Oral CGRP Antagonists

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the criteria is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. The criteria will require the use of the health plan's preferred products, Nurtec ODT (rimegepant) and Reyvow (lasmiditan), before the use of the targeted product, Ubrelvy (ubrogepant), unless there are clinical circumstances that exclude the use of the preferred products. The criteria will require a trial of at least two different triptan medications unless there is a contraindication that would prohibit a trial of these drugs, due to the high evidence of triptan efficacy in the acute treatment of migraine headaches.

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Nurtec ODT (rimegepant) and Ubrelvy (ubrogepant) are both indicated for the acute treatment of migraine with or without aura in adults.

Limitations of Use
Nurtec ODT (rimegepant) and Ubrelvy (ubrogepant) are not indicated for the preventive treatment of migraine.

POLICY

Must meet BOTH the Preferred Drug Plan Design and Criteria for Initial Approval when applicable.

Preferred Drug Plan Design

A. Criteria for initial approval for Ubrelvy (ubrogepant) will only apply when one of the following criteria are met:
    1. The patient has had an inadequate response to treatment, intolerable adverse event, or has a contraindication to therapy with BOTH preferred products, Nurtec ODT and Reyvow
    2. The patient is currently receiving therapy with Ubrelvy, excluding when Ubrelvy is obtained as samples or via manufacturer's patient assistance programs, and experiencing a positive therapeutic outcome

Criteria for Initial Approval

A. Nurtec ODT (rimegepant) and Ubrelvy (ubrogepant) may be considered **medically necessary** for the acute treatment of moderate to severe migraines when the following criteria is met:
    1. The member is 18 years of age or older
    2. The member has a diagnosis of migraine, with or without aura, according to the International Classification of Headache Disorders (ICHD-3) [see Appendices A & B]
    3. The requested medication is prescribed by, or in consultation with, a headache specialist or neurologist
    4. The member has had at least a 30 day trial of and experienced an inadequate treatment response (i.e., little to no relief of moderate/severe migraine symptoms) or intolerance to at least TWO of the preferred generic triptan medications, naratriptan (Amerge), sumatriptan (Imitrex), and rizatriptan (Maxalt); OR the member is currently receiving a positive therapeutic outcome on the requested medication through health insurance (excludes obtainment as samples or via manufacturer's patient assistance programs); OR the member has a contraindication that would prohibit a trial of any triptan medication
    5. The patient has been evaluated for and does not have medication overuse headache (see Appendix C)
    6. Other conditions or aggravating factors that are contributing to the development of migraine headaches are being treated when applicable (e.g., dental or jaw problems, muscle tension, depression, fibromyalgia, sleep disorders and smoking)

    Approval will be for **6 months**

Continuation of Therapy

A. Nurtec ODT (rimegepant) and Ubrelvy (ubrogepant) may be considered **medically necessary** for the continuation of acute treatment of moderate to severe migraines when ALL of the following criteria are met:
    1. The member is 18 years of age or older
    2. The member has a diagnosis of migraine, with or without aura, according to the International Classification of Headache Disorders (ICHD-3) [see Appendices A & B]
    3. The requested medication is prescribed by, or in consultation with, a headache specialist or neurologist
    4. The member has experienced a positive clinical response to therapy (e.g., reduction in headache pain severity, relief from other migraine symptoms [photophobia, phonophobia or nausea], sustained headache pain relief, and improved ability to function normally).
    5. The member continues to be evaluated for and does not have medication overuse headache (see Appendix C)
    6. Other conditions or aggravating factors that are contributing to the development of migraine headaches are being treated when applicable (e.g., dental or jaw problems, muscle tension, depression, fibromyalgia, sleep disorders and smoking)

    Approval will be for **12 months**

Dosage and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

The recommended dose of Nurtec ODT is 75 mg taken orally, as needed. The maximum dose in a 24-hour period is 75 mg. The safety of treating more than 15 migraines in a 30-day period has not been established.

The recommended dose of Ubrelvy is 50 mg or 100 mg taken orally, as needed. If needed, a second dose may be taken at least 2 hours after the initial dose. The maximum dose in a 24-hr period is 200 mg. The safety of treating more than 8 migraines in a 30-day period has not been established.

Quantity Limits

Drug	Standard Benefit Allowance	Post-Limit PA Quantity Limit
Nurtec ODT 75 mg tablet	8 tablets / 30 days	15 tablets / 30 days
Ubrelvy 50 mg tablet	8 tablets / 30 days	16 tablets / 30 days
Ubrelvy 100 mg tablet	8 tablets / 30 days	16 tablets / 30 days

Note: Ubrelvy is supplied in unit-dose packets (each packet contains 1 tablet) in boxes containing 6 packets, 8 packets, 10 packets, 12 packets, or 30 packets. It is the discretion of the dispensing pharmacy to fill quantities per package size up to these quantity limits. In such cases the filling limit and day supply may be less than what is indicated.

Post-Limit Prior Authorization Criteria

A. Additional quantities of Nurtec ODT (rimegepant) and Ubrelvy (ubrogepant) may be considered **medically necessary** for members who meet the criteria for initial approval or continuation of therapy above when ALL of the following criteria are met:
   1. Medication overuse headache has been considered and ruled out
   2. The requested medication is prescribed by, or in consultation with, a headache specialist or neurologist
   3. The member is currently using a migraine prophylactic agent and continues to experience multiple (i.e. ≥ 4) migraine headache days per month OR has a documented intolerance, FDA labeled contraindication, or hypersensitivity to all the migraine prophylactic agents.
   4. The member will continue using a migraine prophylactic agent or has a clinical reason to avoid all migraine prophylactic agents.

   Approval will be for **12 months** for quantities up to 16 tablets per 30 days for Ubrelvy and 15 tablets per 30 days for Nurtec ODT. Any request for quantities above those limits is considered **not medically necessary**.

APPENDICES

Appendix A

International Classification of Headache Disorders (ICHD-3 beta) diagnostic criteria for migraine headache without aura

   A. At least five attacks fulfilling criteria B-D
   B. Headache attacks lasting 4-72 hours (when untreated or unsuccessfully treated)
   C. Headache has at least two of the following four characteristics:
      1. Unilateral location
      2. Pulsating quality
      3. Moderate or severe pain intensity
      4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

D. During headache at least one of the following:
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

Appendix B

International Classification of Headache Disorders (ICHD-3 beta) diagnostic criteria for migraine headache with aura

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
    1. Visual
    2. Sensory
    3. Speech and/or language
    4. Motor
    5. Brainstem
    6. Retinal
C. At least three of the following six characteristics:
    1. At least one aura symptom spready gradually over ≥ 5 minutes
    2. Two or more aura symptoms occur in succession
    3. Each individual aura symptom lasts 5-60 minutes
    4. At least one aura symptom is unilateral
    5. At least one aura symptom is positive
    6. The aura is accompanied, or followed within 60 minutes, by headache
F. Not better accounted for by another ICHD-3 diagnosis.

Appendix C

International Classification of Headache Disorders (ICHD-3 beta) diagnostic criteria for medication-overuse headache

A. Headache present on >15 days/month
B. Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache
C. Headache has developed or markedly worsened during medication overuse
D. One of the following:
    1. Regular intake of ergotamine on ≥10 days per month for >3 months
    2. Regular intake of one or more triptans, in any formulation, on ≥10 days per month for >3 months
    3. Regular intake of Aspirin on ≥15 days per month for >3 months
    4. Regular intake of one or more NSAIDs other than acetylsalicylic acid on ≥15 days per month for >3 months
    5. Regular intake of one or more opioids on ≥10 days per month for >3 months
    6. Regular intake of acetaminophen on ≥15 days per month for >3 months
    7. Regular intake of one or more combination analgesic medications on ≥10 days/month for >3 months
    8. Regular intake of any combination of ergotamine, triptans, simple analgesics, NSAIDs and/ or opioids on ≥10 days per month for >3 months
    9. Regular intake of any combination of ergotamine, triptans, simple analgesics, NSAIDs and/or opioids1 on a total of ≥10 days per month for >3 months without overuse of any single drug or drug class alone
    10. Regular overuse, on ≥10 days per month for >3 months, of one or more medications other than those described above, taken for acute or symptomatic treatment of headache

CLINICAL RATIONALE

Nurtec ODT (rimegepant) and Ubrelvy (ubrogepant) are both small molecule calcitonin gene-related peptide (CGRP) receptor antagonists that work by reversibly blocking CGRP receptors, thereby inhibiting the biologic activity of the CGRP neuropeptide. CGRP is a vasodilating neuropeptide that is released upon activation of the trigeminal system and plays a key role in the pathophysiology of migraine headaches. The circulating level of CGRP results in increased pain, phonophobia, photophobia, and nausea.

Overview of Guidelines/Position Statements

The American Headache Society Position Statement on Integrating New Migraine Treatments into Clinical Practice (2019) recommends that all patients with migraine should be offered a trial of acute treatment and migraine patients who need to use acute treatments on a regular basis should be instructed to limit treatment to an average of 2 headache days per week. Effective acute treatment can reduce the pain, associated symptoms, and disability associated with attacks. Treat at the first sign of pain to improve the probability of achieving freedom from pain and reduce attack-related disability. Acute treatments that the American Headache Society Position Statement considered effective or probably effective are based on a 2015 American Headache Society expert review of evidence from controlled trials.

The American Headache Society Evidence Assessment of Migraine Pharmacotherapies (2015) recommends specific medications within the following classes deemed effective for migraine acute therapy: triptans, ergotamine derivatives, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and combination medications. The American Headache Society Evidence Assessment states that the specific medications – triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan [oral, nasal spray, injectable, transcutaneous patch], zolmitriptan [oral and nasal spray]) and dihydroergotamine (nasal spray, inhaler) are effective. Effective nonspecific medications include acetaminophen, nonsteroidal anti-inflammatory drugs (aspirin, diclofenac, ibuprofen, and naproxen), opioids (butorphanol nasal spray), sumatriptan/naproxen, and the combination of acetaminophen/aspirin/caffeine. The American Headache Society Evidence Assessment, states that although opioids, such as butorphanol, codeine/acetaminophen, and tramadol/ acetaminophen, are probably effective, they are not recommended for regular use. Per the American Headache Society Evidence Assessment, there are many acute migraine treatments for which evidence supports efficacy. Clinicians must consider medication efficacy, potential side effects, and potential medication-related adverse events when prescribing acute medications for migraine.

The American Headache Society Position Statement on Integrating New Migraine Treatments into Clinical Practice (2019) recommends the use of NSAIDs (including aspirin), nonopioid analgesics, acetaminophen, or caffeinated analgesic combinations (e.g., aspirin + acetaminophen + caffeine) for mild-to-moderate attacks and migraine-specific agents (triptans, dihydroergotamine [DHE]) for moderate or severe attacks and mild-to-moderate attacks that respond poorly to NSAIDs or caffeinated combinations. Several different triptans are available on the market with different strengths, dosage forms and routes of administration. The American Headache Society Position Statement recommends choosing a nonoral formulation in patients whose attacks are associated with severe nausea or vomiting or who have trouble swallowing orally administered medications. This includes sumatriptan 3, 4, or 6 mg SC and intranasal and inhaled powder formulations and ketorolac in intranasal and intramuscular (IM) formulations. Dihydroergotamine SC and intranasal spray are alternatives. Nonoral routes of administration should also be considered in patients who do not respond well to traditional oral treatments or experience significant nausea or vomiting early during attacks.

The American Academy of Neurology and the American Headache Society Practice Guideline Update Summary: Acute Treatment of Migraine in Children and Adolescents (2019) states that patients respond differently to the same medication. In adults, failure to respond to 1 triptan does not preclude response to an alternate triptan. Per the American Academy of Neurology and the American Headache Society Practice Guideline Update Summary, in adults who respond to a triptan but have recurrence of their headache within 24 hours, taking a second dose is effective. Also, the American Academy of Neurology and the American Headache Society Practice Guideline Update Summary states that migraine features (severity, associated

symptoms, disability, and most bothersome symptoms) differ among individuals and among different attacks in the same individual. For migraines that rapidly peak in severity or are associated with nausea and vomiting, nonoral forms of treatment may be more effective.

The American Headache Society Position Statement on Integrating New Migraine Treatments into Clinical Practice (2019) states that emerging agents with novel mechanisms of action that have demonstrated efficacy for the acute treatment of migraine include the small molecule CGRP receptor antagonists, ubrogepant and rimegepant, and lasmiditan, a selective serotonin (5-HT1F) receptor agonist. The American Headache Society Position Statement states that unlike triptans and ergotamine derivatives, these novel treatment options do not result in constriction of blood vessels and may have a special role in patients with cardiovascular contraindications to triptans. Patients who have contraindications to the use of triptans or who have failed to respond to or tolerate at least 2 oral triptans, as determined by either a validated acute treatment patient reported outcome questionnaire (e.g., Migraine Treatment Optimization Questionnaire [mTOQ], Migraine Assessment of Current Therapy [Migraine-ACT], Patient Perception of Migraine Questionnaire-Revised [PPMQ-R],Functional Impairment Scale [FIS], Patient Global Impression of Change [PGIC]) or healthcare provider attestation), are eligible for ubrogepant, rimegepant, lasmiditan, or a neuromodulation device.

Per the American Headache Society Position Statement on Integrating New Migraine Treatments into Clinical Practice (2019), 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 (≥ 4 migraine headache days); a contraindication to, failure, or overuse of acute treatments; adverse events with acute treatments; or patient preference. Based on these recommendations, patients requiring treatment for more than 4 migraine headache days per month should be evaluated further for preventive treatment.

For prevention of migraine headache, the American Academy of Neurology and the American Headache Society 2012 guideline update recommendations state that the following medications are established as effective and should be offered for migraine prevention: β-adrenergic blocking agents, metoprolol, propranolol, timolol; and antiepileptic drugs (AEDs), divalproex sodium, topiramate, sodium valproate. Additionally, the following medications are probably effective: antidepressants, amitriptyline, venlafaxine; and β-adrenergic blocking agents, atenolol, nadolol and should be considered for migraine prevention. Efficacy and safety of individual agents, even within the same class of drugs, may vary among patients therefore, if the patient fails one preventive medication, others should be tried as failure of one agent does not rule out success with another one. The Institute for Clinical Systems Improvement (ICSI) headache guidelines state that preventive therapy should be considered for all patients, and the American Academy of Neurology (AAN) guidelines recommend preventive medications when there is either an impact on life and acute therapy is not working or where headache frequency can lead to medication overuse headache. Therefore, patients with migraine headache requesting additional quantities of Nurtec ODT and Ubrelvy must be currently taking prophylactic therapy or are unable to take prophylactic therapy due to an inadequate response, intolerance, or contraindication.

Efficacy

The efficacy of Nurtec ODT for the acute treatment of migraine in adults was established in a randomized, double-blind, placebo-controlled, Phase 3 clinical trial. Patients were randomized to 75 mg of Nurtec ODT (N=732) or placebo (N=734). Patients were instructed to treat a migraine of moderate to severe headache pain intensity. The primary endpoints were pain freedom and most bothersome symptom (MBS) freedom at two hours after dosing. Pain freedom at 2 hours post dose was achieved in 21.2% and 10.9% of patients receiving Nurtec ODT and placebo, respectively ($p < 0.001$). MBS freedom at 2 hours post dose was achieved in 35.1% and 26.8% of patients receiving Nurtec ODT and placebo, respectively ($p = 0.001$).
Nurdec ODT also demonstrated statistical superiority at one hour for pain relief (reduction of moderate or severe pain to no pain or mild pain) and return to normal function. Eighty-six percent of patients treated

with Nurdec ODT did not require rescue medication (e.g., NSAIDS, acetaminophen) within 24 hours post dose.

The efficacy of Ubrelvy for the acute treatment of migraine was demonstrated in two randomized, double-blind, placebo-controlled studies in 1,439 adult patients with a history of migraine. In study 1, patients were randomized to Ubrelvy 50 mg, Ubrelvy 100 mg, or placebo. In study 2, patients were randomized to Ubrelvy 50 mg or placebo. The primary endpoints in both studies were pain freedom at 2 hours post-dose and most bothersome symptom (MBS) freedom at 2 hours post-dose. MBS freedom was defined as the absence of the self-identified MBS (i.e., photophobia, phonophobia, or nausea). In study 1, the percentage of responders who were pain free at 2 hours post-dose was 19.2, 21.2, and 11.8 with Ubrelvy 50 mg ($p = 0.002$ vs. placebo), Ubrelvy 100 mg ($p < 0.001$ vs. placebo), and placebo, respectively. The percentage of responders who were MBS-free at 2 hours post-dose was 38.6, 37.7, and 27.8 with Ubrelvy 50 mg, Ubrelvy 100 mg, and placebo ($p < 0.001$ for both doses vs. placebo). In study 2, the percentage of responders who were pain free at 2 hours post-dose was 21.8 and 14.3 with Ubrelvy 50 mg and placebo, respectively ($p = 0.007$). The percentage of responders who were MBS-free at 2 hours post-dose was 38.9 and 27.4 with Ubrelvy 50 mg and placebo, respectively ($p < 0.001$).

Safety

The most common adverse reaction (≥ 1%) reported in the clinical trial with Nurtec ODT use was nausea. The safety of treating more than 15 migraines per 30-day period has not been established. The use of Nurtec ODT should also be avoided in patients with severe hepatic impairment and end-stage renal disease.

The most common adverse reactions (≥ 2% and greater than placebo) in clinical trials with Ubrelvy use were nausea and somnolence. The safety of treating more than 8 migraines in a 30-day period has not been established. Ubrelvy is contraindicated with concomitant use with strong CYP3A4 inhibitors.

Dosing Limits

Per the American Headache Society Position Statement on Integrating New Migraine Treatments into Clinical Practice (2019), migraine patients who need to use acute treatments on a regular basis should be instructed to limit treatment to an average of 2 headache days per week.

The recommended dose of Nurtec ODT is 75 mg taken orally, as needed. The maximum dose in a 24-hour period is 75 mg. The safety of treating more than 15 migraines in a 30-day period has not been established. The recommended dose of Ubrelvy is 50 mg or 100 mg taken orally. If needed, a second dose may be taken at least 2 hours after the initial dose. The maximum dose in a 24-hour period is 200 mg. The safety of treating more than 8 migraines in a 30-day period has not been established. Dosing modifications should be made for concomitant use of specific drugs and for patients with hepatic or renal impairment.

Ubrelvy is supplied in unit-dose packets (each packet contains 1 tablet) in boxes containing 6 packets, 8 packets, 10 packets, 12 packets, or 30 packets. It is the discretion of the dispensing pharmacy to fill quantities per package size up to these quantity limits. In such cases the filling limit and day supply may be less than what is indicated.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- N/A

REFERENCES

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- Nurtec ODT (rimegepant) [prescribing information]. New Haven, CT: Biohaven Pharmaceuticals Inc; February 2020.
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- Marmura M, Silberstein S, Schwedt T. The Acute Treatment of Migraine in Adults: The American Headache Society Evidence Assessment of Migraine Pharmacotherapies. Headache 2015;55:3-20.
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POLICY HISTORY

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