Rinvoq (upadacitinib) **for Psoriatic Arthritis**

FIRST LOOK: NEW INDICATION

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Introduction

- **Brand name:** Rinvoq
- **Generic name:** Upadacitinib
- **Pharmacologic class:** Janus kinase (JAK) inhibitor
- **Strength and Formulation:** 15mg; extended-release tablets
- **Manufacturer:** AbbVie
- **How supplied:** Bottles—30
- **Legal Classification:** Rx

New Indication

- Treatment of **active psoriatic arthritis** in adults who have had an inadequate response or intolerance to 1 or more tumor necrosis factor (TNF) blockers.
  - **Limitations of Use**: Use of Rinvoq in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine, is not recommended.

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Mechanism of Action

- **Upadacitinib** modulates the signaling pathway at the point of JAKs, thus preventing the phosphorylation and activation of signal transducers and activators of transcription (STATs), which are modulators of intracellular activity including gene expression.

Clinical Trials: Psoriatic Arthritis

- Approval was based on 2 randomized, double-blind, placebo-controlled phase 3 studies (ClinicalTrials.gov Identifier: Study PsA-I [NCT03104400], Study PsA-II [NCT03104374]).
- **Study PsA-I** included 1705 patients who had an inadequate response or intolerance to at least 1 nonbiologic DMARD.
- **Study PsA-II** included 642 patients who had an inadequate response or intolerance to at least 1 biologic DMARD.

Clinical Trials: Psoriatic Arthritis

- **Study PsA-I**: Patients randomly assigned to Rinvoq 15mg or upadacitinib 30mg once daily, adalimumab, or placebo, alone or in combination with background nonbiologic DMARDs.
- **Study PsA-II**: Patients randomly assigned to Rinvoq 15mg or upadacitinib 30mg once daily, or placebo, alone or in combination with background nonbiologic DMARDs.
- At week 24, all patients receiving placebo were switched to Rinvoq 15mg or upadacitinib 30mg once daily in a blinded manner.
- The **primary endpoint** was the proportion of patients who achieved an American College of Rheumatology (ACR) 20 response at week 12.

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Clinical Trials: Psoriatic Arthritis

In both studies, a higher proportion of patients treated with Rinvoq 15mg achieved ACR20, ACR50, and ACR 70 responses at week 12 compared with placebo.

Clinical Response at Week 12				
	Study PsA-I		**Study PsA-II**	
	Rinvoq 15mg (n=429)	**Placebo (n=423)**	**Rinvoq 15mg (n=211)**	**Placebo (n=212)**
ACR20	71%	36%	57%	24%
ACR50	38%	13%	32%	5%
ACR70	16%	2%	9%	1%

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Clinical Trials: Psoriatic Arthritis

- Treatment with Rinvoq 15mg also led to **improvement in dactylitis and enthesitis** in patients with pre-existing dactylitis or enthesitis, as well as **improvements in skin manifestations** in patients with psoriatic arthritis.
- Significant **improvement in physical function**, as assessed by the Health Assessment Questionnaire Disability Index (HAQ-DI), was also observed in both studies. The **mean difference from placebo in HAQ-DI change from baseline** at week 12 was -0.28 (95% CI, -0.35, -0.22) in Study PsA-I and -0.21 (95% CI, -0.30, -0.12) in Study PsA-II.
- **Proportion of HAQ-DI responders** (≥0.35 improvement from baseline in HAQ-DI score) at week 12:
  - Study PsA-I: 58% for Rinvoq 15mg vs 33% for placebo
  - Study PsA-II: 45% for Rinvoq 15mg vs 27% for placebo

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Clinical Trials: Psoriatic Arthritis

- **Inhibition of progression of structural damage** was assessed radiographically in Study PsA-I.
- Treatment with Rinvoq 15mg was found to inhibit progression of structural joint damage compared with placebo at week 24.
- Analyses of erosion and joint space narrowing scores were consistent with overall results.
- **Proportion of patients with no radiographic progression** (modified Total Sharp Score change ≤ 0) at week 24:
  - 93% for Rinvoq 15mg
  - 89% for placebo

Clinical Trials: Psoriatic Arthritis

- **Health-related quality of life** was assessed by Short Form Health Survey (SF-36).
- In both studies, patients receiving Rinvoq 15mg experienced significantly greater improvement from baseline in the Physical Component Summary score compared with placebo at week 12.
- Greater improvement was also observed in the Mental Component Summary score and all 8 domains of SF-36 compared with placebo.
- Compared with placebo, greater improvement from baseline in fatigue, as measured by FACIT-F score, at week 12 was observed with Rinvoq 15mg.

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Dosage & Administration: Psoriatic Arthritis

- Prior to initiating treatment, perform the following evaluations (see **Warnings/Precautions** for further recommendations):
  - Active and latent tuberculosis infection evaluation.
  - Viral hepatitis screening.
  - A complete blood count.
  - Baseline hepatic function.
  - Pregnancy status.
  - Verify all immunizations received prior to initiating therapy.

Dosage & Administration: Psoriatic Arthritis

- Swallow whole.
- ≥18yrs: 15mg once daily.
- Not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants (eg, azathioprine, cyclosporine).
- Concomitant strong CYP3A4 inhibitors: 15mg once daily.
- Dosage interruption may be necessary if a patient develops a serious infection or if laboratory abnormalities occur (see full labeling).

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Other Approved Indication(s)

- 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.

- Treatment of **moderately to severely active rheumatoid arthritis** in adults who have had an inadequate response or intolerance to 1 or more TNF blockers.

Considerations for Specific Populations

- **Pregnancy:** Insufficient data to evaluate a drug-associated risk for major birth defects or miscarriage; may cause fetal harm based on animal studies.
- **Nursing mothers**: Not recommended (during and for 6 days after the last dose).
- **Females and males of reproductive potential**: Verify pregnancy status prior to starting treatment; advise females to use effective contraception during and for 4 weeks after the last dose.
- **Pediatric**: Not established in pediatric patients with psoriatic arthritis and juvenile idiopathic arthritis, or in pediatric patients <12 years of age with atopic dermatitis.
- **Geriatric:** No overall differences in safety or efficacy observed between these patients and younger patients; however, there was a higher rate of overall adverse events, including serious infections and malignancies, in patients aged ≥65yrs.

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Considerations for Specific Populations

- **Renal impairment:**
  - For rheumatoid arthritis and psoriatic arthritis, no dosage adjustment is needed for mild, moderate, or severe renal impairment.
  - For atopic dermatitis, maximum dose is 15mg once daily for those with severe renal impairment (CrCl <30mL/min).
  - Not recommended for use in patients with end stage renal disease.
- **Hepatic impairment:**
  - No dosage adjustment is needed for mild or moderate hepatic impairment.
  - Not recommended for use in patients with severe impairment.

Boxed Warnings

- **Serious Infections**
  - Increased risk for developing serious infections that may lead to hospitalization or death.
  - If serious infection develops, interrupt treatment until the infection is controlled.
  - Reported infections include: active tuberculosis, invasive fungal infections, bacterial, viral, and other infections due to opportunistic pathogens.
  - Carefully consider risks/benefits prior to initiating treatment in patients with chronic or recurrent infection.

Boxed Warnings

- **Mortality**
  - In rheumatoid arthritis (RA) patients aged ≥50yrs with at least 1 cardiovascular (CV) risk factor, a higher rate of all-cause mortality, including sudden CV death, was observed with another JAK inhibitor.

- **Malignancy**
  - Lymphoma and other malignancies have been observed in patients treated with Rinvoq.
  - In RA patients treated with another JAK inhibitor, a higher rate of malignancies (excluding nonmelanoma skin cancer) was observed when compared with TNF blockers.
  - Current or past smokers are at additional risk.

Boxed Warning

- **Major Adverse Cardiovascular Events (MACE)**
  - In RA patients aged ≥50yrs with at least 1 CV risk factor treated with another JAK inhibitor, a higher rate of MACE (defined as CV death, MI, and stroke) was observed compared with TNF blockers.
  - Current or past smokers are at additional risk.
  - Discontinue if patients experience an MI or stroke.

- **Thrombosis**
  - In RA patients aged ≥50yrs with at least 1 CV risk factor treated with another JAK inhibitor, a higher rate of thrombosis was observed compared with TNF blockers.
  - Avoid in patients at risk.
  - Discontinue in patients with symptoms of thrombosis.

Contraindications

- Hypersensitivity to upadacitinib or any of its excipients.

Warnings and Precautions

- Increased risk of serious infections (eg, TB, bacterial, viral, invasive fungal, or other opportunistic pathogens).
- Avoid in active, serious, or localized infections.
- Consider the risks/benefits in chronic, recurrent, or history of serious or opportunistic infections.
- Travel to, or residence in, areas with endemic TB or mycoses.
- Conditions that predispose to infection.
- Test/treat latent TB infection prior to and per applicable guidelines during therapy.

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Warnings and Precautions

- Monitor closely if new infection, active TB (even if initial latent test is negative), reactivation of herpes virus or hepatitis occurs; interrupt treatment if serious or opportunistic infection.
- Screen for viral hepatitis before starting therapy.
- Consider benefits/risks prior to or continuing therapy (esp. smokers, with other CV risk factors, or with a known malignancy).
- GI perforation risk (eg, history of diverticulitis).
- Perform periodic skin exam in those with skin cancer risk.
- Update immunization based on current guidelines prior to initiating therapy.

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Warnings and Precautions

- Do not initiate therapy if lymphocytes <500cells/mm^3, ANC <1000cells/mm^3, or hemoglobin <8g/dL.
- Monitor lymphocytes, neutrophils, and hemoglobin at baseline, then periodically thereafter.
- Routinely monitor liver enzymes; interrupt therapy if ALT/AST elevated and drug-induced liver injury is suspected.
- Monitor lipids 12 weeks following initiation and manage hyperlipidemia.
- Embryo-fetal toxicity: verify pregnancy status prior to initiation.

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Interactions

- Avoid use of live vaccines during, or immediately prior to therapy.
- Concomitant other JAK inhibitors, biologic DMARDs or immunomodulators, or potent immunosuppressants (eg, azathioprine, cyclosporine): not recommended.
- **Potentiated by** strong CYP3A4 inhibitors (eg, ketoconazole): coadministration with 30mg dose not recommended.
- **Antagonized by** strong CYP3A4 inducers (eg, rifampin); not recommended.
- Caution with NSAIDs (risk factor for GI perforations).

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Adverse Reactions

- **Rheumatoid arthritis and psoriatic arthritis: Most common (≥1%):**
  - Upper respiratory tract infections, herpes zoster, herpes simplex, bronchitis, nausea, cough, pyrexia, acne.
- **Atopic dermatitis: Most common (≥1%):**
  - Upper respiratory tract infections, acne, herpes simplex, headache, increased blood creatine phosphokinase, cough, hypersensitivity, folliculitis, nausea, abdominal pain, pyrexia, increased weight, herpes zoster, influenza, fatigue, neutropenia, myalgia, influenza like illness.

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Product Monograph

- For more information view the product monograph available at:

  https://www.empr.com/drug/rinvoq/