

# Drug and Biologic Coverage Policy



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## Sirolimus

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### Related Coverage Resources

#### INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

### Overview

This policy supports medical necessity review for sirolimus topical gel (**Hyftor™**).

Receipt of sample product does not satisfy any criteria requirements for coverage.

### Medical Necessity Criteria

**Sirolimus topical gel (Hyftor) is considered medically necessary when the following are met:**

1. **Facial Angiofibroma Associated with Tuberous Sclerosis.** Individual meets **ALL** of the following criteria (A, B, C, and D):
  - A. 6 years of age or older
  - B. Documented confirmation of tuberous sclerosis complex established by **ONE** of the following (i or ii):
    - i. Molecular genetic testing (for example, a pathogenic variant in the TSC1 or TSC2 gene)

- ii. Clinical diagnostic criteria suggest a definitive diagnosis of tuberous sclerosis complex with either TWO major features [see [Appendix 1](#) for examples] **OR** ONE major feature with TWO minor features [see [Appendix 2](#) for examples]
- C. Three or more facial angiofibromas that are each at least 2 mm in diameter with redness
- D. The medication is prescribed by, or in consultation with, a dermatologist or a prescriber who specializes in the management of tuberous sclerosis complex

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

## Reauthorization Criteria

Sirolimus topical gel (Hyftor) is considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response (for example, reduction in the size and/or redness of the facial angiofibromas).

## Authorization Duration

Initial approval duration: up to 3 months  
Reauthorization approval duration: up to 12 months

## Conditions Not Covered

Any other use is considered experimental, investigational, or unproven.

## Background

### OVERVIEW

*Hyftor, a topical mammalian target of rapamycin inhibitor immunosuppressant, is indicated for the treatment of facial angiofibroma associated with tuberous sclerosis in patients  $\geq$  6 years of age.<sup>1</sup>*

### Disease Overview

Tuberous sclerosis complex is an autosomal dominant genetic disorder caused by mutations in two genes, tuberous sclerosis 1 and tuberous sclerosis 2.<sup>2-4</sup> The incidence rate is approximately one in 6,000 to 10,000 births. It is characterized by non-cancerous (benign) tumors that grow in the brain, as well as in other vital organs such as the kidneys, heart, eyes, lungs, and skin. It can also impact the central nervous system causing seizures, impaired intellectual development, autism, and behavioral issues. The disease has great variability but can occur when patients are very young (around 1 year of age). Most patients (up to 80%) experience various skin conditions due to the disease such as angiofibromas, hypomelanotic macules, and cephalic plaques. Angiofibromas in the face usually appear in young children and gradually proliferate thereafter. This manifestation can be serious as well as disfiguring.

### Clinical Efficacy

The efficacy of Hyftor for its approved use was evaluated in one Phase III, randomized, double-blind, vehicle-controlled, multicenter pivotal study conducted in Japan involving 62 patients who were 6 years of age and older.<sup>1,2</sup> The trial enrolled patients with tuberous sclerosis complex who had three or more facial angiofibromas that were at least 2 mm in diameter with redness present in each. Patients also had a definitive diagnosis of tuberous sclerosis complex. Use of Hyftor reduced the lesion size and redness of the facial angiofibromas after 12 weeks of use compared with vehicle.<sup>1,2</sup> The assessment at 4 weeks after discontinuation of Hyftor suggests that continuation of therapy is required for benefit.<sup>2</sup> It is recommended that if symptoms do not improve within 12 weeks of Hyftor treatment, the need for continuing Hyftor should be reevaluated.<sup>1</sup>

## Appendix 1

Major feature criteria involve angiofibroma (three or more) or fibrous cephalic plaque; angiomyolipomas (two or more); cardiac rhabdomyoma; hypomelanotic macules (three or more; at least 5 mm in diameter); lymphangiomyomatosis; multiple cortical tubers and/or radial migration lines; multiple retinal hamartomas; Shagreen patch; subependymal giant cell astrocytoma; subependymal nodule (two or more); or ungula fibromas (two or more).

## Appendix 2

Minor feature criteria involve “confetti” skin lesions; dental enamel pits (three or more); intraoral fibromas (two or more); multiple renal cysts; nonrenal hamartomas; retinal achromic patch; and sclerotic bone lesions.

## References

1. Hyftor 0.2% topical gel [prescribing information]. Bethesda, MD: Nobelpharma; March 2022.
2. 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;154(7):781-788.
3. Krueger DA, Northrup H, on behalf of the International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 international tuberous sclerosis complex consensus conference. *Pediatric Neurol.* 2013;49(4):255-265.
4. 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.

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