg (n=231)	Upadacitinib 15 mg (n=238)	MTX (n=186)	Continuous RINVOQ 15 mg plus MTX (n=327)	Placebo plus MTX to RINVOQ 15 mg plus MTX (n=529)	Continuous adalimumab plus MTX (n=125)
No Radiographic Progression[d]	91%	89%	76%	82%	77%	75%

* Upadacitinib 30 mg is not an approved dose. RINVOQ is not approved for the treatment of MTX-naïve patients.

[d] No radiographic progression is defined as a change in modified Total Sharp Score (mTSS)≤0.

- Long-term results from the SELECT-COMPARE and SELECT-MONOTHERAPY studies showed that Rinvoq® (upadacitinib, 15 mg) continued to improve signs and symptoms in patients with rheumatoid arthritis through 72 and 84 weeks, respectively.
- Results from SELECT-EARLY and SELECT-COMPARE showed Rinvoq® inhibited structural joint damage in rheumatoid arthritis patients receiving Rinvoq® as monotherapy or in combination with MTX at almost two years.
- Rinvoq® safety profile was consistent across the pivotal Phase 3 program, with no new safety signals identified.
- Treatment with Rinvoq® 15 mg resulted in improvement in skin manifestations in patients with Psoriatic Arthritis. However, Rinvoq® has not been studied in and is not indicated for the treatment of plaque psoriasis.
- Atopic dermatitis symptoms and pain (≥4 point improvement in the Atopic Dermatitis Symptom Scale [ADerm-SS] Skin Pain NRS) has improved in trials AD-1 and AD-2.