Migraine Medications (Oral, Injectable, Transdermal, and Nasal)

Policy # 00337
Original Effective Date: 01/09/2013
Current Effective Date: 10/11/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Ergotamine/dihydroergotamine products are addressed separately in medical policy 00582. Calcitonin Gene-Related Peptide (CGRP) Antagonists for acute and preventative migraine treatment are addressed separately in medical policy 00646.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

For Patients With "Step Therapy" (generic before brand) ONLY:

Based on a review of the available data, brand name oral, injectable, transdermal, and nasal serotonin triptan products, including, but not limited to Zecuity®‡ (sumatriptan transdermal system), Zomig®‡ (zolmitriptan tablets), Zomig-ZMT®‡ (zolmitriptan orally disintegrating tablets), branded Zolmitriptan nasal spray, Axert®‡ (almotriptan tablets), Onzetra®‡ Xsail®‡ (sumatriptan nasal powder), Zembrace™‡ Symtouch™‡ (sumatriptan injection), Tosymra™‡ (sumatriptan nasal spray), Imitrex®‡ Nasal (sumatriptan nasal spray), and Relpax®‡ (eletriptan tablets), as well as the branded non-triptan medications, Cambia®‡ (diclofenac) and Reyvow™‡ (lasmiditan) may be considered **eligible for coverage**** when one of the below patient selection criteria is met:

Patient Selection Criteria

Coverage eligibility will be considered for brand name oral, injectable, transdermal, and nasal triptans or brand name Cambia (diclofenac) or Reyvow (lasmiditan) when one of the following criteria is met:

- Patient has tried and failed a generic triptan medication (e.g., sumatriptan [tablets, injection, or nasal spray], naratriptan tablets, eletriptan tablets, rizatriptan [tablets or orally

disintegrating tablets], almotriptan tablets, frovatriptan tablets, or zolmitriptan [tablets or orally disintegrating tablets]); OR

- There is clinical evidence or patient history that suggests the generically available oral or injectable products will be ineffective or cause an adverse reaction to the patient.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of brand name oral, injectable, transdermal, and nasal triptans or brand name Cambia (diclofenac), Reyvow (lasmiditan) when patient selection criteria are not met or for usage not included in the above patient selection criteria to be **not medically necessary**.**

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

For Patients With "Prior Authorization" ONLY:

Based on review of the available data, the Company may consider select triptan products, including, but not limited to Onzetra Xsail (sumatriptan nasal powder), Zembrace Symtouch (sumatriptan injection), Tosymra (sumatriptan nasal spray), branded Zolmitriptan nasal spray, or Reyvow (lasmiditan) to be **eligible for coverage**** when the below patient selection criteria are met for the requested drug:

Patient Selection Criteria

Coverage eligibility will be considered for select triptan–products, including, but not limited to Onzetra Xsail (sumatriptan nasal powder), Zembrace Symtouch (sumatriptan injection), Tosymra (sumatriptan nasal spray), branded Zolmitriptan nasal spray, or Reyvow (lasmiditan) when the following criteria are met for the requested drug:

- For Onzetra Xsail, Tosymra, or branded Zolmitriptan nasal spray requests: Patient has tried and failed (e.g., intolerance or inadequate response) at least TWO GENERIC triptan agents [one of which must be **oral** (e.g., sumatriptan tablets, naratriptan tablets, eletriptan tablets, rizatriptan (tablets or orally disintegrating tablets), almotriptan tablets, frovatriptan tablets,

or zolmitriptan (tablets or orally disintegrating tablets) AND the other must be **nasal** (e.g., sumatriptan nasal)] unless there is clinical evidence or patient history that suggests the use of TWO GENERIC triptan agents [one of which must be **oral** (e.g., sumatriptan tablets, naratriptan tablets, eletriptan tablets, rizatriptan (tablets or orally disintegrating tablets), almotriptan tablets, frovatriptan tablets, or zolmitriptan (tablets or orally disintegrating tablets) AND the other must be **nasal** (e.g., sumatriptan nasal)] will be ineffective or cause an adverse reaction to the patient.

- For Zembrace Symtouch requests: Patient has tried and failed (e.g., intolerance or inadequate response) at least TWO GENERIC triptan agents [one of which must be **oral** (e.g., sumatriptan tablets, naratriptan tablets, eletriptan tablets, rizatriptan (tablets or orally disintegrating tablets), almotriptan tablets, frovatriptan tablets, or zolmitriptan (tablets or orally disintegrating tablets) AND the other must be **injectable** (e.g., sumatriptan injection)] unless there is clinical evidence or patient history that suggests the use of TWO GENERIC triptan agents [one of which must be **oral** (e.g., sumatriptan tablets, eletriptan tablets, naratriptan tablets, rizatriptan (tablets or orally disintegrating tablets), almotriptan tablets, frovatriptan tablets, or zolmitriptan (tablets or orally disintegrating tablets) AND the other must be **injectable** (e.g., sumatriptan injection)] will be ineffective or cause an adverse reaction to the patient.
- For Reyvow requests:
    - Patient is using the requested drug for the acute treatment of migraine headaches; AND
    - Patient is 18 years of age or older; AND
    - Patient has tried and failed (e.g. intolerance or inadequate response) at least TWO UNIQUE GENERIC active ingredient triptan therapies (oral, nasal, injectable) unless there is clinical evidence or patient history that suggests the use of these GENERIC products will be ineffective or cause an adverse reaction to the patient. Generic products for the acute treatment of migraine include sumatriptan (available in nasal, oral, and injectable), zolmitriptan, almotriptan, frovatriptan, naratriptan, and rizatriptan.
      *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of select triptan products, including, but not limited to Onzetra Xsail (sumatriptan nasal powder), Zembrace Symtouch (sumatriptan injection), branded Zolmitriptan nasal spray, or Tosymra (sumatriptan nasal spray) when the patient selection criteria for the requested drug are not met to be **not medically necessary**.**

Based on review of available data, the Company considers the use of Reyvow (lasmiditan) when the patient has not tried and failed at least TWO UNIQUE GENERIC active ingredient triptan therapies to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of Reyvow (lasmiditan) in patients younger than 18 years of age or who do not have acute treatment of migraine headache to be **investigational.***

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

For Patients With BOTH "Prior Authorization" AND "Step Therapy":

Based on a review of the available data, brand name oral, injectable, transdermal, and nasal triptan products, including, but not limited to Zecuity (sumatriptan transdermal system), Zomig (zolmitriptan tablets), Zomig-ZMT (zolmitriptan orally disintegrating tablets), branded Zolmitriptan nasal spray, Axert (almotriptan tablets), Onzetra Xsail (sumatriptan nasal powder), Zembrace Symtouch (sumatriptan injection), Tosymra (sumatriptan nasal spray), Imitrex Nasal (sumatriptan nasal spray), and Relpax (eletriptan tablets) as well as the branded non-triptan medications, Cambia

(diclofenac) and Reyvow (lasmiditan), may be considered **eligible for coverage**** when one of the below patient selection criteria is met:

Patient Selection Criteria

Coverage eligibility will be considered for brand name oral, injectable, transdermal, and nasal triptans or brand name Cambia (diclofenac) or Reyvow (lasmiditan) when one of the following criteria is met:

- For Onzetra Xsail, Tosymra, or branded Zolmitriptan nasal spray requests: Patient has tried and failed (e.g., intolerance or inadequate response) at least TWO GENERIC triptan agents [one of which must be **oral** (e.g., sumatriptan tablets, naratriptan tablets, eletriptan tablets, rizatriptan (tablets or orally disintegrating tablets), almotriptan tablets, frovatriptan tablets, or zolmitriptan (tablets or orally disintegrating tablets) AND the other must be **nasal** (e.g., sumatriptan nasal)] unless there is clinical evidence or patient history that suggests the use of TWO GENERIC triptan agents [one of which must be **oral** (e.g., sumatriptan tablets, naratriptan tablets, eletriptan tablets, rizatriptan (tablets or orally disintegrating tablets), almotriptan tablets, frovatriptan tablets, or zolmitriptan (tablets or orally disintegrating tablets) AND the other must be **nasal** (e.g., sumatriptan nasal)] will be ineffective or cause an adverse reaction to the patient.
- For Zembrace Symtouch requests: Patient has tried and failed (e.g., intolerance or inadequate response) at least TWO GENERIC triptan agents [one of which must be **oral** (e.g., sumatriptan tablets, naratriptan tablets, eletriptan tablets, rizatriptan (tablets or orally disintegrating tablets), almotriptan tablets, frovatriptan tablets, or zolmitriptan (tablets or orally disintegrating tablets) AND the other must be **injectable** (e.g.,sumatriptan injection)] unless there is clinical evidence or patient history that suggests the use of TWO GENERIC triptan agents [one of which must be **oral** (e.g., sumatriptan tablets, naratriptan tablets, eletriptan tablets, rizatriptan (tablets or orally disintegrating tablets), almotriptan tablets, frovatriptan tablets, or zolmitriptan (tablets or orally disintegrating tablets) AND the other must be **injectable** (e.g., sumatriptan injection)] will be ineffective or cause an adverse reaction to the patient.
- For Reyvow requests:
    - Patient is using the requested drug for the acute treatment of migraine headaches; AND
    - Patient is 18 years of age or older; AND

- Patient has tried and failed (e.g. intolerance or inadequate response) at least TWO UNIQUE GENERIC active ingredient triptan therapies (oral, nasal, injectable) unless there is clinical evidence or patient history that suggests the use of these GENERIC products will be ineffective or cause an adverse reaction to the patient. Generic products for the acute treatment of migraine include sumatriptan (available in nasal, oral, and injectable), zolmitriptan, almotriptan, frovatriptan, naratriptan, and rizatriptan.
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

- For ALL other brand triptan requests or for brand Cambia (diclofenac): The patient has tried and failed a generic triptan medication (e.g., sumatriptan [tablets, injection, or nasal spray] naratriptan tablets, eletriptan tablets, rizatriptan [tablets or orally disintegrating tablets], almotriptan tablets, frovatriptan tablets, or zolmitriptan [tablets or orally disintegrating tablets]) OR there is clinical evidence or patient history that suggests the generically available oral or injectable products will be ineffective or cause an adverse reaction to the patient

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of brand name oral, injectable, transdermal, and nasal triptan products and brand Cambia (diclofenac) when the patient selection criteria for the requested drug are not met to be **not medically necessary**.**

Based on review of available data, the Company considers the use of Reyvow (lasmiditan) when the patient has not tried and failed at least TWO UNIQUE GENERIC active ingredient triptan therapies (unless clinical evidence or patient history suggests these triptan therapies will be ineffective or cause an adverse event) to be **not medically necessary.****

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of Reyvow (lasmiditan) in patients younger than 18 years of age or for indications other than acute treatment of migraine headache to be **investigational.***

Background/Overview

Serotonin (5-HT) 1 receptor agonists (triptans) are used in the treatment of migraines. All of the triptan medications are indicated for the treatment of migraine headache with or without aura and are not intended to be used as prophylactic migraine therapy or to manage hemiplegic or basilar migraine. Most recently, there have been newer and/or reformulated delivery systems introduced to the market for these already existing drug moieties. Zecuity is a transdermal system containing sumatriptan that is indicated for the treatment of acute migraines with or without aura. Zembrace Symtouch is another injectable form of sumatriptan, while Onzetra Xsail is controlled via a novel delivery method that is powered by the patient's breath and delivers the sumatriptan into their nose. Tosymra is another nasal spray version of sumatriptan and there is now a branded generic Zolmitriptan nasal spray. Cambia is a non-steroidal anti-inflammatory drug (NSAID) that is indicated for the acute treatment of migraine attacks with or without aura in adult patients.

Reyvow is a first-in-class serotonin (5-HT) 1F receptor agonist. It acts on the trigeminal system by binding with high affinity to the 5-HT 1F receptor, but it does not cause vasoconstriction like other migraine medications because it has low affinity for the 5-HT 1B receptors. It does, however, cause significant drowsiness and should not be taken unless the patient can wait at least 8 hours between dosing and driving or operating machinery. Additionally, the active ingredient of Reyvow, lasmiditan, has been classified as a Schedule V controlled substance due to the potential for abuse. The recommended dose of Reyvow is 50 mg, 100 mg, or 200 mg taken orally as needed with no more than one dose taken in 24 hours. The safety of treating an average of more than 4 migraine attacks in a 30-day period has not been established.

Rationale/Source

The patient selection criteria presented in this policy take into consideration clinical evidence or patient history that suggests a generic triptan drug will be ineffective or cause an adverse reaction to the patient. Based on a review of the data, in the absence of the above-mentioned caveat, there is no advantage of using a brand name triptan or brand name Cambia (diclofenac) over a generic triptan. There are various routes of administration available generically so as not to go directly to a branded medication. Generic drugs are considered to have equal bioavailability and efficacy in comparison to brand name drugs. Although Reyvow has a novel mechanism of action, generic triptans currently provide a more studied and cost-effective alternative.

Reyvow

The efficacy of Reyvow in the acute treatment of migraine was demonstrated in two randomized, double-blind, placebo-controlled trials, Study 1 and Study 2. These studies enrolled patients with a history of migraine with and without aura according to the International Classification of Headache Disorders (ICHD-II) diagnostic criteria. At baseline 22% of patients were taking preventive medication for migraine. Study 1 randomized patients to Reyvow 100 mg (n=744) or 200 mg (n=745) or placebo (n=742), and Study 2 randomized patients to Reyvow 50 mg (n=750), 100 mg (n=754) or placebo (n=751). Patients were allowed to take rescue medication 2 hours after taking study drug; however, opioids, barbiturates, triptans, and ergots were not allowed within 24 hours of study drug administration.

The primary efficacy analyses were conducted in patients that treated a migraine with moderate to severe pain within 4 hours of the onset of the attack. The efficacy of Reyvow was established by an effect on pain freedom at 2 hours and Most Bothersome Symptom (MBS) freedom at 2 hours compared to placebo. Pain freedom was defined as a reduction of moderate or severe headache pain to no pain, and MBS freedom was defined as the absence of the self-identified MBS (photophobia, phonophobia, or nausea). In both studies, the percentage of patients achieving pain freedom and MBS freedom 2 hours after treatment was significantly greater among patients receiving Reyvow at all doses compared to those receiving placebo. In Study 1, 28.3% of the Reyvow 100 mg group and 31.8% of the Reyvow 200 mg group were pain free at 2 hours compared to 15.3% of the placebo group. In Study 2, 28.3% of the Reyvow 50 mg group and 31.4% of the Reyvow 100 mg group were pain free at 2 hours compared to 21% of the placebo group.

Driving performance was assessed at 90 minutes after administration of Reyvow 50 mg, 100 mg, 200 mg, alprazolam 1 mg, and placebo in a randomized double-blind, placebo- and active-controlled five-period crossover study in 90 healthy volunteers using a computer-based driving simulation. It was found that a dose-dependent impairment of computer-based simulated driving performance was seen with all doses of Reyvow at 90 minutes post-administration. An additional study assessed driving performance at 8, 12, and 24 hours after administration of Reyvow 100 mg or 200 mg in 67 healthy volunteers with diphenhydramine 50 mg as a positive control. The threshold for driving impairment was not met at 8 hours or later after administration of Reyvow 100 or 200 mg.

References

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Policy History

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01/03/2013	Medical Policy Committee review.
01/09/2013	Medical Policy Implementation Committee approval. New Policy
02/19/2013	Format revision. Coding section removed
09/05/2013	Medical Policy Committee review.
09/18/2013	Medical Policy Implementation Committee approval. Changed title. Added Cambia to policy. Removed the criteria regarding being unable to chew/swallow as well as age criteria because generics are now available for those special circumstances.
09/04/2014	Medical Policy Committee review
09/17/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/03/2015	Medical Policy Committee review
09/23/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/05/2016	Medical Policy Committee review
05/18/2016	Medical Policy Implementation Committee approval. Changed title to reflect new transdermal system on the market (Zecuity). Updated all sections of the policy to reflect new route of administration for this policy (transdermal).
02/02/2017	Medical Policy Committee review
02/15/2017	Medical Policy Implementation Committee approval. Added new branded products to the policy. Criteria added for step therapy and prior authorization. Title change adding transdermal and nasal.
02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. Added the generic drug eletriptan to the policy.
02/07/2019	Medical Policy Committee review
02/20/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/02/2020	Medical Policy Committee review

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04/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/04/2020	Medical Policy Committee review
06/10/2020	Medical Policy Implementation Committee approval. Added a new product, Tosymra, to the policy and updated the relevant background information.
09/03/2020	Medical Policy Committee review
09/09/2020	Medical Policy Implementation Committee approval. Added a new product, Reyvow, to the policy and updated the relevant background information. Also updated the step 1 drugs to include the generic sumatriptan nasal spray.
09/02/2021	Medical Policy Committee review
09/08/2021	Medical Policy Implementation Committee approval. Added branded generic Zolmitriptan nasal spray to the policy.

Next Scheduled Review Date: 09/2022

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.