



Louisiana

dichlorphenamide (Keveyis™, generics)

Policy # 00506

Original Effective Date: 05/18/2016

Current Effective Date: 06/10/2024

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.

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.*

Based on review of available data, the Company may consider dichlorphenamide (Keveyis™, Ormalvi™, generics)[‡] for the treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for dichlorphenamide (Keveyis, Ormalvi, generics) will be considered when the following criteria are met:

- Initial (3 months):
 - Patient has a documented diagnosis of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, or related variants; AND
 - Patient has tried and failed oral acetazolamide therapy (e.g., attacks are increasing in frequency or severity) UNLESS there is clinical evidence or patient history that suggests the use of acetazolamide will be ineffective or cause an adverse reaction to the patient.
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
 - If the request is for brand Keveyis or Ormalvi, the patient has tried and failed (e.g., intolerance or inadequate response) generic dichlorphenamide UNLESS there is clinical evidence or patient history that suggests the use of generic dichlorphenamide will be ineffective or cause an adverse reaction to the patient.
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

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- Re-authorization (1 year):
 - Patient received an initial authorization for Keveyis; AND
 - Patient has responded to Keveyis (e.g., patient has experienced a decrease in the frequency or severity of paralytic attacks) as determined by the prescribing physician. *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
 - If the request is for brand Keveyis or Ormalvi, the patient has tried and failed (e.g., intolerance or inadequate response) generic dichlorphenamide UNLESS there is clinical evidence or patient history that suggests the use of generic dichlorphenamide will be ineffective or cause an adverse reaction to the patient. *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of dichlorphenamide (Keveyis, generics) when the patient has NOT tried and failed oral acetazolamide therapy OR if the patient has NOT responded to initial therapy with Keveyis to be **not medically necessary.****

Based on review of available data, the Company considers the use of dichlorphenamide (Keveyis, Ormalvi) when the patient has NOT tried and failed generic dichlorphenamide 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 dichlorphenamide (Keveyis, generics) when patient selection criteria are not met (with the exception of those denoted above as **not medically necessary****) to be **investigational.***

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Background/Overview

Keveyis is an oral carbonic anhydrase inhibitor indicated for the treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants. The precise mechanism by which Keveyis exerts its therapeutic effects in these conditions is unknown. Keveyis is supplied as brand or generic 50 mg tablets. Ormalvi is a generic version of the 50 mg tablets marketed under a brand name. The dose is 50 mg once or twice daily and can be titrated up to a maximum of 200 mg daily. The Keveyis package insert instructs the prescribing physician to evaluate the patient's response after 2 months of treatment in order to decide whether Keveyis should be continued.

Primary Periodic Paralysis

Primary paralysis are rare muscle diseases with an estimated prevalence of 1 case per 100,000 individuals. It is estimated that 5,000 patients in the United States have primary periodic paralysis, and 70% of those are thought to be undiagnosed. Periodic paralysis are called channelopathies since they are frequently caused by genetic mutations in ion channels. In some patients with periodic paralysis, the cause is unknown (and not exactly caused by mutations). The gene mutations cause the ion channels to have a dysregulation of the flow of ions into muscle cells. The dysregulation of ion flow reduces the ability of skeletal muscles to contract, which leads to severe muscle weakness or paralysis. Hyperkalemic and hypokalemic periodic paralysis are inherited in an autosomal dominant manner (meaning that one copy of the altered gene is enough to cause the disorder).

The majority of hypokalemic periodic paralysis cases are caused by point mutations in the voltage gated calcium channel gene. Some clinical features of hypokalemic periodic paralysis include onset of attacks in the first or second decade of life, duration of attacks >2 hours, and the presence of triggers (carbohydrate rich meal, and symptom onset during rest after exercise, stress, etc.). The evolution of symptoms is rapid paralysis over minutes or hours with a duration of several minutes to days. In trials, the mean frequency of attacks was 7 per month. Potassium levels during these attacks typically range from 0.9-3.0 mmol/L.

The majority of hyperkalemic periodic paralysis cases are caused by point mutations in the voltage gated sodium channel gene. Features of this type of paralysis include disease manifestation before 20 years of age, normal potassium levels between attacks, and hyperkalemia during an attack.

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Potassium rich food or rest after exercise can precipitate an attack. Cold, stress, glucocorticoids, or pregnancy can worsen or provoke an attack.

Acetazolamide (a carbonic anhydrase inhibitor) has been historically used to treat these conditions. It is thought that Keveyis is a more potent product than acetazolamide. Keveyis is the first drug FDA-approved specifically for the treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Keveyis was approved in August of 2015 for the treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants. The active ingredient has been FDA approved for quite some time, but was pulled off the market in the past for reasons not due to safety or effectiveness.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Keveyis was evaluated in two clinical studies. The first study was a double blind, placebo controlled, multi-center study that took place over a period of 9 weeks. This study was broken down into two sub-studies: a study in patients with hypokalemic periodic paralysis (n=44) and a study in patients with hyperkalemic periodic paralysis (n=21). The primary endpoint in both sub-studies was the average number of self-reported attacks of muscle weakness per week over the final 8 weeks of the trial. The dose of Keveyis in the first study was 50 mg twice daily for treatment naïve patients. Patients already on dichlorphenamide prior to the study continued on the same dose. In patients taking acetazolamide prior to the study, the Keveyis dose was set at 20% of the acetazolamide dose. In the hypokalemic sub-study, patients treated with Keveyis had 2.2 fewer attacks per week than patients treated with placebo (p=0.02). In the hyperkalemic sub-study, patients treated with Keveyis had 3.9 fewer attacks per week than patients treated with placebo (p=0.08).

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The second study was over a 35 week period and was a double blind, placebo controlled, multi-center, two period crossover study that also included 2 sub-studies. The sub-studies included patients with hypokalemic periodic paralysis as well as patients with hyperkalemic periodic paralysis (including patients with paramyotonia congenita). The primary endpoint in the hypokalemic sub-study was the incidence of acute intolerable worsening (based on attack frequency or severity) necessitating withdrawal. The primary endpoint in the hyperkalemic periodic paralysis sub-study was the average number of self-reported attacks of muscle weakness per week. Dosing was similar to the first study. In the hypokalemic group, acute intolerable worsening was observed in two patients on Keveyis vs. 11 patients on placebo (p=0.02). In the hyperkalemic group, patients treated with Keveyis had 2.3 fewer attacks than those on placebo (p=0.006).

References

1. Keveyis [package insert]. Taro Pharmaceuticals, USA. Hawthorne, New York. November 2019.
2. Keveyis Prior Authorization Policy. Express Scripts. Updated December 2015.
3. Keveyis Drug Evaluation. Express Scripts. Updated September 2015.
4. Ormalvi (dichlorphenamide) [package insert]. Cycle Pharmaceuticals Ltd. Cambridge, CB3 0FA, UK. Updated February 2024.

Policy History

Original Effective Date: 05/18/2016

Current Effective Date: 06/10/2024

- 05/05/2016 Medical Policy Committee review
- 05/18/2016 Medical Policy Implementation Committee approval. New Policy.
- 05/04/2017 Medical Policy Committee review
- 05/17/2017 Medical Policy Implementation Committee approval. No change to coverage.
- 05/03/2018 Medical Policy Committee review
- 05/16/2018 Medical Policy Implementation Committee approval. No change to coverage.
- 05/02/2019 Medical Policy Committee review
- 05/15/2019 Medical Policy Implementation Committee approval. No change to coverage.
- 05/07/2020 Medical Policy Committee review
- 05/13/2020 Medical Policy Implementation Committee approval. Updated re-authorization criteria to match similar policies.
- 05/06/2021 Medical Policy Committee review

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- 05/12/2021 Medical Policy Implementation Committee approval. Updated the dosing in the background information per the FDA package insert. No change to coverage.
- 05/05/2022 Medical Policy Committee review
- 05/11/2022 Medical Policy Implementation Committee approval. No change to coverage.
- 05/04/2023 Medical Policy Committee review
- 05/10/2023 Medical Policy Implementation Committee approval. Added generic dichlorphenamide to policy. Updated criteria to require trial and failure of generic dichlorphenamide before brand Keveyis. Updated title to reflect that Keveyis is available generically.
- 05/02/2024 Medical Policy Committee review
- 05/08/2024 Medical Policy Implementation Committee approval. Updated initial authorization approval length to 3 months. Added new generic, Ormalvi, to policy.
- Next Scheduled Review Date: 05/2025

*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 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.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

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