Oral and Nasal 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 Oral CGRP Antagonists policy is to ensure appropriate selection of patients for therapy based on product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines while steering utilization to the most cost-effective medication within the therapeutic class. For this program, Nurtec ODT (rimegepant), Reyvow (Lasmiditan), Ajovy (fremanezumab), and Emgality (galcanezumab) are the preferred products and will apply to members requesting treatment for an indication that is FDA-approved for the preferred product. The criteria will require the use of all of the preferred products before the use of the targeted products, Ubrelvy (ubrogepant), Qulipta (atogepant), and Zavzpret (zavegepant) unless there are clinical circumstances that exclude the use of all the preferred products, the patient is currently receiving treatment with the non-preferred drug and experience a positive therapeutic outcome, or there is only one preferred product for an indication. 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) is indicated for the acute treatment of migraine with or without aura in adults and for the preventive treatment of episodic migraine in adults.

Ubrelvy (ubrogepant) is indicated for the acute treatment of migraine with or without aura in adults.

Qulipta (atogepant) is indicated for the preventive treatment of migraine in adults.

Zavzpret (zavegepant) is indicated for the acute treatment of migraine with or without aura in adults.

Limitations of Use
Ubrelvy (ubrogepant) and Zavzpret (zavegepant) 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 and continuation of therapy 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

B. Criteria for initial approval and continuation of therapy for Qulipta (atogepant) 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 the preferred products:
        a. Nurtec ODT, Ajovy, AND Emgality for preventative treatment of episodic migraine in adults

        OR

        b. Ajovy AND Emgality for preventative treatment of chronic migraine in adults
    2. The patient is currently receiving therapy with Qulipta, excluding when Qulipta is obtained as samples or via manufacturer's patient assistance programs, and experiencing a positive therapeutic outcome

C. Criteria for initial approval and continuation of therapy for Zavzpret (zavegepant) 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 Zavzpret, excluding when Zavzpret 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 (e.g., naratriptan [Amerge], sumatriptan [Imitrex], rizatriptan [Maxalt], and zolmitriptan [Zomig]); 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**

B. Zavzpret (zavegepant) nasal spray 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 patient has nausea and/or vomiting associated with migraine
4. The requested medication is prescribed by, or in consultation with, a headache specialist or neurologist
5. 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 (e.g., naratriptan [Amerge], sumatriptan [Imitrex], rizatriptan [Maxalt], zolmitriptan [Zomig]) one of which must be an intranasal formulation; 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
6. The patient has been evaluated for and does not have medication overuse headache (see Appendix C)
7. 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**

C. Nurtec ODT (rimegepant) may be considered **medically necessary** for the preventive treatment of episodic migraine in patients 18 years of age and older when ALL the following criteria are met:
1. The patient has a diagnosis of episodic migraine defined as at least 4 and fewer than 15 migraine days per month and fewer than 15 headache days per month on average during the previous 3-month period
2. The patient has had a trial of at least ONE of the listed medications from any of the following migraine prophylactic agent classes and experienced an inadequate response, has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the alternative migraine prophylactic agents, OR is currently receiving treatment with the requested product through insurance (excludes obtainment as samples or via manufacturer's patient assistance programs) and experiencing a positive therapeutic outcome:
    a.) Anticonvulsants (e.g., divalproex, valproate, topiramate)
    b.) Beta blockers (e.g., atenolol, metoprolol, nadolol, propranolol, timolol)
    c.) Antidepressants (e.g., amitriptyline, nortriptyline, venlafaxine)

3. The patient had an adequate trial of one migraine prophylaxis agent as defined by BOTH of the following unless the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the alternative migraine prophylactic agents, OR the patient is currently receiving treatment with the requested product through insurance (excludes obtainment as samples or via manufacturer's patient assistance programs) and experiencing a positive therapeutic outcome:
    a.) The trial length was at least 8 weeks at maximum tolerated dose
    b.) The patient was adherent to the prophylaxis agent during the trial
4. The patient has been evaluated for and does not have medication overuse headache (see Appendix C)
5. Other conditions or aggravating factors that are contributing to the development of episodic migraine headaches are being treated when applicable (e.g. dental or jaw problems, muscle tension, depression, fibromyalgia, sleep disorders and smoking)
6. The requested medication will not be used in combination with another CGRP antagonist (e.g., Vyepti, Aimovig, Emgality, Ajovy, Ubrelvy)

Approval will be for **6 months**

D. Qulipta (atogepant) may be considered **medically necessary** for the preventive treatment of **chronic migraine** in patients 18 years of age and older when ALL of the following criteria are met:
1. The patient has a diagnosis of chronic migraine defined as a headache occurring on 15 or more days per month for more than 3 months, which, on at least 8 days per month, has features of a migraine headache
2. The patient has had a trial of at least TWO of the listed medications from any of the following migraine prophylactic agent classes and or has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the alternative migraine prophylactic agents, OR is currently receiving treatment with the requested product through insurance (excludes obtainment as samples or via manufacturer's patient assistance programs) and experiencing a positive therapeutic outcome:
    a.) Anticonvulsants (e.g., divalproex sodium, sodium valproate, topiramate)
    b.) Beta blockers (e.g., atenolol, metoprolol, nadolol, propranolol, timolol)
    c.) Antidepressants (e.g., amitriptyline, nortriptyline, venlafaxine)
3. The patient had an adequate trial for each migraine prophylaxis class as defined by BOTH of the following unless the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the alternative migraine prophylactic agents, OR the patient is currently receiving treatment with the requested product through insurance (excludes obtainment as samples or via manufacturer's patient assistance programs) and experiencing a positive therapeutic outcome:
    a.) The trial length was at least 8 weeks at maximum tolerated dose
    b.) The patient was adherent to the prophylaxis agent during the trial
4. The patient has been evaluated for and does not have medication overuse headache (see Appendix C)
5. Other conditions or aggravating factors that are contributing to the development of chronic migraine headaches are being treated when applicable (e.g., dental or jaw problems, muscle tension, depression, fibromyalgia, sleep disorders and smoking)
6. If the patient is also currently receiving botulinum toxin injection for chronic migraine prophylaxis and is going to be using the requested drug and botulinum toxin together for preventative treatment of chronic migraine (i.e., not switching from one agent to another), BOTH of the following must apply:
    a.) Patient has had a reduction in the overall number of migraine days or reduction in number of severe migraine days per month with botulinum toxin use
    b.) Patient continues to experience a significant number of migraine headache days or severe migraine days per month requiring additional therapy for migraine prevention

7. The requested medication will not be used in combination with another CGRP antagonist or inhibitor also being used for the preventive treatment of migraine (e.g., Vyepti, Aimovig , Ajovy, or Emgality)

Approval will be for **6 months**

E. Qulipta (atogepant) may be considered **medically necessary** for the preventive treatment of **episodic migraine** in patients 18 years of age and older when ALL the following criteria are met:
   1. The patient has a diagnosis of episodic migraine defined as at least 4 and fewer than 15 migraine days per month and fewer than 15 headache days per month on average during the previous 3-month period
   2. The patient has had a trial of at least TWO of the listed medications from any of the following migraine prophylactic agent classes and experienced an inadequate response, has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the alternative migraine prophylactic agents, OR is currently receiving treatment with the requested product through insurance (excludes obtainment as samples or via manufacturer's patient assistance programs) and experiencing a positive therapeutic outcome:
      a.) Anticonvulsants (e.g., divalproex, valproate, topiramate)
      b.) Beta blockers (e.g., atenolol, metoprolol, nadolol, propranolol, timolol)
      c.) Antidepressants (e.g., amitriptyline, nortriptyline, venlafaxine)
   3. The patient had an adequate trial of both migraine prophylaxis agents as defined by BOTH of the following unless the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the alternative migraine prophylactic agents, OR the patient is currently receiving treatment with the requested product through insurance (excludes obtainment as samples or via manufacturer's patient assistance programs) and experiencing a positive therapeutic outcome:
      a.) The trial length was at least 8 weeks at maximum tolerated dose
      b.) The patient was adherent to the prophylaxis agent during the trial
   4. The patient has been evaluated for and does not have medication overuse headache (see Appendix C)
   5. Other conditions or aggravating factors that are contributing to the development of episodic migraine headaches are being treated when applicable (e.g., dental or jaw problems, muscle tension, depression, fibromyalgia, sleep disorders and smoking)
   6. The requested medication will not be used in combination with another CGRP antagonist (e.g., Vyepti, Aimovig, Emgality, Ajovy, Ubrelvy, Nurtec)

Approval will be for **6 months**

<u>Continuation of Therapy</u>

A. Nurtec ODT (rimegepant), Ubrelvy (ubrogepant), and Zavzpret (zavegepant) 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**

B. Nurtec ODT (rimegepant) may be considered medically necessary for the continuation of preventive treatment of episodic migraine in adults when ALL of the following criteria are met:
1. The patient's condition has responded to therapy as defined by ONE of the following:
    a.) The patient has achieved or maintained a 50% reduction in monthly headache frequency or severity with requested medication since starting therapy with medical records that support such benefit
    OR
    b.) The patient has had a reduction in headache frequency and/or severity resulting in an improvement in productivity and attendance at school or work since starting therapy with requested medication with medical records that support such benefit
2. The patient has had a reduction in the number of days of use of acute migraine-specific medications from baseline with medical records that support such benefit
3. The patient has been evaluated for and does not have medication overuse headache (see Appendix C)
4. 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)
5. The patient has not been receiving botulinum toxin injection for headache prophylaxis **AND** will not be initiating botulinum toxin headache prophylaxis while using the requested medication
6. The requested medication will not be used in combination with another CGRP antagonist or inhibitor also being used for preventive treatment of migraine (e.g., Vyepti, Aimovig, Emgality, Ajovy)

Approval will be for **12 months**

C. Qulipta (atogepant) may be considered medically necessary for the continuation of preventive treatment of chronic migraine or episodic migraine in adults when ALL of the following criteria are met:
1. The patient's condition has responded to therapy as defined by ONE of the following:
    a.) The patient has achieved or maintained a 50% reduction in monthly headache frequency or severity with requested medication since starting therapy with medical records that support such benefit
    OR
    b.) The patient has had a reduction in headache frequency and/or severity resulting in an improvement in productivity and attendance at school or work since starting therapy with requested medication with medical records that support such benefit
2. The patient has had a reduction in the number of days of use of acute migraine-specific medications from baseline with medical records that support such benefit
3. The patient has been evaluated for and does not have medication overuse headache (see Appendix C)
4. 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)

5. If the patient is also currently receiving botulinum toxin injection for chronic migraine prophylaxis and using the requested drug and botulinum toxin together for preventative treatment of chronic migraine (i.e., not switching from one agent to another), BOTH of the following must apply:
    a.) Patient has had a reduction in the overall number of migraine days or reduction in number of severe migraine days per month with botulinum toxin use
    b.) Patient continues to experience a significant number of migraine headache days or severe migraine days per month requiring additional therapy for migraine prevention
6. The patient has not been receiving botulinum toxin injection for headache prophylaxis **AND** will not be initiating botulinum toxin headache prophylaxis while using the requested medication for preventative treatment of episodic migraine.
7. The requested medication will not be used in combination with another CGRP antagonist or inhibitor also being used for preventive treatment of migraine (e.g., Vyepti, Aimovig, Emgality, Ajovy, or Nurtec ODT)

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 for the acute treatment of migraine is 75 mg taken orally, as needed. The recommended dose of Nurtec ODT for the preventive treatment of episodic migraine is 75 mg taken orally every other day. The maximum dose in a 24-hour period is 75 mg. The safety of using more than 18 doses 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.

The recommended dose of Qulipta for the preventive treatment of episodic migraine is 10 mg, 30 mg, or 60 mg taken orally once daily.

The recommended dose of Zavzpret for the acute treatment of migraine is 10 mg (1 spray) in a single nostril, as needed. The maximum dose in a 24-hour period is 10 mg.

Quantity Limits

Drug	Standard Benefit Allowance	Post-Limit PA Quantity Limit
Nurtec ODT 75 mg tablet	Acute treatment: 8 tablets / 30 days Preventive: 16 tablets / 30 days	Acute treatment: 16 tablets / 30 days
Ubrelvy 50 mg tablet	10 tablets / 30 days	16 tablets / 30 days
Ubrelvy 100 mg tablet	10 tablets / 30 days	16 tablets / 30 days
Qulipta 10 mg tablet	30 tablets / 30 days	N/A
Qulipta 30 mg tablet	30 tablets / 30 days	N/A
Qulipta 60 mg tablet	30 tablets / 30 days	N/A
Zavzpret 10 mg nasal spray unit	6 nasal spray units / 30 days	N/A

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. Zavzpret is supplied in unit-dosed spray units in cartons containing 1 spray unit or 6 spray units. 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 for acute treatment 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 16 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. 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 acetaminophen, acetylsalicylic acid, NSAIDs, or another non-opioid analgesic on ≥15 days per month for >3 months
   4.
   5. Regular intake of one or more opioids on ≥10 days per month for >3 months
   6. Regular intake of one or more combination analgesic medications on ≥10 days/month for >3 months
   7. Regular intake of any combination of ergotamine, triptans, non-opioid analgesics, and/ or opioids on a total of ≥10 days per month for >3 months
   8. Regular intake of any combination of ergotamine, triptans, non-opioid analgesics and/or opioids on a total of ≥10 days per month for >3 months and the identity, quantity and/or pattern of use or overuse of these classes of drug cannot be reliably established
   9. 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), Ubrelvy (ubrogepant), and Qulipta (atogepant) are 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 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 Consensus Statement: Update on Integrating New Migraine Treatments into Clinical Practice (2021) 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], small-molecule CGRP receptor antagonists [gepants], selective serotonin (5-HT1F) receptor agonist [ditan]) for moderate or severe attacks and mild-to-moderate attacks that respond poorly to nonspecific therapy. Several different triptans are available on the market with different strengths, dosage forms and routes of administration. The American Headache Society Consensus 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 Consensus Statement recommends initiating acute treatment with gepants, ditans, or neuromodulatory devices when contraindications to or inability to tolerate triptans, or inadequate response to two or more oral triptans. 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.

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.

The American Headache Society Consensus Statement recommends giving oral preventive treatments an adequate trial of at least 8 weeks at a target or usual effective dose to optimize the possibility of a therapeutic response. Before lack of effectiveness can be determined in patients with chronic migraine, prevention plans should be followed for a minimum of 8 weeks at a target therapeutic dose for oral treatments. If there is no response to treatment after 8 weeks at a target or usual effective dose, switching preventive treatments is recommended. Therefore, for coverage of the requested drug, patients with migraine headache must have had a trial for eight weeks, or had an intolerance or contraindication that would prohibit an eight-week trial.

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 ($p = 0.001$).
Nurtec 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 Nurtec ODT did not require rescue medication (e.g., NSAIDS, acetaminophen) within 24 hours post dose.

The efficacy of Nurtec ODT for the prevention of episodic migraine headaches was established in a Phase 3, randomized, double-blind placebo-controlled clinical trial. Patients were randomized to 75 mg of rimegepant every other day (N=348) or placebo every other day (N=347) for 12 weeks. The trial enrolled adult patients with at least a 1-year history of migraine (with or without aura). Patients experienced an average of 10.9 headache days during the 28-day observational period. Patients were allowed to use acute headache treatments (i.e., triptans, NSAIDs, acetaminophen, antiemetics, muscle relaxants, and aspirin) as needed. Approximately 10% of patients were taking one preventive medication for migraine at baseline. The use of a concomitant medication that acts on the CGRP pathway was not permitted for either the acute or preventive treatment of migraine. The primary endpoint was the change from baseline in the mean number of monthly migraine days (MMDs) during weeks 9 through 12 of the double-blind treatment phase. The percentage of patients who achieved at least a 50% reduction from baseline in moderate to severe MMDs during Weeks 9 through 12 of the double-blind treatment phase compared to placebo was also evaluated. Rimegepant 75 mg dosed every other day demonstrated statistically significant improvements for these efficacy endpoints compared to placebo with a -4.3 change from baseline in MMDs compared to -3.5 in the placebo group. 49.1% of responders achieved at least a 50% reduction from baseline in the mean number of MMDs during weeks 9-12 compared to 41.5% in the placebo group.

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 ($p < 0.001$).

The efficacy of Qulipta for the preventive treatment of episodic migraine in adults was demonstrated in two randomized, multicenter, double-blind, placebo-controlled studies. Additionally, the efficacy of Qulipta for the preventive treatment of chronic migraine in adults was demonstrated in a randomized, multicenter, double-blind, placebo-controlled study. The use of a concomitant medication that acts on the CGRP pathway was not permitted for either acute or preventive treatment of migraine in any study. For all three studies, the primary efficacy endpoint was the change from baseline in mean monthly migraine days (MMD) across the 12-week treatment period. In Study 1, the changes from baseline in mean number of migraine days across the 12-week trial were −1.2 days with the 10 mg strength, −1.4 days with the 30 mg strength, and −1.7 days with the 60 mg strength compared to placebo. In Study 2, the changes from baseline in mean number of migraine days were, -1.1 days with the 10 mg strength, -0.9 with the 30 mg strength, and -0.7 with the 60 mg strength compared to placebo. In Study 3, the changes from baseline in mean number of migraine days across the 12-week trial were -1.8 days with the 60 mg strength compared to placebo.

The efficacy of Zavzpret nasal spray for the acute treatment of migraine with or without aura in adults was demonstrated in two randomized, multicenter, double-blind, placebo-controlled studies. In Study 1, patients were randomized to Zavzpret 10 mg or placebo. In Study 2, patients were randomized to Zavzpret 5 mg, Zavzpret 10 mg, Zavzpret 20 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 23.6% with Zavzpret 10 mg versus 14.9% with placebo for a difference of 8.8% ($p < 0.001$). The percentage of responders who were MBS-free at 2 hours post-dose was 39.6% with Zavzpret 10 mg versus 31.1% with placebo for a difference of 8.7% ($p = 0.001$). In Study 2, the percentage of responders who were pain free at 2 hours post-dose was 19.6%, 22.5%, 23.1%, and 15.5% with Zavzpret 5 mg ($p = 0.1214$ vs. placebo), Zavzpret 10 mg ($p = 0.0113$ vs. placebo), Zavzpret 20 mg ($p = 0.0055$ vs. placebo), and placebo, respectively. The percentage of responders who were MBS-free at 2 hours post-dose was 39%, 41.9%, 42.5%, and 33.7% with Zavzpret 5 mg ($p = 0.1162$ vs. placebo), Zavzpret 10 mg ($p = 0.0155$ vs. placebo), Zavzpret 20 mg ($p = 0.0094$ vs. placebo), and placebo, respectively. In the Zavzpret studies, none of these patients were on concomitant preventative medication that act on the CGRP pathway.

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.

The most common adverse reactions (≥ 4% and greater than placebo) in the Qulipta clinical trials were nausea, constipation, and fatigue. In Study 1 and Study 2, the rate of transaminase elevations over 3 times the upper limit of normal was similar between patients treated with Qulipta (1.0%) and those treated with placebo (1.8%). However, there were cases with transaminase elevations over 3 times the upper limit of normal that were temporally associated with Qulipta treatment; these were asymptomatic and resolved within 8 weeks of discontinuation. There were no cases of severe liver injury or jaundice.

The most common adverse reactions (≥ 2% and greater than placebo) in the clinical trials with Zavzpret nasal spray use were taste disorders, nausea, nasal discomfort, and vomiting.

Dosing Limits

Per the American Headache Society Consensus Statement: Update on Integrating New Migraine Treatments into Clinical Practice (2021), 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 for the acute treatment of migraine is 75 mg taken orally, as needed. The maximum dose in a 24-hour period is 75 mg. The recommended dose of Nurtec ODT for the preventive treatment of episodic migraine is 75 mg taken orally every other day. The safety of using more than 18 doses 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. The recommended dose of Qulipta for the preventive treatment of episodic migraine is 10 mg, 30 mg, or 60 mg taken orally once daily and the recommended dose for preventative treatment of chronic migraine is 60 mg taken orally once daily. Therefore, the quantity limit is set at 30 tablets/30 days. Qulipta is suppled in bottles containing 30 tablets

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.

The recommended dose of Zavzpret for the acute treatment of migraine is 10 mg nasally, as needed. The maximum dose in a 24-hour period is 10 mg. The safety of treating more than 8 migraines in a 30-day period has not been established. Zavzpret is supplied as read-to-use, unit-dose disposable devices. Each box contains 1 unit or 6 units. It is the discretion of the dispensing pharmacy to fill quantities per package size up to the 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

- Ubrelvy [package insert]. Madison, NJ: Allergan USA, Inc.; March 2021.
- Nurtec ODT (rimegepant) [package insert]. New Haven, CT: Biohaven Pharmaceuticals Inc; May 2021.
- Qulipta [package insert]. Madison, NJ: Allergan USA, Inc.; April 2023.
- Zavzpret [package insert]. New York, NY: Pfizer Labs; March 2023.
- Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. Lancet. 2019;394(10200):737-745
- American Headache Society. The American Headache Society Position Statement on Integrating New Migraine Treatments into Clinical Practice. Headache 2019; 59:1-18.
- Ailani J, Burch RC, Robbins MS et al. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. 2021; 61:1021-1039.
- 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.
- Oskoui M, Pringsheim T, Holler-Managan Y, et al. Practice guideline update summary: Acute Treatment of Migraine in Children and Adolescents. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2019;93:487-499.
- Silberstein S, Holland S, Freitag F, et al. Evidence-Based Guideline Update: Pharmacologic Treatment for Episodic Migraine Prevention in Adults: Report of the Quality and the American Headache Society Standards Subcommittee of the American Academy of Neurology. Neurology 2012;78;1337-1346.
- Silberstein S, Holland S, Freitag F, et al. Evidence-Based Guideline Update: Pharmacologic Treatment for Episodic Migraine Prevention in Adults: Report of the Quality and the American Headache Society Standards Subcommittee of the American Academy of Neurology. Neurology 2013;80;871
- American Academy of Neurology. Update: Pharmacologic Treatments for Episodic Migraine Prevention in Adults. Available at: https://www.aan.com/Guidelines/Home/GetGuidelineContent/545. Accessed June 2021.

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