sirolimus topical gel (Hyftor™)

Policy # 00813
Original Effective Date: 12/12/2022
Current Effective Date: 12/11/2023

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 sirolimus topical gel (Hyftor™)‡ for the treatment of facial angiofibromas associated with tuberous sclerosis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for sirolimus topical gel (Hyftor) will be considered when the following criteria are met:

Initial

- Patient has a diagnosis of tuberous sclerosis complex as confirmed by one of the following:
  - There is identification of a pathogenic variant in the tuberous sclerosis complex 1 (*TSC1*) gene or tuberous sclerosis complex 2 (*TSC2*) gene by genetic testing; OR
  - Clinical diagnostic criteria suggest a definitive diagnosis of tuberous sclerosis complex by meeting either two major features or one major feature and two minor features. Major features include the following: hypomelanotic macules (≥3, at least 5 mm diameter), angiofibromas (≥3) or fibrous cephalic plaque, ungual fibromas (≥2), Shagreen patch, multiple retinal hamartomas, multiple cortical tubers and/or radial migration lines, subependymal nodules (≥2), subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis (LAM), and angiomyolipomas (≥2). Minor features include the following: 'confetti' skin lesions (1 to 2 mm hypomelanotic macules), dental enamel pits (≥3), intraoral fibromas (≥2), retinal achromic patch, multiple renal cysts, nonrenal hamartomas, and sclerotic bone lesions; AND

- Patient is 6 years of age or older; AND
- Patient has 3 or more angiofibromas on the face that are greater than or equal to 2 mm in diameter with redness in each; AND
  *(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.)*
- Patient is not a candidate for laser therapy or surgery; AND
  *(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.)*
- Requested dose for patients aged 6-11 years of age is less than or equal to 600 mg/day OR requested dose for patients ages 12 and older is less than or equal to 800 mg/day.

Continuation

- Patient has received at least 3 months of therapy with Hyftor; AND
  *(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.)*
- Patient has had a clinical response to the requested drug as evidenced by improvement from baseline in size and redness of facial angiofibroma.
  *(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 sirolimus topical gel (Hyftor) when the patient does not have 3 or more angiofibromas on the face that are greater than or equal to 2 mm in diameter with redness in each to be **not medically necessary.****

Based on review of available data, the Company considers the use of sirolimus topical gel (Hyftor) when the patient is a candidate for laser therapy or surgery to be **not medically necessary.****

For continuation requests: Based on review of available data, the Company considers the use of sirolimus topical gel (Hyftor) when the patient has not received at least 3 months of therapy with Hyftor to be **not medically necessary.****

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For continuation requests: Based on review of available data, the Company considers the use of sirolimus topical gel (Hyftor) when the patient has not had a clinical response 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 sirolimus topical gel (Hyftor) for any non-FDA approved indication to be **investigational.***

Based on review of available data, the Company considers the use of sirolimus topical gel (Hyftor) when the patient selection criteria are not met (EXCEPT those denoted as **not medically necessary****) to be **investigational.***

Background/Overview

Hyftor is a topical mammalian target of rapamycin (mTOR) inhibitor indicated for the treatment of facial angiofibroma associated with tuberous sclerosis. It is available as a 0.2% gel in 10-gram tubes. Hyftor should be applied to the affected areas of the face twice daily. The maximum recommended daily dose of Hyftor is 600 mg, which is 2 cm, for pediatric patients 6 to 11 years of age and 800 mg, which is 2.5 cm, for adults and pediatric patients 12 years of age and older. If symptoms have not improved after 12 weeks of therapy with Hyftor, the need for continuing therapy needs to be reevaluated, according to the package insert.

Tuberous sclerosis complex is a genetic disorder caused by mutations in two genes, *TCS1* or *TCS2*. This condition impacts multiple organ systems and can cause benign tumors to grow in the brain and other vital organs, including the kidneys, skin, heart, eyes, and lungs. Tuberous sclerosis complex can also affect the central nervous system causing patients to experience symptoms such as seizures, impaired intellectual development, autism, and behavioral issues. Facial angiofibromas are very common in patients with tuberous sclerosis complex. They are reddish-brown spots or bumps that consist of blood vessels and fibrous tissue. They generally begin to appear in young children and begin to proliferate and worsen on a yearly basis thereafter. Other common skin conditions associated with tuberous sclerosis complex include hypomelanotic macules, shagreen patches, and

confetti skin lesions. Treatment options for facial angiofibromas associated with tuberous sclerosis complex have not been widely studied. Treatment generally consists of off-label use of compounded topical mTOR inhibitors, but no standardized dosing regimen has been established. Hyftor is the first drug to be approved for this condition.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Hyftor is approved for the treatment of facial angiofibroma associated with tuberous sclerosis in adults and pediatric patients 6 years of age and older.

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.

A single, randomized, double-blind, vehicle-controlled, multi-center, Phase 3 trial was conducted in Japan to evaluate Hyftor for the treatment of adults and pediatric patients 6 years of age and older with facial angiofibroma associated with tuberous sclerosis. A total of 62 Japanese subjects with 3 or more angiofibromas (≥2 mm in diameter with redness in each) on the face were enrolled in this trial. In this trial, subjects applied either Hyftor or vehicle twice daily to the skin of their face affected with angiofibroma for 12 weeks.

The efficacy was assessed by the investigator (live assessment) based on the composite improvement from baseline in size and redness of facial angiofibroma, using subjects' baseline photographs as reference. An assessment of 'Improved' was defined as at least a 50% reduction in the size and a 2-level reduction in redness and an assessment of 'Markedly Improved' was defined as at least a 75% reduction in the size and a 3-level reduction in redness. At week 12, the proportion of patients assessed by the investigator as 'Improved' or 'Markedly Improved' was 23% for patients given Hyftor compared to 6% of patients randomized to receive vehicle. More specifically, 13% of patients given Hyftor compared to 3% of patients randomized to receive vehicle were categorized as

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'Improved.' A rating of 'Markedly Improved' was attained by 10% and 3% of patients randomized to Hyftor and vehicle, respectively.

References

1. Hyftor [package insert]. Noblepharma America, LLC. Bethesda, Maryland. Updated March 2022.
2. Hyftor Drug Evaluation. Express Scripts. April 2022.

Policy History

Original Effective Date: 12/12/2022
Current Effective Date: 12/11/2023
11/03/2022 Medical Policy Committee review
11/09/2022 Medical Policy Implementation Committee approval. New policy.
11/02/2023 Medical Policy Committee review
11/08/2023 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 11/2024

*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);

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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**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: 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.

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.