BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

NURTEC™ ODT (rimegepant)
QULIPTA™ (atogepant)
REYVOW™ (lasmiditan)
UBRELVY™ (ubrogepant)
ZAVZPRET™ (zavegepant)
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

NURTEC ODT (rimegepant)

- **Criteria for initial therapy:** Nurtec ODT (rimegepant) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is **ONE** of the following:
     a. A Neurologist

b. A licensed professional **and ONE** of the following:
   i. Is prescribing in consultation with a Neurologist or Pain Specialist
   ii. Is certified as a headache specialist by the United Council for Neurologic Subspecialties (UCNS)
   iii. Has earned a Certificate in Added Qualifications (CAQ) in Headache Medicine from the National Headache Foundation

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following: (see Definitions section)
   a. **Acute migraine** of moderate to severe headache pain intensity

   b. **Episodic migraine (moderate to severe headache pain intensity)** defined as 4 to 14 headache days per month of which at least 4 were migraine days

4. Individual does **NOT** have chronic migraine defined as headache occurring 15 or more days a month for more than 3 months, which has the features of migraine headache on at least 8 days a month

5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual meets **ONE** of the following:
   a. When request is for **acute (abortive) treatment of migraine only:**
      i. Documented failure (used for at least 2-months), contraindication per FDA label, intolerance, or is not a candidate for **at least TWO** triptan drugs (naratriptan, rizatriptan, sumatriptan, and zolmitriptan)
      ii. For individuals with 4 or more headache days per month, **ONE** of the following:
         1. Currently treated with **ONE** of the following agents for migraine prevention:
            a. A beta-blocker (atenolol, metoprolol, nadolol, propranolol, or timolol)
            b. An anticonvulsant (topiramate, divalproex sodium, or sodium valproate)
            c. An antidepressant (amitriptyline or venlafaxine)
         2. Documented failure (used for at least 2-months), contraindication per FDA label, intolerance, or not a candidate for **ONE** of the following agents for migraine prevention
            a. A beta-blocker (atenolol, metoprolol, nadolol, propranolol, or timolol)
            b. An anticonvulsant (topiramate, divalproex sodium, or sodium valproate)
            c. An antidepressant (amitriptyline or venlafaxine)
   b. When request is for **prevention of episodic migraine only:**
      i. **TWO** agents for prevention selected from any of the following classes (must not be within the same class)**:**
         1. A beta-blocker (atenolol, metoprolol, nadolol, propranolol, or timolol)
         2. An anticonvulsant (topiramate, divalproex sodium, or sodium valproate)
         3. An antidepressant (amitriptyline or venlafaxine)
   c. When request is for **acute (abortive) treatment AND prevention of episodic migraine**:
      i. **At least ONE** triptan drugs (naratriptan, rizatriptan, sumatriptan, and zolmitriptan)
      ii. **At least TWO** agents for prevention selected from any of the following classes (must not be within same class):
         1. A beta-blocker (atenolol, metoprolol, nadolol, propranolol, or timolol)

2. An anticonvulsant (topiramate, divalproex sodium, or sodium valproate)
3. An antidepressant (amitriptyline or venlafaxine)

7. **For acute migraine treatment**: Agent will not be used in combination with another CGRP antagonist or inhibitor used for acute (abortive) migraine treatment (e.g., Nurtec ODT, Ubrelvy, Zavzpret)

8. **For episodic migraine prevention**: Agent will not be used in combination with another CGRP antagonist or inhibitor used for the preventative treatment of migraines (e.g., Aimovig, Ajovy, Emgality, Nurtec ODT, Qulipta, Vyepti)

9. Will not be used in patient with end-stage renal disease (CrCl < 15 mL/min)

10. Will not be used in patient with severe hepatic impairment (Child-Pugh C)

11. There are no significant interacting drugs such as:
    a. Strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, others)
    b. Strong or moderate CYP3A4 inducers (e.g., rifampin, phenytoin, St. John's Wort, phenobarbital, primidone, others)
    c. P-gp or BCRP inhibitors (e.g., amiodarone, clarithromycin, cyclosporine, itraconazole, verapamil, others)

Initial approval duration: 12 months
When used for acute treatment only: no more than 8 ODT per month
When used for Episodic Migraine prevention only: no more than 15 ODT per month
Per labeling safety concerns: no more than 18 ODT per 30 days

- **Criteria for continuation of coverage (renewal request):** Nurtec ODT (rimegepant) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by **ONE** of the following:
    a. A Neurologist
    b. A licensed professional **and ONE** of the following:
        i. Is prescribing in consultation with a Neurologist or Pain Specialist
        ii. Is certified as a headache specialist by the United Council for Neurologic Subspecialties (UCNS)
        iii. Has earned a Certificate in Added Qualifications (CAQ) in Headache Medicine from the National Headache Foundation

2. Individual's condition has responded while on therapy with response defined as **ALL** of the following:
    a. Achieved and maintains a reduction of moderate or severe headache pain to no pain and absence of the most bothersome symptom (such as photophobia, phonophobia, or nausea)
    b. Significant reduction in emergency room or urgent care visits for acute migraine treatment
    c. No evidence of disease progression

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual does **NOT** have chronic migraine (see Definitions section)

6. **For acute migraine treatment**: Agent will not be used in combination with another CGRP antagonist or inhibitor used for acute (abortive) migraine treatment (e.g., Nurtec ODT, Ubrelvy, Zavzpret)

7. **For episodic migraine prevention**: Agent will not be used in combination with another CGRP antagonist or inhibitor used for the preventative treatment of migraines (e.g., Aimovig, Ajovy, Emgality, Nurtec ODT, Qulipta, Vyepti)

8. Will not be used in patient with end-stage renal disease (CrCl < 15 mL/min)

9. Will not be used in patient with severe hepatic impairment (Child-Pugh C)

10. There are no significant interacting drugs
    a. Strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, other)
    b. Strong or moderate CYP3A4 inducers (e.g., rifampin, phenytoin, St. John's Wort, phenobarbital, primidone, other)
    c. P-gp or BCRP inhibitors (e.g., amiodarone, clarithromycin, cyclosporine, itraconazole, verapamil, other)

Renewal duration: 12 months
When used for acute treatment only: no more than 8 ODT per month
When used for Episodic Migraine prevention only: no more than 15 ODT per month
Per labeling safety concerns: no more than 18 ODT per 30 days

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

QULIPTA (atogepant)

- **Criteria for initial therapy:** Qulipta (atogepant) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is **ONE** of the following:
    a. A Neurologist
    b. A licensed professional **and ONE** of the following:
        i. Is prescribing in consultation with a Neurologist or Pain Specialist
        ii. Is certified as a headache specialist by the United Council for Neurologic Subspecialties (UCNS)

iii. Has earned a Certificate in Added Qualifications (CAQ) in Headache Medicine from the National Headache Foundation

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following: (see Definitions section)
   a. **Episodic migraine (moderate to severe headache pain intensity)** defined as 4 to 14 headache days per month, of which at least 4 were migraine days
   b. **Chronic migraine of moderate to severe headache pain intensity)** defined as 15 or more headache days a month for more than 3 months, of which 8 days per month meet the features of migraine with or without aura

4. Individual does **NOT** have **ANY** of the following:
   a. Persistent daily headache
   b. Trigeminal autonomic cephalgia (cluster headache)
   c. Painful cranial neuropathy

5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Documented failure (used for at least 2-months), contraindication per FDA label, intolerance, or not a candidate for **at least TWO** agents for prevention selected from any of the following classes (must not be within same class):
   a. A beta-blocker (atenolol, metoprolol, nadolol, propranolol, or timolol)
   b. An anticonvulsant (topiramate, divalproex sodium, or sodium valproate)
   c. An antidepressant (amitriptyline or venlafaxine)

7. Agent will not be used in combination with another CGRP antagonist or inhibitor used for the preventative treatment of migraines (e.g., Aimovig, Ajovy, Emgality, Nurtec ODT, Qulipta, Vyepti)

8. Individual requesting recommended dose of 60 mg once daily for chronic migraine **does not have ANY** of the following:
   a. Use of strong CYP3A4 inhibitors (such as itraconazole, others)
   b. Use of strong, moderate, or weak CYP3A4 inducers (such as rifampin, dexamethasone, topiramate, others)
   c. Severe renal impairment and end-stage renal disease (CrCl less than 30 mL/min)

9. Will not be used in patient with severe hepatic impairment (Child-Pugh C)

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Qulipta (atogepant) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by **ONE** of the following:
   a. A Neurologist

b. A licensed professional **and ONE** of the following:
   i. Is prescribing in consultation with a Neurologist or Pain Specialist
   ii. Is certified as a headache specialist by the United Council for Neurologic Subspecialties (UCNS)
   iii. Has earned a Certificate in Added Qualifications (CAQ) in Headache Medicine from the National Headache Foundation

2. Individual's condition has responded while on therapy with response defined as **ALL** of the following:
   a. Achieved and maintains at least a 50% reduction in number of monthly migraine days from baseline
   b. Achieved and maintains a reduction in number of monthly headache days
   c. Achieved and maintains a reduction in the number of days of use of acute migraine-specific medications from baseline
   d. Significant reduction in emergency room or urgent care visits for acute migraine treatment

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual does **NOT** have persistent daily headache, trigeminal autonomic cephalgia (cluster headache) or painful cranial neuropathy

6. Agent will not be used in combination with another CGRP antagonist or inhibitor used for the preventative treatment of migraines (e.g., Aimovig, Ajovy, Emgality, Nurtec ODT, Qulipta, Vyepti)

7. Individual requesting recommended dose of 60 mg once daily for chronic migraine **does not have ANY** of the following:
   a. Use of strong CYP3A4 inhibitors (such as itraconazole, others)
   b. Use of strong, moderate, or weak CYP3A4 inducers (such as rifampin, dexamethasone, topiramate, others)
   c. Severe renal impairment and end-stage renal disease (CrCl less than 30 mL/min)

8. Will not be used in patient with severe hepatic impairment (Child-Pugh C)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

REYVOW (lasmiditan)

- **Criteria for initial therapy:** Reyvow (lasmiditan) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is **ONE** of the following:
    a. A Neurologist
    b. A licensed professional **and ONE** of the following:
        i. Is prescribing in consultation with a Neurologist or Pain Specialist
        ii. Is certified as a headache specialist by the United Council for Neurologic Subspecialties (UCNS)
        iii. Has earned a Certificate in Added Qualifications (CAQ) in Headache Medicine from the National Headache Foundation

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **abortive treatment of acute migraine** of moderate to severe headache pain intensity

4. Individual does not have more than 4 migraine attacks in a 30-day period

5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual meets **ALL** the following:
    a. Documented failure (used for at least 2-months), contraindication per FDA label, intolerance, or is not a candidate for **TWO** triptan drugs (naratriptan, rizatriptan, sumatriptan, and zolmitriptan)
    b. Documented failure (used for at least 2-months), contraindication per FDA label, intolerance, or is not a candidate for **BOTH** of the following:
        i. Nurtec
        ii. Ubrelvy
    c. For individuals with 4 or more headache days per month, **ONE** of the following:
        i. Currently treated with **ONE** of the following agents for migraine prevention:
            1. A beta-blocker (atenolol, metoprolol, nadolol, propranolol, or timolol)
            2. An anticonvulsant (topiramate, divalproex sodium, or sodium valproate)
            3. An antidepressant (amitriptyline or venlafaxine)
        ii. Documented failure (used for at least 2-months), contraindication per FDA label, intolerance, or not a candidate for **ONE** of the following agents for migraine prevention
            1. A beta-blocker (atenolol, metoprolol, nadolol, propranolol, or timolol)
            2. An anticonvulsant (topiramate, divalproex sodium, or sodium valproate)
            3. An antidepressant (amitriptyline or venlafaxine)

7. Agent will not be used in combination with another CGRP antagonist or inhibitor used for acute (abortive) migraine treatment (e.g., Nurtec ODT, Ubrelvy, Zavzpret)

8. Will not be used for the preventive treatment of migraine

9. Will not be used in patient with severe hepatic impairment (Child-Pugh Class C)

10. Will not be used with drugs that are substrates for P-gp or BCRP substrates such as dabigatran, digoxin, fexofenadine, rosuvastatin, sulfasalazine, others

Initial approval duration:
12 months; no more than 1 tab per 24 hours and no more than 4 tabs per 30-day period

- **Criteria for continuation of coverage (renewal request):** Reyvow (lasmiditan) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met (**samples are not considered for continuation of therapy**):

1. Individual continues to be seen by **ONE** of the following:
    a. A Neurologist
    b. A licensed professional **and ONE** of the following:
        i. Is prescribing in consultation with a Neurologist or Pain Specialist
        ii. Is certified as a headache specialist by the United Council for Neurologic Subspecialties (UCNS)
        iii. Has earned a Certificate in Added Qualifications (CAQ) in Headache Medicine from the National Headache Foundation

2. Individual's condition has responded while on therapy with response defined as **ALL** of the following:
    a. Achieved and maintains a reduction of moderate or severe headache pain to no pain and absence of the most bothersome symptom (such as, photophobia, phonophobia, or nausea)
    b. No evidence of disease progression
    c. Significant reduction in emergency room or urgent care visits for acute migraine treatment

3. Agent will not be used in combination with another CGRP antagonist or inhibitor used for acute (abortive) migraine treatment (e.g., Nurtec ODT, Ubrelvy, Zavzpret)

4. Uses **at least ONE** migraine prevention agent

5. Will not be used for the preventive treatment of migraine

6. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

7. Will not be used in patient with severe hepatic impairment (Child-Pugh Class C)

8. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
    a. Central nervous system depression, including dizziness and sedation
    b. Serotonin syndrome

9. Will not be used with drugs that are substrates for P-gp or BCRP substrates such as dabigatran, digoxin, fexofenadine, rosuvastatin, sulfasalazine, others

Renewal duration:
12 months; no more than 1 tab per 24 hours and no more than 4 tabs per 30-day period

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

UBRELVY (ubrogepant)

- **Criteria for initial therapy:** Ubrelvy (ubrogepant) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is **ONE** of the following:
    a. A Neurologist
    b. A licensed professional **and ONE** of the following:
        i. Is prescribing in consultation with a Neurologist or Pain Specialist
        ii. Is certified as a headache specialist by the United Council for Neurologic Subspecialties (UCNS)
        iii. Has earned a Certificate in Added Qualifications (CAQ) in Headache Medicine from the National Headache Foundation

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **abortive treatment of acute migraine** of moderate to severe headache pain intensity

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual meets **BOTH** of the following:
    a. Documented failure (used for at least 2-months), contraindication per FDA label, intolerance, or is not a candidate for **TWO** triptan drugs (naratriptan, rizatriptan, sumatriptan, and zolmitriptan)
    b. For individuals with 4 or more headache days per month, **ONE** of the following:
        i. Currently treated with **ONE** of the following agents for migraine prevention:
            1. A beta-blocker (atenolol, metoprolol, nadolol, propranolol, or timolol)
            2. An anticonvulsant (topiramate, divalproex sodium, or sodium valproate)
            3. An antidepressant (amitriptyline or venlafaxine)
        ii. Documented failure (used for at least 2-months), contraindication per FDA label, intolerance, or not a candidate for **ONE** of the following agents for migraine prevention
            1. A beta-blocker (atenolol, metoprolol, nadolol, propranolol, or timolol)
            2. An anticonvulsant (topiramate, divalproex sodium, or sodium valproate)
            3. An antidepressant (amitriptyline or venlafaxine)

6. There are **NO** FDA-label contraindications, such as concurrent use with a strong CYP3A4 inhibitor (e.g., itraconazole, ketoconazole, clarithromycin, other)

7. Agent will not be used in combination with another CGRP antagonist or inhibitor used for acute (abortive) migraine treatment (e.g., Nurtec ODT, Ubrelvy, Zavzpret)

8. Will not be used for the preventive treatment of migraine

9. Will not be used in a patient with end-stage renal disease (CrCl < 15 mL/min)

10. Will not be used with strong CYP3A4 inducers (e.g., rifampin, phenytoin, St. John's Wort, other)

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Ubrelvy (ubrogepant) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by **ONE** of the following:
    a. A Neurologist
    b. A licensed professional **and ONE** of the following:
        i. Is prescribing in consultation with a Neurologist or Pain Specialist
        ii. Is certified as a headache specialist by the United Council for Neurologic Subspecialties (UCNS)
        iii. Has earned a Certificate in Added Qualifications (CAQ) in Headache Medicine from the National Headache Foundation

2. Individual's condition has responded while on therapy with response defined as **ALL** of the following:
    a. Achieved and maintains a reduction of moderate or severe headache pain to no pain and absence of the most bothersome symptom (such as photophobia, phonophobia, or nausea)
    b. No evidence of disease progression
    c. Significant reduction in emergency room or urgent care visits for acute migraine treatment

3. Will not be used for the preventive treatment of migraine

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Agent will not be used in combination with another CGRP antagonist or inhibitor used for acute (abortive) migraine treatment (e.g., Nurtec ODT, Ubrelvy, Zavzpret)

6. Will not be used in patient with end-stage renal disease (CrCl < 15 mL/min)

7. Will not be used with strong CYP3A4 inducers (e.g., rifampin, phenytoin, St. John's Wort, other)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of Non-Cancer Medications**

  2. **Off-Label Use of Cancer Medications**

ZAVZPRET (zavegepant)

- **Criteria for initial therapy:** Zavzpret (zavegepant) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is **ONE** of the following:
     a. A Neurologist
     b. A licensed professional **and ONE** of the following:
        i. Is prescribing in consultation with a Neurologist or Pain Specialist
        ii. Is certified as a headache specialist by the United Council for Neurologic Subspecialties (UCNS)
        iii. Has earned a Certificate in Added Qualifications (CAQ) in Headache Medicine from the National Headache Foundation

  2. Individual is 18 years of age or older

  3. Individual has a confirmed diagnosis of **abortive treatment of acute migraine** of moderate to severe headache pain intensity

  4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

  5. Individual meets **ALL** the following:
     a. Documented failure (used for at least 2-months), contraindication per FDA label, intolerance, or is not a candidate for **TWO** triptan drugs (naratriptan, rizatriptan, sumatriptan, and zolmitriptan)
     b. Documented failure (used for at least 2-months), contraindication per FDA label, intolerance, or is not a candidate for **BOTH** of the following:
        i. Nurtec
        ii. Ubrelvy
     c. For individuals with 4 or more headache days per month, **ONE** of the following:
        i. Currently treated with **ONE** of the following agents for migraine prevention:
           1. A beta-blocker (atenolol, metoprolol, nadolol, propranolol, or timolol)
           2. An anticonvulsant (topiramate, divalproex sodium, or sodium valproate)
           3. An antidepressant (amitriptyline or venlafaxine)
        ii. Documented failure (used for at least 2-months), contraindication per FDA label, intolerance, or not a candidate for **ONE** of the following agents for migraine prevention
           1. A beta-blocker (atenolol, metoprolol, nadolol, propranolol, or timolol)
           2. An anticonvulsant (topiramate, divalproex sodium, or sodium valproate)
           3. An antidepressant (amitriptyline or venlafaxine)

6. Agent will not be used in combination with another CGRP antagonist or inhibitor used for acute (abortive) migraine treatment (e.g., Nurtec ODT, Ubrelvy, Zavzpret)

7. Will not be used for the preventive treatment of migraine

8. Will not be used in a patient with renal impairment (CrCl < 30 mL/min)

9. Will not be used in a patient with severe hepatic impairment (Child-Pugh Class C)

10. Will not be used with drugs that inhibit organic anion transporting polypeptide 1B3 (OATP1B3) or sodium taurocholate co-transporting polypeptide (NTCP) transporters (e.g., rifampin)

11. Will not be used with drugs that induce OATP1B3 or NTCP transporters

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Zavzpret (zavegepant) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by **ONE** of the following:
    a. A Neurologist
    b. A licensed professional **and ONE** of the following:
        i. Is prescribing in consultation with a Neurologist or Pain Specialist
        ii. Is certified as a headache specialist by the United Council for Neurologic Subspecialties (UCNS)
        iii. Has earned a Certificate in Added Qualifications (CAQ) in Headache Medicine from the National Headache Foundation

2. Individual's condition has responded while on therapy with response defined as **ALL** of the following:
    a. Achieved and maintains a reduction of moderate or severe headache pain to no pain and absence of the most bothersome symptom (such as, photophobia, phonophobia, or nausea)
    b. No evidence of disease progression
    c. Significant reduction in emergency room or urgent care visits for acute migraine treatment

3. Uses **at least ONE** migraine prevention agent

4. Will not be used for the preventive treatment of migraine

5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Agent will not be used in combination with another CGRP antagonist or inhibitor used for acute (abortive) migraine treatment (e.g., Nurtec ODT, Ubrelvy, Zavzpret)

7. Will not be used for the preventive treatment of migraine

8. Will not be used in a patient with renal impairment (CrCl < 30 mL/min)
9. Will not be used in a patient with severe hepatic impairment (Child-Pugh Class C)
10. Will not be used with drugs that inhibit organic anion transporting polypeptide 1B3 (OATP1B3) or sodium taurocholate co-transporting polypeptide (NTCP) transporters (e.g., rifampin)
11. Will not be used with drugs that induce OATP1B3 or NTCP transporters

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**
2. **Off-Label Use of Cancer Medications**

Description:

Nurtec ODT (rimegepant) is a calcitonin gene-related peptide (CGRP) receptor antagonist indicated for the acute treatment of migraine with or without aura in adults and for preventive treatment of episodic migraine in adults. Reyvow (lasmiditan) is a serotonin (5-HT) 1F receptor agonist indicated for the acute treatment of migraine with or without aura in adults.

Ubrelvy (ubrogepant) is a CGRP receptor antagonist indicated for the acute treatment of migraine with or without aura. It is not indicated for the preventive treatment of migraine.

Qulipta (atogepant) is a CGRP receptor antagonist indicated for the preventive treatment of episodic migraine in adults.

Zavzpret (zavegepant) is a CGRP receptor antagonist indicated for the acute treatment of migraine with or without aura in adults. It is not indicated for the preventive treatment of migraine. The safety of treating more than 8 migraines in a 30-day period has not been established.

The CGRP pathway is important in pain modulation, and CGRP has been observed to increase during a migraine. CGRP is a 37-amino acid peptide and functions as a neurotransmitter in the central and peripheral nervous system and as a vasodilator. The involvement of CGRP in migraine was suggested in the 1980s. Since then, new agents affecting the CGRP pathway have been developed and studied. Some approaches focused on small molecule CGRP receptor antagonists to be used to treat migraine attacks, or monoclonal antibodies to be used for migraine prevention.

Lasmiditan binds with high affinity to the 5-HT1F receptor. Lasmiditan presumably exerts its therapeutic effects in the treatment of migraine through agonist effects at the 5-HT1F receptor; however, the precise mechanism is unknown.

Migraine is a common episodic disorder, the hallmark of which is a disabling headache generally associated with nausea, and/or light and sound sensitivity. Migraine with aura refers to the occurrence of transient visual, sensory, language, or motor disturbance that is followed by a migraine headache. The exact mechanisms of migraine are unknown, but currently it is believed to initiate from a primary neuronal dysfunction that leads to a sequence of intracranial and extracranial changes accounting for migraine, including the four phases of premonitory symptoms, aura, headache and post-drome. Specifically, activation of the trigeminovascular system, cortical spreading depression, and neuronal sensitization all seem to play a role.

Pharmacologic therapies for migraine can be categorized broadly into agents used for treatment once symptoms have started ("acute" or "abortive" medications) and agents used to decrease the frequency or severity of migraines ("preventive" or "prophylactic" therapies).

Selection of medication for acute treatment is directed by the severity of the attacks, presence of associated nausea and vomiting, treatment setting, and patient-specific factors. Abortive treatments are usually more effective if they are given early in the course of the headache (within in the first hour if possible). A 2015 guideline assessment published by the American Headache Society lists the following medications as Level A (established as effective) for acute migraine treatment: all triptan drugs, NSAIDs (naproxen, ibuprofen, aspirin, diclofenac), combination of sumatriptan and naproxen, acetaminophen/aspirin/caffeine, acetaminophen (for acute treatment of non-incapacitating migraine), and dihydroergotamine nasal spray.

Prophylactic headache treatment is indicated if the headaches are frequent, long lasting, or account for a significant amount of total disability. A number of drug classes are used for the prevention of migraine. Medications that are effective in controlled trials include: beta blockers (metoprolol, propranolol, and timolol); anticonvulsants (valproate, divalproex, and topiramate); and antidepressants (amitriptyline and venlafaxine).

Outcomes of clinical trials of acute treatment of migraine commonly include relief of symptoms including pain, nausea/vomiting, photophobia and phonophobia; pain freedom; freedom from the most bothersome symptom (MBS); pain relief; and sustained symptom response.

The Migraine Disability Assessment (MIDAS) is a brief, 7-item, self-administered questionnaire designed to quantify headache-related disability. Respondents answer five questions about activity limitations in the past 3 months due to migraine including (1) missed work or school days, (2) missed household chores days, (3) missed non-work activity days, and days at work or school (4) plus days of household chores (5) where productivity was reduced by half or more. Two additional questions about the number of headaches and average pain level associated with headaches over the past 3 months are not used in deriving the MIDAS score, but they are for use by the respondent's clinician.

The MIDAS score is the sum of the number of days reported for each of the five questions. Respondents with a MIDAS score of 0-5 are rated as having little or no disability, 6-10 as having mild disability, 11-20 as having moderate disability, and 21 or greater as having severe disability.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Migraine day:

- Any calendar day in which the patient experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache)
- A qualified migraine is defined as migraine with or without aura, lasting ≥ 30 minutes that meets at least one of the following:
  - ≥ 2 of the following pain features: unilateral, throbbing, moderate to severe, or exacerbated with exercise/physical activity
  - > 1 of the following associated non-pain features: nausea and or vomiting, or both photophobia, and phonophobia
- Any calendar day on which acute migraine-specific medication was used is counted as a migraine day

Treatment considerations:

- There are no strict definitions for the precise frequency or duration of migraine headaches that would prompt preventive therapy
- Migraine prevention therapy may be indicated for those with migraine headaches that are frequent (ex. as ≥ 4 headaches/month) or long-lasting (ex. ≥12 hours) and those that cause significant disability or diminished quality of life
- The goals of preventive therapy are to reduce the frequency, severity, and duration of headaches, to improve treatment responsiveness of therapies for acute attacks, prevent progression or transformation of episodic migraine to chronic migraine and to improve overall function or reduce the risk of neurologic impairment

Episodic migraine:

- Individual with migraine who has between 1 to 14 headache days per month, of which at least 4 were migraine days

Chronic migraine:

- Chronic migraine is defined as headache occurring 15 or more days a month for more than 3 months, which 8 days per month meet the features of migraine with or without aura.
- Some patients with an episodic migraine pattern (<15 headache days a month) transition to a chronic migraine pattern (≥15 headache days a month), a transition that has been called "transformation" and "chronification"
- Features of migraine headache include:
  - Lasts 4-72 hours **AND** has at least 2 of the following 4 characteristics:
    - Unilateral, pulsating, moderate or severe pain intensity, aggravates or causes avoidance of routine physical activity
  - **AND** associated with at least one of the following during the headache:
    - Nausea and/or vomiting or photophobia and phonophobia.
- The management of chronic migraine should focus on prophylactic therapy and avoidance of acute headache medication overuse

Pain freedom:

- A ***reduction in severity*** of headache from mild, moderate or severe pain ***at baseline to none*** at a given follow-up time point

Freedom from most bothersome symptoms (MBS):

- ***Total absence*** of nausea/vomiting, photophobia or phonophobia at a given follow-up time point

Pain relief:

- ***Having mild to no pain*** at a given follow-up time point

Sustained symptom response after 2-hours:

- Those with an initial response that is sustained at subsequent follow-up time points ***without*** the use of repeat dosing or rescue medications

Migraine Disability Assessment (MIDAS):

Please answer the following questions about **ALL** of the headaches you have had over the last 3 months. Select zero if you did not have the activity in the last 3 months.

1. _____ On how many days in the last 3 months did you miss work or school because of your headaches?

2. _____ How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.)

3. _____ On how many days in the last 3 months did you not do household work (such as housework, home repairs and maintenance, shopping, caring for children and relatives) because of your headaches?

4. _____ How many days in the last 3 months was your productivity in household work reduced by half of more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.)

5. _____ On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?

6. Total number of days (from questions 1 through 5): _____

Answer the following for your provider:

1. _____ On how many days in the last 3 months did you have a headache? (If a headache lasted more than 1 day, count each day.)

2. _____ On a scale of 0 - 10, on average how painful were these headaches? (where 0 = no pain at all, and 10 = pain as bad as it can be.)

MIDAS Grade	Definition	MIDAS Score
I	Little or No disability	0-5
II	Mild disability	6-10
III	Moderate disability	11-20
IV	Severe disability	21+

AHS Consensus 2021
Patients with migraine should be considered for preventive treatment in **any** of the following situations:
• Attacks significantly interfere with patients' daily routines despite acute treatment
• Frequent attacks as described in following table
• Contraindication to, failure, or overuse of acute treatments, with overuse defined as follows: a. Ten or more days per month for ergot derivatives, triptans, opioids, combination analgesics, and a combination of drugs from different classes that are not individually overused b. Fifteen or more days per month for nonopioid analgesics, acetaminophen, and NSAIDs

• Adverse events with acute treatments
• Patient preference

AHS Consensus 2021		
Identifying Patients for Preventive Treatment		
Prevention should be:	Headache days/month	Degree of MIDAS required
Offered	6 or more	None
	4 or more	Some
	3 or more	Severe
Considered	4 or 5	None
	3	Some
	2	Moderate

Migraine Severity:

- **Mild Pain Level / Pain Score**
  - Does not interfere with most activities and is easy to manage both physically and psychologically. Individual able to adapt to these levels of pain with low doses of medication (e.g., acetaminophen), dietary changes, or bed rest.

- **Moderate Uncomfortable Pain Level / Pain Score**
  - Interferes with many activities of daily living and requires changes to daily lifestyle to manage pain symptoms. Migraine pain is more noticeable but is not incapacitating.
- **Severe Pain Level / Pain Score**
  - Individual is no longer able to engage in normal activities and seeks stronger medications to help improve ability to function independently.

Identification of headache type: migraine, tension, or cluster			
	Migraine	**Tension**	**Cluster**
Location	Unilateral	Bilateral	Supraorbital/temporal
Pain intensity[1]	Moderate to severe	Mild to moderate	Severe
Duration	4–72 hours	30 minutes to 7 days	15–180 minutes
Characterization of pain	Pulsing	Pressure/squeezing	Boring/stabbing
Sensitivity to light/sound	One or both may be present	Both are absent or only one is present	No
Nausea/vomiting	One or both may be present	No	One or both may be present
Aggravated by routine activity	Yes	No	No
Aura	May be present	No	No
Associated symptoms	None	None	Miosis, ptosis, rhinorrhea

1 Pain intensity
• Mild—Patient is aware of a headache but is able to continue daily routine with minimum alterations.
• Moderate—The headache inhibits daily activities; migraine pain is more noticeable but is not incapacitating.
• Severe—The headache is incapacitating such that patient is no longer able to engage in normal activities.

2013 Canadian Headache Society (CHS) – medications for acute migraine:

2013 Canadian Headache Society (CHS) Summary of Recommendations*		
Recommended for Use in Episodic Migraine** (Use)		
	Recommendation	
Drug	**Recommendation Strength**	**Quality of Evidence**
Almotriptan	Strong	High
Eletriptan	Strong	High
Frovatriptan	Strong	High
Naratriptan	Strong	High
Rizatriptan	Strong	High
Sumatriptan	Strong	High
Zolmitriptan	Strong	High
Aspirin	Strong	High
Diclofenac	Strong	High
Ibuprofen	Strong	High
Naproxen	Strong	High
Acetaminophen	Strong	High
Domperidone	Strong	Low
Metoclopramide	Strong	Moderate
Dihydroergotamine	Weak	Moderate
Ergotamine	Weak, not recommended for routine use	Moderate
Opioid containing compounds	Weak, not recommended for routine use	Low
Tramadol containing compounds	Weak, not recommended for routine use	Moderate
Not Recommended for Use in Episodic Migraine (Do not use***)**		
Butalbital containing compounds	Strong	Low
Butorphanol	Strong	Low
*Utilizing Grading of Recommendations Assessment, Development and Evaluation (GRADE) Criteria **Migraine with headache on less than 15 days a month *** Except under exceptional circumstances		

Metoclopramide strongly recommended for use when necessary

Abortive (symptomatic) treatment of acute migraine:

- Simple analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, triptans, antiemetics, calcitonin gene-related peptide (CGRP) antagonists (remigepant, ubrogepant, zavegepant), lasmiditan, and dihydroergotamine

Non-Calcitonin gene-related peptide (Non-CGRP) preventative (episodic or chronic) migraine agent(s):

- Beta-blocker: atenolol, metoprolol, nadolol, propranolol, or timolol
- Antidepressant: amitriptyline or venlafaxine
- Anticonvulsant: topiramate, divalproex sodium, or sodium valproate

Botulinum toxin injection:

- Treatment of chronic migraine:
  - Botox (onabotulinumtoxinA)

CGRP related agents:

- Preventive treatment of episodic or chronic migraine:
  - Vyepti (eptinezumab-jjmr)
  - Aimovig (erenumab)

  - Ajovy (fremanezumab-vfrm)
  - Emgality (galcanezumab) – also used in cluster headache
- Preventive treatment of episodic migraine:
  - Qulipta (atogepant)
  - Nurtec ODT (rimegepant)
- Acute (abortive) treatment of migraine:
  - Oral:
    - Nurtec ODT (rimegepant)
    - Ubrelvy (ubrogepant)
  - Nasal:
    - Zavzpret (zavegepant)

Serotonin (5-HT) 1F receptor agonist:

- Acute (abortive) treatment of migraine
  - Reyvow (lasmiditan)

Resources:

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