# **Rinvoq** (upadacitinib) **for Ulcerative Colitis**


## 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, 30mg, 45mg; extended-release tablets
- **Manufacturer:** AbbVie
- **How supplied:** 15mg, 30mg—30; 45mg—28
- **Legal Classification:** Rx

# New Indication

- Treatment of **moderately to severely active ulcerative colitis** in adults who have had an inadequate response or intolerance to 1 or more tumor necrosis factor (TNF) blockers.

  - **Limitations of Use**: Rinvoq is not recommended for use in combination with other JAK inhibitors, biological therapies for ulcerative colitis, or with potent immunosuppressants such as azathioprine and cyclosporine.

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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: Ulcerative Colitis

- Approval was based on 2 randomized, double-blind, placebo-controlled phase 3 induction studies (ClinicalTrials.gov Identifier: UC-1 [NCT02809635], UC-2 [NCT03653026]), and one phase 3 maintenance study (ClinicalTrials.gov Identifier: UC-3 [NCT02819635]).

# Clinical Trials: Ulcerative Colitis

- **UC-1** and **UC-2** Induction Studies
  - Total of 988 adults with moderately to severely active ulcerative colitis who had an inadequate response, loss of response, or intolerance to oral aminosalicylates, corticosteroids, immunosuppressants, and/or biologic therapy.
  - Patients were randomly assigned 2:1 to receive Rinvoq 45mg once daily or placebo for 8 weeks.

- **UC-3** Maintenance Study
  - Total of 451 patients who received Rinvoq 45mg once daily in UC-1, UC-2, or UC-4 (double-blind, placebo-controlled dose-finding study [ClinicalTrials.gov Identifier: NCT02819635]) and achieved clinical response.
  - Patients were re-randomized to receive Rinvoq 15mg, 30mg, or placebo once daily for up to 52 weeks.

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# Clinical Trials: Ulcerative Colitis

- **UC-1** and **UC-2** Induction Studies
  - **Primary endpoint**: Clinical remission using the modified Mayo score (mMS), consisting of the following subscores (0-3 for each subscore): stool frequency (SFS), rectal bleeding (RBS), and findings on centrally read endoscopy score (ES), at week 8.
  - **Clinical remission**: SFS ≤1 and not greater than baseline, RBS = 0, ES of ≤1 without friability.
  - **Secondary endpoints**
    - Clinical response: Decrease ≥2 points and ≥30% from baseline and a decrease in RBS ≥1 from baseline or an absolute RBS ≤1.
    - Endoscopic improvement: ES ≤1 without friability.
    - Histologic endoscopic mucosal improvement: ES ≤1 without friability and Geboes score ≤3.1 (indicating neutrophil infiltration in <5% of crypts, no crypt destruction and no erosions, ulcerations or granulation tissue).

# Clinical Trials: Ulcerative Colitis

In **UC-1** and **UC-2**, a greater proportion of patients treated with Rinvoq 45mg achieved clinical remission at week 8 compared with placebo (*P* <.001).

| | Study UC-1 | | | Study UC-2 | | |
|---|---|---|---|---|---|---|
| | **Rinvoq 45mg (n=319)** | **Placebo (n=154)** | **Treatment difference (95% CI)** | **Rinvoq 45mg (n=341)** | **Placebo (n=174)** | **Treatment difference (95% CI)** |
| **Clinical remission** | 26% | 5% | 22% (16-27) | 33% | 4% | 29% (23-35) |
| **Clinical response** | 73% | 27% | 46% (38-54) | 74% | 25% | 49% (42-57) |
| **Endoscopic improvement** | 36% | 7% | 29% (23-36) | 44% | 8% | 35% (29-42) |
| **Histologic endoscopic mucosal improvement** | 30% | 7% | 24% (17-30) | 37% | 6% | 30% (24-36) |

# Clinical Trials: Ulcerative Colitis

- **UC-1** and **UC-2** Induction Studies
  - **Onset of response** (assessed using SFS and RBS) occurred as early as week 2 in a greater proportion of patients treated with Rinvoq 45mg vs placebo.
  - A greater proportion of patients treated with Rinvoq 45mg achieved **endoscopic remission** (defined as ES of 0) at week 8 vs placebo (UC-1: 14% vs 1%; UC-2: 18% vs 2%).
    - **Endoscopic remission with Geboes histologic score <2.0**: UC-1: 11% vs 1%; UC-2: 13% vs 2%.
  - A greater proportion of patients treated with Rinvoq 45mg vs placebo had **no abdominal pain** (UC-1: 47% vs 23%; UC-2: 54% vs 24%) and **no bowel urgency** (UC-1: 48% vs 21%; UC-2: 54% vs 26%) at week 8.

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# Clinical Trials: Ulcerative Colitis

- **UC-3** Maintenance Study
  - **Primary endpoint**:
    - Clinical remission defined using the mMS at week 52.
    - SFS ≤1 and not greater than baseline, RBS = 0, ES ≤1 without friability.
  - **Secondary endpoints:**
    - Corticosteroid-free clinical remission: Clinical remission per mMS at week 52 and corticosteroid free for ≥90 days immediately preceding week 52 among patients who achieved clinical remission at the end of the induction treatment.
    - Endoscopic improvement: ES ≤1 without friability.
    - Histologic endoscopic mucosal improvement: ES ≤1 without friability and Geboes score ≤3.1 (indicating neutrophil infiltration in <5% of crypts, no crypt destruction and no erosions, ulcerations or granulation tissue).

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# Clinical Trials: Ulcerative Colitis

In **UC-3**, a greater proportion of patients treated with Rinvoq 15mg or 30mg achieved clinical remission at week 52 compared with placebo (*P* <.001).

**Study UC-3**

| | Rinvoq 15mg | Rinvoq 30mg | Placebo | Treatment difference 15mg vs placebo (95% CI) | Treatment difference 30mg vs placebo (95% CI) |
|---|---|---|---|---|---|
| **Clinical remission** | 42% (n=148) | 52% (n=154) | 12% (n=149) | 31% (22-40) | 39% (30-48) |
| **Corticosteroid-free clinical remission** | 57% (n=47) | 68% (n=58) | 22% (n=54) | 35% (18-53) | 45% (29-62) |
| **Endoscopic improvement** | 49% (n=148) | 62% (n=154) | 14% (n=149) | 34% (25-44) | 46% (37-56) |
| **Histologic endoscopic mucosal improvement** | 35% (n=148) | 50% (n=154) | 12% (n=149) | 24% (15-33) | 37% (28-47) |

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# Clinical Trials: Ulcerative Colitis

- UC-3 Maintenance Study
  - A greater proportion of patients treated with Rinvoq 15mg and 30mg achieved **endoscopic remission** (defined as ES of 0) at week 52 vs placebo (24% and 26% vs 6%, respectively).
    - **Endoscopic remission with Geboes histologic score** <2.0: 18% and 19% for 15mg and 30mg, respectively, vs 5% for placebo.
  - A greater proportion of patients treated with Rinvoq 15mg and 30mg vs placebo had **no abdominal pain** (46% and 55% vs 21%, respectively) and **no bowel urgency** (56% and 64% vs 17%, respectively) at week 52.

# Dosage & Administration: Ulcerative Colitis

- 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: Ulcerative Colitis

- Swallow whole.
- ≥18yrs (**Induction**): 45mg once daily for 8 weeks.
- ≥18yrs (**Maintenance**): 15mg once daily; may consider 30mg once daily for patients with refractory, severe or extensive disease.
  - Discontinue if an adequate response is not achieved with 30mg dosage.
  - Use lowest effective dose needed to maintain response.
- For patients with severe renal impairment (eGFR 15-<30mL/min/1.73m$^2$), mild to moderate hepatic impairment, or with concomitant strong CYP3A4 inhibitors:
  - Induction: 30mg once daily for 8 weeks.
  - Maintenance: 15mg once daily.

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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.
- Treatment of **active psoriatic 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 ulcerative colitis, psoriatic arthritis and juvenile idiopathic arthritis, or in pediatric patients <12 years of age with atopic dermatitis.
- **Geriatric:** Clinical studies did not include sufficient numbers of patients ≥65yrs with ulcerative colitis to determine whether they respond differently from younger adult patients.

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# Considerations for Specific Populations

- **Renal impairment:**
  - For ulcerative colitis, reduce dose for those with severe renal impairment (eGFR 15-<30mL/min/1.73m$^2$) – see *Dosage & Administration: Ulcerative Colitis*.
  - 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:**
  - For ulcerative colitis, reduce dose for those with mild to moderate hepatic impairment – see *Dosage & Administration: Ulcerative Colitis*.
  - For rheumatoid arthritis, psoriatic arthritis, and atopic dermatitis, no dosage adjustment is needed for mild or moderate hepatic impairment.
  - Not recommended for use in patients with severe impairment.

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# 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, biologic immunomodulators, biological therapies for ulcerative colitis, or potent immunosuppressants (eg, azathioprine, cyclosporine): not recommended.
- **Potentiated by** strong CYP3A4 inhibitors (eg, ketoconazole, clarithromycin).
  - For ulcerative colitis, reduce dose – see *Dosage & Administration: Ulcerative Colitis.*
  - For atopic dermatitis, coadministration with 30mg dose is 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.
- **Ulcerative colitis: Most common (≥5%):**
  - Upper respiratory tract infections, increased blood creatine phosphokinase, acne, neutropenia, elevated liver enzymes, rash.

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# Product Monograph

- For more information view the product monograph available at:

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