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| **Clinical Policy Title:** | upadacitinib |
| **Policy Number:** | RxA.745 |
| **Drug(s) Applied:** | Rinvoq® |
| **Original Policy Date:** | 04/18/2022 |
| **Last Review Date:** | 04/18/2022 |
| **Line of Business Policy Applies to:** | All lines of business |

## Background

**Rheumatoid Arthritis (RA)**
Rinvoq® is a Janus kinase (JAK) inhibitor 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 of Rinvoq® in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

**Psoriatic Arthritis (PsA)**
Rinvoq® is indicated for the treatment of adults with adults with active psoriatic arthritis who have had an inadequate response or intolerance to one or more 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.

**Atopic Dermatitis (AD)**
Rinvoq® is 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: Rinvoq® is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants.

## Dosing Information

| Drug Name | Indication | Dosing Regimen | Maximum Dose |
|---|---|---|---|
| upadacitinib (Rinvoq®) | RA, PsA | 15 mg orally once daily<br>Can be used as monotherapy or in combination with methotrexate (MTX) or other non biologic DMARDs.<br>*For use in adults who have had an inadequate response or intolerance to one or more TNF | 15 mg/day |

| Dosing Information | | | |
|---|---|---|---|
| **Drug Name** | **Indication** | **Dosing Regimen** | **Maximum Dose** |
| | | blockers | |
| upadacitinib (Rinvoq®) | AD | **Pediatric Patients:**<br>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.<br><br>**Adults:**<br>65 Years of Age and Older: Recommended dosage is 15 mg once daily.<br><br>**Severe renal impairment** (CrCl less than 30 mL/minute): The recommended dose is 15 mg orally daily. | **Pediatric Patients:**<br>30 mg/day orally<br><br>**Adults:**<br>15 mg once daily |

## Dosage Forms

- upadacitinib (Rinvoq®): Tablets, extended release: 15 mg and 30 mg

## Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

**I. Initial Approval Criteria**

**A. Rheumatoid Arthritis** (must meet all):

1. Diagnosis of Rheumatoid Arthritis (RA);
2. Age ≥ 18 years of age;
3. Prescribed by or in consultation with a rheumatologist;
4. Trial and failure of a ≥ 3 months of at least one conventional systemic therapy (methotrexate [MTX], sulfasalazine, leflunomide, hydroxychloroquine) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   *Exception: If one biologic DMARD that is FDA-approved for rheumatoid arthritis has been previously tried, then trial of a conventional systemic agent is not required;
5. Trial and failure of a ≥ 3 months of at least one (1) TNF inhibitor (Cimzia®, Humira®, Simponi®/ Simponi Aria, Enbrel®) , unless contraindicated or clinically significant affects are experienced;

6. Dose does not exceed 15 mg (one tablet) per day.

**Approval Duration**
**Commercial:** 12 months
**Medicaid:** 12 months

**B. Psoriatic Arthritis** (must meet all):

1. Diagnosis of PsA;
2. Age ≥ 18 years of age;
3. Prescribed by or in consultation with a dermatologist or a rheumatologist;
4. Trial and failure of a ≥ 3 months of at least one (1) TNF inhibitor (Cimzia®, Humira®, Simponi®/ Simponi Aria, Enbrel®) , unless contraindicated or clinically significant affects are experienced;
5. Dose does not exceed 15 mg (one tablet) per day.

**Approval Duration**
**Commercial:** 12 months
**Medicaid:** 12 months

**C. Atopic Dermatitis** (must meet all):

1. Diagnosis of refractory, moderate to severe atopic dermatitis;
2. Age ≥ 12 years of age;
3. Prescribed by or in consultation with a dermatologist;
4. Member meets one of the following (a or b);
   a. Trial and failure of at least one (1) systemic agent (e.g. corticosteroids, azathioprine, methotrexate, mycophenolate mofetil, or cyclosporine) at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;
   b. Trial and failure of Dupixent at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;
   *Exception: If one biologic DMARD that is FDA approved for atopic dermatitis has been previously tried (e.g, Dupixent, Adbry) , then trial of a systemic agent is not required;
c. Request meets one of the following (a or b):
   a. Age 65 years of age and older: Dose does not exceed 15 mg per day;
   b. Age 12 years and less than 65 years & weighing at least 40 kg: Dose does not exceed 30 mg orally once daily.

**Approval Duration**
**Commercial:** 12 months
**Medicaid:** 12 months

## II. Continued Therapy Approval

**A. All Indications in Section I** (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed one of the following (a or b):
   a. RA, PsA: Dose does not exceed 15 mg (one tablet) per day;
   b. AD (i or ii)**:**
      i. Age 65 years and older: Dose does not exceed 15 mg per day;
      ii. Age 12 years of age and less than 65 years & weighing at least 40 kg: Dose does not exceed 30 mg orally once daily.

**Approval Duration**

**Commercial:** 12 months
**Medicaid:** 12 months

## III. Appendices

**APPENDIX A: Abbreviation/Acronym Key**

RA: Rheumatoid Arthritis
PsA: Psoriatic Arthritis
AD: Atopic Dermatitis
TNF: Tumor Necrosis Factor
DMARDs: Disease-Modifying Antirheumatic Drugs
FDA: Food and Drug Administration
TB: Tuberculosis
JAK: Janus kinase
MTX: methotrexate
PUVA: psoralen plus ultraviolet A light

**APPENDIX B: Therapeutic Alternatives**

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| azathioprine (Azasan®, Imuran®) | **RA:** 1 mg/kg/day orally once daily or divided twice daily | 2.5 mg/kg/day |
| d-penicillamine (Cuprimine®) | **RA (off-label)**<br>Initial dose: 125 or 250 mg orally once daily<br>Maintenance dose: 500 – 750 mg/day orally once daily | 1,500 mg/day |
| cyclosporine (Sandimmune®, Neoral®) | **RA:** 2.5 – 4 mg/kg/day orally divided twice daily | RA: 4 mg/kg/day |
| hydroxychloroquine (Plaquenil®) | **RA (off-label)**<br>Initial dose: 400 – 600 mg/day orally once daily<br>Maintenance dose: 200 – 400 mg/day orally once daily | 600 mg/day |
| leflunomide (Arava®) | **RA:** 100 mg orally once daily for 3 days, then 20 mg orally once daily | 20 mg/day |
| methotrexate | **RA:** 7.5 mg/week orally, subcutaneously, or intramuscularly or 2.5 mg orally every 12 hours for 3 doses/week | 30 mg/week |
| Ridaura® | **RA:** 6 mg orally once daily or 3 mg orally twice daily | 9 mg/day (3 mg Three times daily) |
| sulfasalazine (Azulfidine®) | **RA:** 2 g/day orally in divided doses | RA: 3 g/day |
| **Biologic DMARDs** | | |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| Humira® | **RA:** Some patients with RA not receiving concomitant methotrexate may benefit from increasing the frequency to 40 mg every Week or 80 mg every other week<br><br>**PsA:** 40 mg subcutaneously every other week | 40 mg every other week |
| Cosentyx® | **PsA:** <u>With loading dose:</u><br>150 mg subcutaneously at week 0, 1, 2, 3, and 4, followed by 150 mg subcutaneously every 4 weeks<br><u>Without loading dose:</u><br>150 mg subcutaneously every 4 weeks<br>If a patient continues to have active psoriatic arthritis, consider a dosage of 300 mg every 4 weeks.<br>Pediatric Patients 2 years and older: Recommended dosage is administered by subcutaneously injection at weeks 0,1 ,2,3, and 4 and every 4 weeks after:<br>For patients weighing ≥ 15 kg and < 50 kg the dose is 75 mg.<br>For patients weighing ≥ 50 kg the dose is 150 mg. | PsA: 300 mg every 4 weeks |
| infliximab (Remicade®), Renflexis®, Avsola®, Inflectra® | **PsA:** <u>Initial dose:</u><br>5 mg/kg intravenously at weeks 0, 2 and 6<br><u>Maintenance dose:</u><br>5 mg/kg intravenously every 8 weeks<br><br>**RA:** In conjunction with MTX<br><u>Initial dose:</u><br>3 mg/kg intravenously at weeks 0, 2 and 6<br><u>Maintenance dose:</u><br>3 mg/kg intravenously every 8 weeks<br>Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks | PsA: 5 mg/kg every 8 weeks<br><br>RA:10 mg/kg every 4 weeks |
| Simponi Aria® | **PsA, RA:** <u>Initial dose:</u><br>2 mg/kg intravenously at weeks 0 and 4<br><u>Maintenance dose:</u><br>2 mg/kg intravenously every 8 weeks | PsA, RA: 2 mg/kg every 8 weeks |
| Skyrizi® | **PsA:** 150 mg subcutaneously at Week 0, Week 4, and every 12 weeks thereafter. | 150 mg every 12 weeks |
| Otezla® | **PsA:** <u>Initial dose:</u><br>Day 1: 10 mg orally in morning<br>Day 2: 10 mg orally in morning and 10 mg orally in evening<br>Day 3: 10 mg orally in morning and 20 mg orally in evening<br>Day 4: 20 mg orally in morning and 20 mg orally in evening<br>Day 5: 20 mg orall in morning and 30 mg orally in evening<br><u>Maintenance dose:</u><br>Day 6 and thereafter: 30 mg orally twice daily | 60 mg/day |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| Xeljanz® / Xeljanz® oral Solution, Xeljanz® XR | Xeljanz®: **PsA, RA**: 5 mg orally twice daily<br>PsA: use in combination with nonbiologic disease-modifying antirheumatic drugs<br>RA: monotherapy or use in combination with nonbiologic disease-modifying antirheumatic drugs<br><br>Xeljanz® XR: **PsA, RA**: 11 mg orally once daily | Xeljanz®: PsA<br>RA<br>Xeljanz® / Xeljanz® oral Solution: 5 mg or 5 ml twice daily<br><br>Xeljanz® XR: 11 mg/day |
| | **RA, PsA:**<br><u>Initial dose:</u><br>400 mg subcutaneously at 0, 2, and 4 weeks.<br><br><u>Maintenance dose:</u><br>200 mg subcutaneously every other week (or 400 mg subcutaneously every 4 weeks) | 400 mg<br>every 4 weeks |
| Kevzara® | **RA:** 200 mg subcutaneously once every two weeks | 200 mg/2 Weeks |
| Enbrel® | **RA:** 25 mg subcutaneously twice weekly or 50 mg subcutaneously once weekly<br><br>**PsA**: Adult: 50 mg once weekly with or without methotrexate (MTX) | **RA, PsA:** Adults 50 mg/week subcutaneously. Induction therapy for psoriatic arthritis should not exceed 100 mg/week with no more than 50 mg/dose subcutaneously. |
| Orencia® | **RA, PsA:** Intravenous: weight-based dose at weeks 0, 2, and 4, followed by every 4 weeks<br><br>Weight < 60 kg: 500 mg per dose<br>Weight 60 to 100 kg: 750 mg per dose<br>Weight > 100 kg: 1,000 mg per dose<br><br>Subcutaneous: 125 mg once weekly<br>RA and PsA: Patients switching from intravenous use to subcutaneous use, administer first subcutaneous dose instead of next scheduled intravenous dose.<br>(For RA: Prior to the first subcutaneously dose, may administer an optional loading dose as a single intravenous infusion as per body weight categories above.)<br>For PsA: Intravenous loading dose is not recommended | **RA, PsA:** Intravenous: 1,000 mg every 4 weeks<br><br>Subcutaneous: 125 mg/week |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| Inflectra® | **RA:** In conjunction with MTX<br>Initial dose:<br>3 mg/kg intravenously at weeks 0, 2 and 6<br>Maintenance dose:<br>3 mg/kg intravenously every 8 weeks<br>Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks<br><br>**PsA:** Initial dose:<br>5 mg/kg intravenously at weeks 0, 2 and 6<br>Maintenance dose:<br>5 mg/kg intravenously every 8 weeks | **RA:** 10 mg/kg every 4 weeks<br><br>**PsA:** 5 mg/kg every 8 weeks |
| Simponi® | **RA, PsA:** 50 mg subcutaneously once monthly | RA, PsA :50 mg/month |
| Tremfya® | **PsA:** Initial dose:<br>100 mg subcutaneously at weeks 0 and 4<br><br>Maintenance dose:<br>100 mg subcutaneously every 8 weeks<br>Can be used alone or in combination with conventional DMARD e.g. methotrexate | 100 mg every 8 weeks |
| Taltz® | **PsA:** Initial dose:<br>160 mg (two 80 mg injections) subcutaneously<br><br>Maintenance dose:<br>80 mg subcutaneously every 4 weeks. | **PsA:** 80 mg every 4 weeks |
| Stelara® | **PsA:** 45 mg subcutaneously at weeks 0 and 4, followed by 45 mg every 12 weeks | **PsA:** 45 mg every 12 weeks |
| Actemra® | **RA**: Intravenous: 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg every 4 weeks based on clinical response.<br>Subcutaneous:<br>Weight < 100 kg: 162 mg every other week, followed by an increase to every week based on clinical response.<br>Weight ≥ 100 kg: 162 mg every week. | Intravenous: 800 mg every 4 weeks<br><br>Subcutaneous: 162 mg every week |
| Kineret® | **RA:** 100 mg subcutaneously once daily | 100 mg/day |
| Olumiant® | **RA:** 2 mg orally once daily | 2 mg/day |

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.
*Off-label

**APPENDIX C: Contraindications*/Boxed Warnings**

- Contraindication(s):
  - Hypersensitivity to upadacitinib or any of the excipients.

*Contraindications listed reflect direct statements made in the manufacturer's package insert; for additional uses, warnings, and precautions, please refer to clinical guidelines.

- Boxed Warning(s):
  - Increased risk of serious bacterial, fungal, viral, and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Interrupt treatment with Rinvoq® if serious infection occurs until the infection is controlled.
  - Higher rate of all-cause mortality, including sudden cardiovascular death with another Janus kinase (JAK) inhibitor vs. tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients.
  - Malignancies have occurred in patients treated with Rinvoq®. Higher rate of lymphomas and lung cancers with another JAK inhibitor vs. TNF blockers in RA patients.
  - Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) with another JAK inhibitor vs. TNF blockers in RA patients.
  - Thrombosis has occurred in patients treated with Rinvoq®. Increased incidence of pulmonary embolism, venous and arterial thrombosis with another JAK inhibitor vs. TNF blockers.

**APPENDIX D: General Information**

- PsA: According to the 2018 American College of Rheumatology and National Psoriasis Foundation guidelines, TNF inhibitors or oral small molecules (e.g., methotrexate, sulfasalazine, cyclosporine, leflunomide, apremilast) are preferred over other biologics (e.g., interleukin-17 inhibitors or interleukin-12/23 inhibitors) for treatment-naïve disease. TNF inhibitors are also generally recommended over oral small molecules as first-line therapy unless disease is not severe, member prefers oral agents, or TNF inhibitor therapy is contraindicated.
- Lactation: Advise not to breastfeed.
- Hepatic Impairment: Rinvoq® is not recommended in patients with severe hepatic impairment.

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| Review/Revision History | Review/Revision Date | P&T Approval Date |
|---|---|---|
| RxA.592.Biologic_DMARDs was last reviewed and updated on 01/05/2022 and archived on 04/18/2022. For details, please refer to RxA.592.Biologics_DMARDs. | 02/16/2022 | 04/18/2022 |
| Drug specific policy for Inflectra was created based on RxA.592.Biologics_DMARDs:<br>1. Background: Updated to include new indication Atopic Dermatitis.<br>2. Dosing Information, Indication: : Updated to include new indication PsA.<br>3. Dosing Information, Indication: Updated to include new indication AD.<br>4. Dosage Forms: Updated to include new dosage form, Tablets, extended-release: 30 mg.<br>5. Initial Approval Criteria, I.A.6: Updated dosing criteria from Dose does not exceed maximum dose indicated in background to Dose does not exceed 15 mg (one tablet) per day.<br>6. Initial Approval Criteria, I.B: Updated to include approval criteria for indication, Psoriatic Arthritis.<br>7. Initial Approval Criteria, I.C: Updated to include approval criteria for indication, Atopic Dermatitis.<br>8. Continued Therapy Approval, II.A.3: Updated to include new dosing criteria for indication PsA & RA.<br>9. Appendix A: Updated to include abbreviations PUVA.<br>10. Appendix B, Drug Name: Updated to include | 02/16/2022 | 4/18/2022 |

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| brand-name therapeutic alternative of other biological DMARDs.<br>11. Appendix C, Contraindications: Updated contraindication from None reported to Hypersensitivity to upadacitinib or any of the excipients.<br>12. Disclaimer about contraindications "Contraindications listed reflect statements made in the manufacturer's package insert..." was added to Appendix C.<br>13. Appendix C, Boxed Warnings: Updated to include following new boxed warning (a or b)<br>a. Higher rate of all-cause mortality, including sudden cardiovascular death with another Janus kinase (JAK) inhibitor vs. tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients.<br>b. Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) with another JAK inhibitor vs. TNF blockers in RA patients.<br>14. Appendix D, General Information: Updated to remove information regarding Rheumatoid Arthritis.<br>15. References were reviewed and updated. | | |