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Policy Number: C17882-A

Rinvoq (upadacitinib)

PRODUCTS AFFECTED

Rinvoq (upadacitinib)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Atopic Dermatitis (AD), Ulcerative Colitis (UC), Ankylosing Spondylitis (AS), Non-Radiographic Axial Spondyloarthritis, Crohn's Disease (CD)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

FOR ALL INDICATIONS:

1. (a) Prescriber attests, or clinical reviewer has found, member has had a negative TB screening* or TB test (if indicated)** result within the last 12 months for initial and continuation of therapy requests

*MOLINA REVIEWER NOTE: TB SCREENING assesses patient for future or ongoing TB exposure or risk and includes reviewing if they have been exposed to tuberculosis, if they have resided or traveled to areas of endemic tuberculosis, if patient resides or works in a congregate setting (e.g., correctional facilities, long-term care facilities, homeless shelters), etc.
**MOLINA REVIEWER NOTE: TB SKIN TEST (TST, PPD) AND TB BLOOD TEST (QuantiFERON TB Gold, T-Spot) are not required or recommended in those without risk factors for tuberculosis
OR
(b) For members who have a positive test for latent TB, provider documents member has completed a treatment course (a negative chest x-ray is also required every 12 months) OR that member has been cleared by an infectious disease specialist to begin treatment
AND

2. Prescriber attests member has been evaluated and screened for the presence of hepatitis B virus (HBV) prior to initiating treatment
AND
3. Member is not on concurrent treatment or will not be used in combination with TNF- inhibitor, biologic response modifier or other biologic DMARDs, Janus kinase Inhibitors, or Phosphodiesterase 4 inhibitor (i.e., apremilast, tofacitinib, baricitinib), or potent immunosuppressants such as azathioprine or cyclosporine, as verified by prescriber attestation, member medication fill history, or submitted documentation
AND
4. Prescriber attests member does not have an active infection, including clinically important localized infections
AND
5. Prescriber attests that member does NOT have an absolute lymphocyte count (ALC) less than 500/mm3, absolute neutrophil count (ANC) less than 1000 cells/mm3, or hemoglobin less than 8 g/dL
AND
6. For females of child-bearing potential: prescriber attestation that the member has been counseled on the risk of fetal harm and recommended use of effective contraception.
AND
7. IF THIS IS A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of or serious side effects to a majority (not more than 2) of the preferred formulary/PDL alternatives for the given diagnosis. Submit documentation including medication(s) tried, dates of trial(s) and reason for treatment failure(s) [DOCUMENTATION REQUIRED]

A. MODERATE TO SEVERE RHEUMATOID ARTHRITIS:
1. Documentation of moderate to severe rheumatoid arthritis diagnosis
AND
2. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]
AND
3. (a) Member is currently receiving maximally tolerated dose of methotrexate and is not at goal disease activity-
OR
(b) Member has an FDA labeled contraindication or serious side-effects to methotrexate, as determined by the prescribing physician AND Member has tried one additional disease-modifying antirheumatic drug (DMARD) (brand or generic; oral or injectable) for at least 3 months
(NOTE: An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the member has already had a 3-month trial at least one biologic. These members who have already tried a biologic for RA are not required to "step back" and try a conventional synthetic DMARD.)
AND
4. Documentation of treatment failure or serious side effects to a trial (> 3 months) of ONE FORMULARY OR PREFERRED TNF-inhibitor

B. PSORIATIC ARTHRITIS (PsA):
1. Documentation of active psoriatic arthritis
AND
2. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]
AND
3. (a) Documented treatment failure, serious side effects or clinical contraindication to a minimum 3-month trial of ONE of the following: Leflunomide, Methotrexate, Sulfasalazine, Cyclosporine
OR
(b) Documentation member has severe psoriatic arthritis [erosive disease, elevated markers of inflammation, long term damage that interferes with function, highly active disease that causes a major impairment in quality of life, active PsA at many sites including dactylitis, enthesitis, function limiting PsA at a few sites or rapidly progressive disease]
OR
(c) Documentation member has severe psoriasis [PASI ≥12, BSA of >5-10%, significant involvement in specific areas (e.g., face, hands or feet, nails, intertriginous areas, scalp), impairment of physical or mental functioning with lower amount of surface area of skin involved]
AND
4. Documentation of treatment failure or serious side effects to a trial (> 3 months) of ONE FORMULARY OR PREFERRED TNF- inhibitor

C. MODERATE TO SEVERE ATOPIC DERMATITIS:
1. Documented diagnosis of moderate to severe chronic atopic dermatitis (eczema)
AND
2. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal (e.g., erythema, induration/papulation/edema, excoriations, lichenification, pruritis, BSA affected, topical requirement, etc.) [DOCUMENTATION REQUIRED]
AND
3. (a) Member has atopic dermatitis involvement estimated to be ≥ 10% of the body surface area (BSA) according to the prescribing physician; AND meets all of the following criteria:
   i. Member has used at least TWO of the following: a medium potency prescription topical corticosteroid, a medium-high potency prescription topical corticosteroid, a high potency prescription topical corticosteroid, OR a super high- potency prescription topical corticosteroid
   AND
   ii. Each topical corticosteroid was applied daily for at least 14 consecutive days
   AND
   iii. Inadequate efficacy was demonstrated with this topical corticosteroid therapy, according to the prescribing physician
   AND
   iv. Documentation of inadequate response, serious side effects, contraindication, or clinical rationale of the inappropriateness to ONE of the following: trial (6 weeks) of preferred/formulary topical calcineurin inhibitor (tacrolimus, pimecrolimus), OR trial (4 weeks) of crisaborole (Eucrisa) OR trial (8 weeks) of Opzelura (ruxolitinib)

   OR

   (b) Member has atopic dermatitis involvement estimated to be < 10% of the BSA according to the prescribing physician and meets ALL of the following criteria:
   i. Member has atopic dermatitis affecting ONLY the following areas: face, eyes/eyelids, skin folds, and/or genitalia.
   AND
   ii. Documentation of inadequate response, serious side effects, contraindication, or clinical rationale of inappropriateness to BOTH of the following (when age appropriate): trial (6 weeks) of tacrolimus ointment (Protopic, generics) AND trial (8 weeks) of Opzelura (ruxolitinib)

AND

4. FOR REQUESTS FOR ADULT MEMBERS: Documented compliant short course of at least ONE systemic immunosuppressant OR documentation of FDA labeled contraindication to systemic immunosuppressants

D. ULCERATIVE COLITIS:
   1. Documentation of ulcerative colitis diagnosis with evidence of moderate to severe disease activity
      AND
   2. (a) Documentation of treatment failure, serious side effects or clinical contraindication to a 2-month trial of one systemic agent (e.g., 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone, methylprednisolone) for ulcerative colitis or will continue to take concurrently.
      NOTE: A previous trial of a biologic (e.g., an adalimumab product [e.g., Humira], Simponi SC [golimumab SC injection], or Entyvio [vedolizumab IV infusion]) also counts as a trial of one systemic agent for UC
      OR
      (b) The Member has pouchitis AND has tried therapy with an antibiotic (e.g., metronidazole, ciprofloxacin), probiotic, corticosteroid enema [for example, Cortenema® (hydrocortisone enema, generics)], or topical mesalamine
      AND
   3. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]
      AND
   4. Documentation of treatment failure or serious side effects to a trial (> 3 months) of ONE FORMULARY OR PREFERRED TNF-inhibitor

E. MODERATE TO SEVERE ANKYLOSING SPONDYLITIS:
   1. Documented diagnosis of ankylosing spondylitis
      AND
   2. Documentation of treatment failure, serious side effects or clinical contraindication to TWO NSAIDs (e.g., ibuprofen, naproxen, etodolac, meloxicam, indomethacin) for ≥3 consecutive months at maximal recommended or tolerated anti- inflammatory doses
      AND
   3. FOR MEMBER WITH PROMINENT PERIPHERAL ARTHRITIS: Documentation of treatment failure, serious side effects or clinical contraindicatin to a trial (≥3 consecutive months) of methotrexate OR sulfasalazine
      AND
   4. Documentation of treatment failure or serious side effects to a trial (> 3 months) of ONE FORMULARY OR PREFERRED TNF-inhibitor
      AND
   5. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]

F. NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS:
   1. Prescriber attests to diagnosis of adult-onset axial spondylarthritis
      AND
   2. Documentation that C-reactive protein (CRP) levels are above the upper limit of normal and/or sacroiliitis on magnetic resonance imaging (MRI), indicative of inflammatory disease
      AND
   3. Documentation that there is no definitive radiographic evidence of structural damage on sacroiliac joints
      AND
   4. Documentation member has active disease and prescriber provides baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]

AND

5. Documentation of treatment failure, serious side effects or clinical contraindication to TWO NSAIDs (e.g., ibuprofen, naproxen, etodolac, meloxicam, indomethacin) for ≥3 consecutive months at maximal recommended or tolerated anti- inflammatory doses
   AND
6. Documentation of treatment failure or serious side effects to a trial (> 3 months) of ONE FORMULARY OR PREFERRED TNF-inhibitor

G. CROHN'S DISEASE:
1. Documentation of a diagnosis of Crohn's Disease
   AND
2. Member has one or more high risk features:
   i. Diagnosis at a younger age (<30 years old)
   ii. History of active or recent tobacco use
   iii. Elevated C-reactive protein and/or fecal calprotectin levels
   iv. Deep ulcers on colonoscopy
   v. Long segments of small and/or large bowel involvement
   vi. Perianal disease
   vii. Extra-intestinal manifestations
   viii. History of bowel resections
   AND
3. (a) Documentation of treatment failure, serious side effects or clinical contraindication to an adequate trial (> 3 months) of ONE immunomodulator (e.g., azathioprine, 6-mercaptopurine, methotrexate) up to maximally indicated doses
   OR
   (b) Prescriber provides documented medical justification that supports the inability to use immunomodulators
   i. Inability to induce short-term symptomatic remission with a 3-month trial of systemic glucocorticoids
   ii. High-risk factors for intestinal complications may include: Initial extensive ileal, ileocolonic, or proximal GI involvement, Initial extensive perianal/severe rectal disease, Fistulizing disease (e.g., perianal, enterocutaneous, and rectovaginal fistulas), Deep ulcerations, Penetrating, stricturing or stenosis disease and/or phenotype, Intestinal obstruction or abscess
   iii. High risk factors for postoperative recurrence may include: Less than 10 years duration between time of diagnosis and surgery, Disease location in the ileum and colon, Perianal fistula, Prior history of surgical resection, Use of corticosteroids prior to surgery
   AND
4. Documentation of treatment failure or serious side effects to a trial (> 3 months) of ONE FORMULARY OR PREFERRED TNF-inhibitor
   AND
5. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]

CONTINUATION OF THERAPY:

A. FOR ALL INDICATIONS:
1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
   AND
3. Documentation of positive clinical response as demonstrated by low disease activity and/or

improvements in the condition's signs and symptoms. [DOCUMENTATION REQUIRED]
AND

4. Prescriber attests to continued appropriate monitoring of ALL of the following: absolute neutrophil count (ANC) at least 1000 cell/mm3, lymphocyte count at least 500 cells/mm, Hemoglobin level at least 8 g/dL.
AND
5. (a) Prescriber attests, or clinical reviewer has found, member has had a negative TB screening* or TB test (if indicated)** result within the last 12 months for initial and continuation of therapy requests
*MOLINA REVIEWER NOTE: TB SCREENING assesses patient for future or ongoing TB exposure or risk and includes reviewing if they have been exposed to tuberculosis, if they have resided or traveled to areas of endemic tuberculosis, if patient resides or works in a congregate setting (e.g., correctional facilities, long-term care facilities, homeless shelters), etc.
**MOLINA REVIEWER NOTE: TB SKIN TEST (TST, PPD) AND TB BLOOD TEST (QuantiFERON TB Gold, T-Spot) are not required or recommended in those without risk factors for tuberculosis
OR
(b) For members who have a positive test for latent TB, provider documents member has completed a treatment course (a negative chest x-ray is also required every 12 months) OR that member has been cleared by an infectious disease specialist to begin treatment

DURATION OF APPROVAL:
Initial authorization: 6 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a board-certified rheumatologist, allergist, immunologist, gastroenterologist, or dermatologist [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
Rheumatoid Arthritis, Psoriatic Arthritis, Ulcerative Colitis, Ankylosing Spondylitis, Non-radiographic axial spondyloarthritis: Crohn's disease: 18 years of age and older
Atopic Dermatitis: 12 years and older

QUANTITY:
Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, and Non-radiographic Axial Spondyloarthritis:
15mg once daily (#30 tablets per 30 days)

Ulcerative Colitis
Induction dosage: 45 mg once daily for 8 weeks. THEN recommended maintenance dosage is 15 mg once daily.
A maintenance dosage of 30 mg once daily may be considered for patients with refractory, severe, or extensive disease. Discontinue RINVOQ if adequate therapeutic response is not achieved with the 30 mg dosage.
FOR APPROVAL OF 30MG ONCE DAILY MAINTENANCE DOSING:
Prescriber must provide medical chart note documentation to support a member's initial adequate response to a compliant 8-week consecutive course of 45mg daily (or appropriate starting dose per necessary modification), evidence member has refractory, severe or extensive disease and therapeutic plan for evaluating the response to the 30mg dosing.

Atopic Dermatitis:
Adults 65 Years of Age and Older: Recommended dosage is 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 orally once daily.

If an adequate response is not achieved, consider increasing the dosage to 30 mg orally once daily.

FOR APPROVAL OF 30MG ONCE DAILY DOSING:

Prescriber must provide medical chart note documentation to support a member's initial inadequate response to a compliant 12-week consecutive course of 15mg daily (or appropriate starting dose per necessary modification) and therapeutic plan for evaluating the response to the 30mg dosing.

Crohn's Disease:

Induction dosage: 45 mg once daily for 12 weeks. THEN recommended maintenance dosage is 15 mg once daily.

A maintenance dosage of 30 mg once daily may be considered for patients with refractory, severe, or extensive disease. Discontinue RINVOQ if adequate therapeutic response is not achieved with the 30 mg dosage.

FOR APPROVAL OF 30MG ONCE DAILY MAINTAINENCE DOSING:

Prescriber must provide medical chart note documentation to support a member's initial adequate response to a compliant 12-week consecutive course of 45mg daily (or appropriate starting dose per necessary modification), evidence member has refractory, severe or extensive disease and therapeutic plan for evaluating the response to the 30mg dosing.

PLACE OF ADMINISTRATION:

The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:

Oral

DRUG CLASS:

Antirheumatic-Janus Kinase (JAK) Inhibitors

FDA-APPROVED USES:

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.
- Adults with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers
- 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.
- Adults with moderately to severely active ulcerative colitis who have had an inadequate response or intolerance to one or more TNF blockers.
- Adults with active ankylosing spondylitis who have had an inadequate response or intolerance to one or more TNF blockers
- Adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation who have had an inadequate response or intolerance to TNF blocker therapy
- Adults with moderately to severely active Crohn's disease who have had an inadequate response or intolerance to one or more TNF blockers

Limitation 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.

COMPENDIAL APPROVED OFF-LABELED USES:

None

APPENDIX

APPENDIX:

Example of defining overall ulcerative colitis disease activity:

Mild – Patients with mild clinical disease have ≤4 stools per day with or without small amounts of blood, no signs of systemic toxicity (eg, no tachycardia), and a normal C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR). Mild crampy abdominal pain, tenesmus, and periods of constipation are also common, but severe abdominal pain, profuse bleeding, fever, and weight loss are not part of the spectrum of mild disease.

Moderate – Patients with moderate clinical disease may have frequent (four to six per day) loose, bloody stools, mild anemia not requiring blood transfusions (hemoglobin >10 g/dL [100 g/L]), and abdominal pain that is not severe. Patients have no or minimal signs of systemic toxicity. Adequate nutrition is usually maintained, and weight loss is not associated with moderate clinical disease.

Severe – Patients with severe clinical disease typically have frequent loose bloody stools (≥6 per day) with severe cramps and evidence of systemic toxicity as demonstrated by a fever (temperature ≥37.8°C), tachycardia (heart rate ≥90 beats per minute), anemia (hemoglobin <10.0 g/dL [100 g/L]), and/or an elevated CRP or ESR. Patients may have weight loss. Management of hospitalized patients with severe UC is discussed separately

Montreal classification of severity of ulcerative colitis (UC)

Severity		Definition
S0	Clinical remission	Asymptomatic
S1	Mild UC	Passage of four or fewer stools/day (with or without blood), absence of any systemic illness, and normal inflammatory markers (ESR)
S2	Moderate UC	Passage of more than four stools per day but with minimal signs of systemic toxicity
S3	Severe UC	Passage of at least six bloody stools daily, pulse rate of at least 90 beats per minute, temperature of at least 37.5°C, haemoglobin of less than 10.5 g/100 ml, and ESR of at least 30 mm/h

Satsangi, J., Silverberg, M. S., Vermeire, S., & Colombel, J. F. (2006). The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut*, *55*(6), 749–753. https://doi.org/10.1136/gut.2005.082909

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Rinvoq (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. Rinvoq modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs.

Rheumatoid Arthritis

The efficacy and safety of Rinvoq 15 mg once daily were assessed in five Phase 3 randomized, double-blind, multicenter studies in patients with moderately to severely active rheumatoid arthritis and fulfilling the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR 2010) classification criteria. Patients over 18 years of age were eligible to participate. Although other doses have been studied, the recommended dose of Rinvoq is 15 mg once daily.

Study RA-I (NCT02706873) was a 24-week monotherapy trial in 947 patients with moderately to severely active rheumatoid arthritis who were naïve to methotrexate. Patients received Rinvoq 15 mg or upadacitinib 30 mg once daily or methotrexate as monotherapy. At week 26, nonresponding patients on upadacitinib could be rescued with the addition of methotrexate, while patients on methotrexate could be rescued with the addition of blinded Rinvoq 15 mg or upadacitinib 30 mg once daily. The primary endpoint was the proportion of patients who achieved an ACR50 (50% or greater improvement) response at week 12. For the primary endpoint at week 12, 28% of patients achieved an ACR50 in the methotrexate group vs. 52% of patients in the Rinvoq group.
Study RA-II (NCT02706951) was a 14-week monotherapy trial in 648 patients with moderately to severely active rheumatoid arthritis who had an inadequate response to methotrexate. Patients received Rinvoq 15 mg or upadacitinib 30 mg once daily monotherapy or continued their stable dose of methotrexate monotherapy. At week 14, patients who were randomized to methotrexate were advanced to Rinvoq 15 mg or upadacitinib 30 mg once daily monotherapy in a blinded manner based on pre-determined assignment at baseline. The primary endpoint was the proportion of patients who achieved an ACR20 (20% or greater improvement) response at week 14. For the primary endpoint
at week 14, 41% of patients achieved an ACR20 in the methotrexate group vs. 68% of patients in the Rinvoq group.
Study RA-III (NCT02675426) was a 12-week trial in 661 patients with moderately to severely active rheumatoid arthritis who had an inadequate response to traditional disease modifying anti-rheumatic drugs (DMARDs). Patients received Rinvoq 15 mg or upadacitinib 30 mg once daily or placebo added to background traditional DMARD therapy. At week 12, patients who were randomized to
placebo were advanced to Rinvoq 15 mg or upadacitinib 30 mg once daily in a blinded manner based on predetermined assignment at baseline. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 12. For the primary endpoint at week 12, 36% of patients achieved an ACR20 in the placebo group vs. 64% of patients in the Rinvoq group.
Study RA-IV (NCT02629159) was a 48-week trial in 1,629 patients with moderately to severely active rheumatoid arthritis who had an inadequate response to methotrexate. Patients received Rinvoq 15 mg once daily, active comparator, or placebo added to background methotrexate. From week 14, non-responding patients on Rinvoq 15 mg could be rescued to active comparator in a blinded manner, and nonresponding patients on active comparator or placebo could be rescued to Rinvoq 15 mg in a blinded manner. At week 26, all patients randomized to placebo were switched to Rinvoq 15 mg once daily in a blinded manner. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 12 versus placebo. For the primary endpoint at week 12, 36% of patients achieved an ACR20 in the placebo group vs. 71% of patients in the Rinvoq group.
Study RA-V (NCT02706847) was a 12-week trial in 499 patients with moderately to severely active rheumatoid arthritis who had an inadequate response or intolerance to biologic DMARDs. Patients received Rinvoq 15 mg or upadacitinib 30 mg once daily or placebo added to background traditional DMARD therapy. At week 12, patients who were randomized to placebo were advanced to Rinvoq 15 mg or upadacitinib 30 mg once daily in a blinded manner based on pre-determined assignment at baseline. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 12. For the primary endpoint at week 12, 28% of patients achieved an ACR20 in the placebo group vs. 65% of patients in the Rinvoq group.
Treatment with Rinvoq 15 mg, alone or in combination with traditional DMARDs, resulted in a
greater improvement in physical function at week 12/14 compared to all comparators as measured by HAQ-DI (Health Assessment Questionnaire Disability Index).
In all studies except for Study RA-V, patients receiving Rinvoq 15 mg had greater improvement from baseline in physical component summary (PCS) score, mental component summary (MCS) scores, and in all 8 domains of the Short Form Health Survey (SF-36) compared to placebo in combination with traditional DMARDs or methotrexate monotherapy at week 12/14.
Fatigue was assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACITF) in Studies RA-I, RA-III, and RA-IV. Improvement in fatigue at week 12 was observed in patients treated with Rinvoq 15 mg compared to patients on placebo in combination with traditional DMARDs or methotrexate

monotherapy.

Psoriatic Arthritis

The efficacy and safety of Rinvoq 15 mg once daily were assessed in two Phase 3 randomized, double-blind, multicenter, placebo-controlled studies in patients 18 years of age or older with moderately to severely active psoriatic arthritis. All patients had active psoriatic arthritis for at least 6 months based upon the Classification Criteria for Psoriatic Arthritis (CASPAR), at least 3 tender joints and at least 3 swollen joints, and active plaque psoriasis or history of plaque psoriasis.

Although another dose has been studied, the recommended dose of Rinvoq is 15 mg once daily for psoriatic arthritis.

Study PsA-I (NCT03104400) was a 24-week trial in 1,705 patients with moderately to severely active psoriatic arthritis who had an inadequate response or intolerance to at least one non -biologic (i.e., traditional) DMARD. Patients received Rinvoq 15 mg or upadacitinib 30 mg once daily, adalimumab, or placebo, alone or in combination with background traditional DMARDs. At week 24, all patients randomized to placebo were switched to Rinvoq 15 mg or upadacitinib 30 mg once daily in a blinded manner. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 12. The ACR20 response at week 12 was 71% in the Rinvoq 15 mg group vs. 36% in the placebo group.

Study PsA-II (NCT03104374) was a 24-week trial in 642 patients with moderately to severely active psoriatic arthritis who had an inadequate response or intolerance to at least one biologic DMARD. Patients received Rinvoq 15 mg or upadacitinib 30 mg once daily or placebo, alone or in combination with background traditional DMARDs. At week 24, all patients randomized to placebo were switched to Rinvoq 15 mg or upadacitinib 30 mg once daily in a blinded manner. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 12. The ACR20 response at week 12 was 57% in the Rinvoq 15 mg group vs. 24% in the placebo group.

Atopic Dermatitis

The approval of Rinvoq® (upadacitinib) for the treatment of refractory, moderate to severe atopic dermatitis in patients 12 years of age and older whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable, was based on data from 3 randomized, double-blind, phase 3 trials (Measure Up 1 [ClinicalTrials.gov Identifier: NCT03569293]; Measure Up 2 [ClinicalTrials.gov Identifier: NCT03607422]; AD Up [ClinicalTrials.gov Identifier: NCT03568318]), which evaluated the efficacy and safety of upadacitinib 15mg and 30mg orally once daily in a total of 2584 patients 12 years of age and older with moderate to severe atopic dermatitis who were candidates for systemic therapy. In Measure Up 1 and 2, upadacitinib was evaluated as monotherapy; in AD Up, upadacitinib was evaluated in combination with topical corticosteroids.

The coprimary endpoints for all of the trials were the proportion of patients achieving at least a 75% improvement in the Eczema Area Severity Index (EASI 75) and a validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD) of clear or almost clear (0/1) at week 16.

Findings from the Measure Up 1 and Measure Up 2 trials showed that a significantly greater proportion of patients treated with upadacitinib 15mg and 30mg achieved EASI 75 and vIGA-AD 0/1 at week 16 compared with placebo. Moreover, a significantly higher proportion of patients treated with upadacitinib met key secondary endpoints including EASI 90, EASI 100, and at least a 4-point improvement in the Worst Pruritus Numerical Rating Scale (NRS) at week 16. Patients treated with upadacitinib reported a clinically meaningful reduction in itch as early as day 2.

In the AD Up trial, 65% and 77% of patients treated with upadacitinib 15mg and 30mg plus topical corticosteroids, respectively, achieved EASI 75 at week 16 compared with 26% of patients in the placebo plus topical corticosteroids arm. Moreover, 40% and 59% of patients treated with upadacitinib 15mg and 30mg plus topical corticosteroids, respectively, achieved vIGA-AD 0/1 at week 16 compared with 11% of patients who received placebo plus topical corticosteroids. Upadacitinib also met all key secondary endpoints: EASI 90, EASI 100, and at least a 4-point improvement in the Worst Pruritus NRS at week 16.

Ulcerative Colitis

The approval of Rinvoq® (upadacitinib) for the treatment of adults with moderately to severely active ulcerative colitis was based on data from 2 randomized, double-blind, placebo-controlled phase 3 induction studies, U-ACHIEVE (ClinicalTrials.gov Identifier: NCT02819635) and U-ACCOMPLISH (ClinicalTrials.gov Identifier: NCT03653026), and one phase 3 maintenance study, U-ACHIEVE (ClinicalTrials.gov Identifier: NCT02819635).

The studies evaluated the efficacy and safety of upadacitinib in 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. In the induction studies, patients were randomly assigned to receive upadacitinib 45mg or placebo once daily for 8 weeks. In the maintenance study, patients were re-randomized to receive upadacitinib 15mg, 30mg, or placebo once daily for up to 52 weeks.

Findings from all studies showed that a greater proportion of patients treated with upadacitinib achieved clinical remission (defined using the modified Mayo Score) compared with those who received placebo (primary endpoint):

- U-ACHIEVE Induction: 26% vs 5% at week 8 (P <.001);
- U-ACCOMPLISH Induction: 33% vs 4% at week 8 (P <.001);
- U-ACHIEVE Maintenance: 42% (15mg) and 52% (30mg) vs 12% at week 52 (P <.001). Results from the maintenance study also showed that 57% and 68% of patients receiving upadacitinib 15mg or 30mg, respectively, achieved corticosteroid free remission, defined as clinical remission (per modified Mayo Score) and corticosteroid free for at least 90 days immediately preceding week 52 among patients who achieved clinical remission at the end of the induction treatment, compared with 22% of patients on placebo.

Additionally, the studies met all ranked secondary endpoints including clinical response per modified Mayo Score, endoscopic improvement (defined as endoscopic subscore of 1 or less), and histologic endoscopic mucosal improvement (defined as an endoscopic subscore of 1 or less and Geboes score of 3.1 or less).

The safety profile of upadacitinib was consistent with that seen in previous studies across indications. There were no new safety risks identified. Adverse reactions reported during induction or maintenance included upper respiratory tract infections, increased blood creatine phosphokinase, acne, neutropenia, elevated liver enzymes, and rash.

Ankylosing Spondylitis

The approval of Rinvoq® (upadacitinib) for the treatment of adults with active ankylosing spondylitis was based on efficacy and safety data from the SELECT-AXIS 1 and SELECT-AXIS 2 studies. The Phase 2/3 SELECT-AXIS 1 clinical trial evaluated Rinvoq in patients who were naïve to biologic disease-modifying antirheumatic drugs (DMARDs) and had an inadequate response or intolerance to at least two nonsteroidal anti-inflammatory drugs (NSAIDs). The Phase 3 SELECT-AXIS 2 trial evaluated Rinvoq in patients who had an inadequate response or intolerance to one or two biologic DMARDs.

In both trials, a significantly greater proportion of patients who received Rinvoq 15 mg achieved a SpondyloArthritis International Society (ASAS) 40% response criteria (ASAS40) response (51% and 44.5%, respectively) compared to those receiving placebo (26% and 18.2%, respectively) at Week 14. Additionally, clinical responses were reported by Week 4 in the SELECT-AXIS 2 trial. Overall, the safety profile observed in patients with active AS treated with Rinvoq 15 mg was consistent with the safety profile observed in patients with RA and PsA. Rinvoq has a second-line indication in AS, behind the TNF inhibitors.

Non-radiographic Axial Spondyloarthritis

The efficacy and safety of RINVOQ 15 mg once daily were assessed in a randomized, doubleblind, multicenter, placebo-controlled trial in patients 18 years of age or older with active nonradiographic axial spondyloarthritis. Trial nr-axSpA (NCT04169373) was a 52-week placebo controlled trial in 314 patients (of which 313 patients received study treatment) with active nonradiographic axial spondyloarthritis with an inadequate response to at least two NSAIDs or intolerance to or contraindication for NSAIDs. Patients must have had objective signs of inflammation indicated by elevated C-reactive protein (CRP) (defined as > upper

limit of normal), and/or sacroiliitis on magnetic resonance imaging (MRI), and no definitive radiographic evidence of structural damage on sacroiliac joints. Patients had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4, and a Patient's Assessment of Total Back Pain score ≥ 4 based on a 0 – 10 numerical rating scale (NRS) at the Screening and Baseline Visits. At baseline, approximately 29.1% of the patients were on a concomitant cDMARD. 32.9% of the patients had an inadequate response or intolerance to bDMARD therapy. Patients received RINVOQ 15 mg once daily or placebo. The primary endpoint was the proportion of patients achieving an Assessment of SpondyloArthritis international Society 40 (ASAS40) response at Week 14. In Trial nr-axSpA, a significantly greater proportion of patients treated with RINVOQ 15 mg achieved an ASAS40 response compared to placebo at Week 14.

Crohn's Disease
The approval of Rinvoq (upadacitinib) for Crohn's disease was supported by data from two Phase 3 induction trials, U-EXCEED (NCT03345836) and U-EXCEL (NCT03345849), and the Phase 3 U-ENDURE (NCT03345823) maintenance trial. Across all three studies, significantly more patients treated with Rinvoq achieved the co-primary endpoints of clinical remission and endoscopic response at Week 12 and Week 52 versus placebo. In the two induction studies, 36% and 46% of patients treated with Rinvoq 45 mg achieved clinical remission (defined as a Crohn's Disease Activity Index [CDAI] of less than 150) at 12 weeks, respectively, compared to 18% and 23% of patients receiving placebo. Additionally, in the maintenance trial, 42% and 55% of patients treated with Rinvoq 15 mg and 30 mg achieved clinical remission at 52 weeks, respectively, compared to 14% of patients receiving placebo. In addition, among patients taking corticosteroids at baseline, a higher proportion of patients treated with Rinvoq achieved corticosteroid-free remission compared to placebo at 52 weeks. In the U-ENDURE trial, approximately 75% of patients had previously failed biologics, and a significant number of patients failed more than one biologic. Overall, the safety profile observed in all three trials was consistent with the known safety profile for Rinvoq in other indications and included upper respiratory tract infections, anemia, fever, acne, herpes zoster, and headache.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Rinvoq (Upadacitinib) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Rinvoq (Upadacitinib) include: Known hypersensitivity to upadacitinib or any of the excipients, patients with active, serious infection, including localized infections, use with live vaccines, absolute lymphocyte count (ALC) less than 500/mm3, absolute neutrophil count (ANC) less than 1000 cells/mm3, or hemoglobin less than 8 g/dL, patients at risk for thrombosis. Coadministration of RINVOQ with strong CYP3A4 inducers is not recommended, and not recommended in patients with severe hepatic impairment.

OTHER SPECIAL CONSIDERATIONS:
Rinvoq (upadacitinib) has a Black Box Warning for serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis.
Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving Rinvoq.

- If a serious infection develops, interrupt Rinvoq until the infection is controlled.
- Prior to starting Rinvoq, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting Rinvoq.
- Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative.
- Lymphoma and other malignancies have been observed in patients treated with Rinvoq.
- Thrombosis, including deep vein thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated with Janus kinase inhibitors used to treat inflammatory conditions

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not

HCPCS CODE	DESCRIPTION
N/A	

AVAILABLE DOSAGE FORMS:
Rinvoq TB24 15mg, 30mg, 45mg

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Diagnosis Required Medical Information Age Restriction Quantity FDA Approved Uses Background References	Q3 2023
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Duration of Approval Contraindications/Exclusions/Discontinuation Other Special Considerations Available Dosage Forms References	Q4 2022
REVISION- Notable revisions: Diagnosis Required Medical Information Age Restrictions Quantity FDA-Approved Uses Background	Q3 2022
REVISION- Notable revisions: Required Medical Information Prescriber Requirements Quantity FDA-Approved Uses Appendix	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file