sirolimus (Hyftor™)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO259

Description

Sirolimus (Hyftor) is a topically administered mammalian target of rapamycin (mTOR) inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
sirolimus (Hyftor)	Facial angiofibroma associated with Tuberous Sclerosis	0.2% topical gel	6-11 years of age: 20 grams/30 days
			12 years of age and older: 30 grams/30 days

Initial Evaluation

I. **Sirolimus (Hyftor)** may be considered medically necessary when the following criteria are met:
   A. Member is 6 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a dermatologist or neurologist; **AND**
   C. Provider attestation that the member has facial angiofibroma, associated with tuberous sclerosis confirmed by genetic testing and/or clinical symptoms; **AND**
   D. Provider attestation that facial angiofibroma is associated with one or more of the following: bleeding, intense itching, pain, change in physical appearance, recent enlargement, or recent increase in number of lesions; **AND**
   E. Treatment with topical compounded sirolimus (gel, cream, or ointment) has been ineffective, contraindicated, or not tolerated; **AND**
   F. Previous treatment with surgery (shave excision, cryotherapy, electrodessication, radiofrequency ablation, dermabrasion) has been ineffective, contraindicated, or not tolerated; **OR**
      1. Previous treatment with laser therapy (ablative laser resurfacing, pulse dye laser) has been ineffective, contraindicated, or not tolerated.

II. Sirolimus (Hyftor) is considered investigational when used for all other conditions, including but not limited to:
   A. Tufted angiomas
   B. Fibroma or angiofibroma not associated with tuberous sclerosis complex
   C. Non FDA-approved dermatologic conditions

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation that member has exhibited improvement or stability in extent and/or severity of angiofibroma (e.g., reduction in angiofibroma size and redness).

Supporting Evidence

I. Tuberous sclerosis complex (TSC) is a rare genetic multisystem disorder associated with the formation of benign tumors in various organ systems throughout the body, most commonly including the skin, brain, eyes, heart, kidneys, and lungs. Skin manifestations of TSC occur in up to 95% of individuals and include facial angiofibromas, hypomelanotic macules, fibrous plaques, Shagreen patches, and ungual fibromas. Most patients with TSC present with angiofibromas with onset commonly occurring in early childhood or early adulthood. Angiofibromas are benign reddish pink bumps located on the face, and without treatment they can cause facial disfigurement, bleeding, itching, erythema, and significant psychosocial consequences.
II. Per the International Tuberous Sclerosis Complex Diagnostic Criteria Surveillance and Management Recommendations, the diagnosis of tuberous sclerosis should be confirmed by genetic testing through identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue. In the absence of TSC mutations, diagnosis can be made through identification of clinical features including but not limited to fibrous cephalic plaque, hypomelanotic macules, ungual fibromas, Shagreen patch, multiple retinal hamartomas, cortical dysplasia, subependymal nodules, subependymal giant cell astrocytoma's, cardiac rhabdomyoma, lyphangiolelomyomatosis, and angiomyolipomas.
III. While there are limited treatment options for this condition, the International Tuberous Sclerosis Complex Diagnostic Criteria Surveillance and Management Recommendations recommend the use of topical compounded sirolimus (category 1 recommendation, based on a

high-level of evidence and uniform consensus). Studies have evaluated compounded formulations ranging from 0.1% to 1% in a variety of vehicles. Smaller and flatter appearing lesions tend to respond better to topical sirolimus, so early treatment is recommended. Sirolimus (Hyftor) has not been evaluated against compounded sirolimus for the treatment of TSC angiofibroma, therefore comparative efficacy and safety remain uncertain. However, the chemical entity in both products is the same, therefore they are expected to provide similar safety and efficacy, even in the absence of a commercially available, FDA-labeled indication for compounded sirolimus. Further, given the long-established safety, efficacy, and cost effectiveness of compounded sirolimus, trial is required prior to use of sirolimus (Hyftor).

IV. Guidelines recommend surgical approaches (category 2B, based on lower-level evidence and consensus that the intervention is appropriate) for angiofibromas rapidly changing in size and/or number, causing pain, bleeding, irritation, disfigurement, or impaired function. These procedures include shave excision, cryotherapy, electrodessication, radiofrequency ablation, dermabrasion, and laser therapy. They have been standardly used for angiofibroma management, though patients may not be candidates for surgery depending on anesthetic risk, age, active infection, uncontrolled diabetes, pregnancy, etc. Contraindications for laser therapy may include malignant carcinoma, irradiation of neck, epilepsy, exposure of retina, cognitive impairment, and pregnancy. Specifically, younger children may benefit from pulsed-dye laser therapy and adolescence ablative laser therapy to reduce facial erythema.

V. The FDA-approval of sirolimus (Hyftor) was based off a phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled trial. The study population included 62 adults and pediatric patients greater than 6 years of age, with a definitive diagnosis of TSC, 3 or more reddish papules of facial angiofibromas (> 2 mm diameter), and a past difficulty with or did not want laser or surgical therapy. The concurrent use of any mTOR inhibitor, topical tacrolimus, topical steroids, topical antibiotics, topical vitamin D, adapalene, benzyl peroxide, ibuprofen piconol, resorcinol, and zinc-salicylic acid, were prohibited. Population characteristics were as follows: mean age 22 years (range of 6-53 years), 42% of patients had intellectual impairment, 60% had epilepsy,28% had prior mTOR use (including topical sirolimus), and 32% had prior laser therapy, surgical resection, or liquid nitrogen therapy. The primary endpoint was composite improvement of angiofibroma size and color at week 12, which was met with 5 (17%) improved and 13 (43%) markedly improved in the sirolimus group compared to zero participants in the placebo group, with 84% rated unchanged. The secondary endpoints were response rates for composite, size, color, and plaques, and change in Dermatology Life Quality Index (DLQI) and Children's DLQI (CDQLI). The response rates for size, color, and plaques were statistically significant while the change from baseline in DLQI and CDLQI was not. The most common adverse events included dry skin (40%), application site irritation (37%), and itching (17%). Overall, this was a well-designed phase 3 clinical trial that showed statistical improvement in composite response rate and individual size, color and plaque response rates, however clinical meaningfulness of these endpoints and measurement tool remain unknown. Applicability to the

larger TSC population is limited due to a large proportion of the population having previously been treated with surgery, laser or mTOR inhibitor therapy.

VI. The initial authorization length of three months is supported by clinical study duration of 12 weeks and prescribing information guidance which indicates that if symptoms do not improve by week 12 of treatment, prescriber should reevaluate the need for continuation of the medication.

VII. Quantity limits are based on the maximum daily doses used in pivotal study and as indicated by the FDA, and are expected to be sufficient, even if a large majority of the face is impacted. If symptoms do not improve within 12 weeks of consistent use and excessive quantities are needed, alternative treatment strategies that have the potential to be more efficacious and cost effective should be considered.

References

1. Hyftor [Prescribing Information]. Bethesda, MD: Noblepharma. February 2022.
2. Macri A, Kwan E, Tanner LS. Cutaneous angiofibroma. In: StatPearls. StatPearls Publishing; 2022.
3. Northrup H, Aronow ME, Bebin EM, et al. Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. Pediatric Neurology. 2021;123:50-66.
4. 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.
5. UpToDate. Tuberous sclerosis complex: Genetics, clinical features, and diagnosis. Updated April 6, 2022. Accessed May 5, 2022.
6. UpToDate. Tuberous sclerosis complex: Management and prognosis. Updated April 6, 2022. Accessed May 5, 2022
7. Navratil L, Kymplova J. Contraindications in noninvasive laser therapy: truth and fiction. Journal of Clinical Laser Medicine & Surgery. 2002;20(6):341-343.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
everolimus (Afinitor®, Afinitor Disperz®)	Partial seizure, adjunct, tuberous sclerosis syndrome
	Angiomyolipoma of the kidney, tuberous sclerosis syndrome
	Breast cancer, advanced, HR+, HER2 -, in combination with exemestane after failure with letrozole or anastrozole
	Subependymal giant cell astrocytoma
	Renal cell carcinoma, advanced disease
	Neuroendocrine tumor, gastrointestinal, lung or pancreatic, unresectable locally advanced or metastatic
cannabidiol (Epidiolex®)	Tuberous Sclerosis Complex
	Lennox-Gastaut Syndrome

	Dravet Syndrome

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	07/2022