BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

HYFTOR™ (sirolimus) topical gel Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Hyftor (sirolimus) topical gel and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Dermatologist

2. Individual is 6 years of age or older

3. Individual has a diagnosis of facial angiofibroma associated with tuberous sclerosis confirmed by **ONE** of the following:
    a. Genetic testing of non-lesional tissue that reveals a disease-causing pathogenic variant of *TSC1* or *TSC2* gene
    b. Clinical features that are definite for tuberous sclerosis as defined by the 2012 International Tuberous Sclerosis Complex Consensus Conference (see Definitions section)

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has three or more papules of facial angiofibroma (each with ≥ 2 mm in diameter of redness)

6. There are no erosions, ulcerations, or eruptions on or around the lesion of angiofibroma

7. Individual is not a suitable candidate for laser therapy or surgery (including liquid nitrogen therapy and phototherapy)

8. Individual has completed all age-appropriate vaccinations as recommended by current immunization guidelines

9. Live vaccines will not be used during treatment with Hyftor (sirolimus) topical gel

10. Individual does not use other drugs with mTOR inhibitory action such as: everolimus (generic, brand Afinitor, or brand Zortress), sirolimus (generic, brand Rapamune or brand Fyarro), or temsirolimus (generic or brand Torisel)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Hyftor (sirolimus) topical gel and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Dermatologist

2. Individual's condition has responded while on therapy with response defined as **ONE** of the following:
    a. Individual is assessed as 'Markedly Improved' defined as at least a 75% reduction in angiofibroma size and improvement in angiofibroma redness and reddishness in at least 50% of lesions (see Definitions section)
    b. Individual is assessed as 'Improved' defined as at least a 50% reduction in angiofibroma size and improvement in angiofibroma redness and reddishness in at least 25% of lesions (see Definitions section)

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
    a. Serious infection including opportunistic infections
    b. Progressive multifocal leukoencephalopathy (PML)

c. Interstitial lung disease (including pneumonitis, bronchiolitis obliterans organizing pneumonia [BOOP], and pulmonary fibrosis)
d. Non-infectious pneumonitis

6. Live vaccines will not be used during treatment with Hyftor (sirolimus) topical gel

7. Individual does not use other drugs with mTOR inhibitory action such as everolimus (generic, brand Afinitor, or brand Zortress), sirolimus (generic, brand Rapamune or brand Fyarro), or temsirolimus (generic or brand Torisel)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Hyftor (sirolimus) topical gel is a mammalian target of rapamycin (mTOR) inhibitor immunosuppressant indicated for the treatment of facial angiofibroma associated with tuberous sclerosis in adults and pediatric patients 6 years of age and older.

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder caused by *TSC1* or *TSC2* mutations. It is characterized by hamartomas of the skin, brain, kidneys, and other organs. TSC causes skin lesions (e.g., hypomelanotic macules, angiofibromas and cephalic plaques), epilepsy, neurodevelopmental disorders, and other clinical manifestations. TSC is thought to be caused by the constitutive activation of mammalian target of rapamycin (mTOR).

Oral mammalian targets of rapamycin complex (mTOR) inhibitors are effective for subependymal giant cell astrocytoma, renal angiomyolipoma, lymphangioleiomyomatosis (LAM), epilepsy associated with TSC, and skin lesions.

Angiofibromas are the most common skin lesions observed in patients with TSC older than 5 years of age. Numerous pink to reddish papules or nodules are found on the cheeks, nose, and chin. Patients also develop plaques, hypomelanotic macules, ungual fibromas, and/or shagreen patches. These skin lesions are permanent. Treatment modalities may include liquid nitrogen, phototherapy, surgery and laser therapy.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

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Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations (2021):

Genetic diagnosis: A pathogenic variant in TSC1 or TSC2 is diagnostic for TSC (most TSC-causing variants are sequence variants that clearly prevent TSC1 or TSC2 protein production. Some variants compatible with protein production [e.g., some missense changes] are well established as disease-causing; other variant types should be considered with caution).

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)
- Angiomyolipomas (≥2) [**Note**: A combination of the 2 major clinical features LAM and angiomyolipomas without other features does not meet criteria for a definite diagnosis]

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
- Sclerotic bone lesions

Definite TSC: 2 major features or 1 major feature with 2 minor features.

Possible TSC: either 1 major feature or ≥2 minor features.

Rating criteria for improvements in cutaneous lesions from baseline:

	Angiofibroma Size	Angiofibroma Color
Markedly improved	Reduced in ≥ 75% of lesions	Improved by ≥ 3 reddishness levels in ≥ 50% of lesions
Improved	Reduced in 50-75% of lesions	Improved by 2 reddishness levels in ≥ 50% of lesions or by ≥ 3 reddishness levels in 25-50% of lesions
Slightly improved	Reduced in 25-50% of lesions	Improved by 1 reddishness level in ≥ 50% of lesions or by 2 reddishness levels in 25-50% of lesions
Unchanged	Not obviously changed	Not obviously changed
Slightly aggravated	Increased or newly formed papules in 25-50% of lesions	Aggravated by 1 reddishness level in ≥ 50% of lesions or by 2 reddishness levels in 25-50% of lesions

Aggravated	Increased or newly formed papules in ≥ 50% of lesions	Aggravated by ≥ 2 reddishness level in ≥ 50% of lesions or by ≥ 3 reddishness levels in 25-50% of lesions

Resources:

Hyftor (sirolimus) topical gel product information, revised by Nobelpharma America, LLC. 03-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed August 26, 2024.

Randle S. Tuberous sclerosis complex: Clinical features. In: UpToDate, Firth HV, Pappo AS, Patterson MC, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through August 2024. Last updated January 08, 2024. Accessed September 23, 2024.

Randle S. Tuberous sclerosis complex: Management and prognosis. In: UpToDate, Firth HV, Pappo AS, Patterson MC, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through August 2024. Last updated July 24, 2024. Accessed September 23, 2024.

Northrup H, Aronow ME, Bebin EM, et al, on behalf of the International Tuberous Sclerosis Complex Consensus Group. Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. Pediatric Neurol. 2021;123:50-66. Accessed September 23, 2024.

Wataya-Kaneda M, Ohno Y, Fujita Y, et al: Sirolimus gel treatment vs placebo for facial angiofibromas in patients with tuberous sclerosis complex: A randomized clinical trial. JAMA Dermatol. 2018 Jul; 154(7): 781–788. Access on August 17, 2022. Re-evaluated September 23, 2024.

Wataya-Kaneda M, Nagai H, Ohno Y, et al: Safety and efficacy of the sirolimus gel for TSC patients with facial skin lesions in a long-term, open-label, extension, uncontrolled clinical trial. Dermatol Ther (Heidelb) 2020 10:635–650. Access on August 17, 2022. Re-evaluated September 23, 2024.