Hyftor (sirolimus) Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
2/1/2024	4/1/2023

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
HYFTOR® (sirolimus) Topical gel	Treatment of facial angiofibroma associated with tuberous sclerosis in adults and pediatric patients 6 years of age and older		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Tuberous Sclerosis Complex	Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder caused by a mutation in either the *TSC1* gene or the *TSC2* gene. TSC is characterized by the development of a variety of benign tumors in multiple organs, including the brain, heart, skin, eyes, kidney, lung, and liver. Seizures are the most frequent presenting neurologic feature of TSC, with more than 80% of patients developing seizures during childhood. Facial angiofibromas, the most obvious cutaneous manifestation of TSC, appear as innumerable pink papules that progressively enlarge and multiply over time. The lesions, which are highly visible markers of disease, may spontaneously bleed, impair vision, and cause emotional distress.(2,3,6) Diagnosis of TSC is made by clinical diagnostic criteria or genetic analysis.(2,6) Identification of a pathogenic variant in *TSC1* or *TSC2* is sufficient for the diagnosis or prediction of TSC regardless of clinical findings, however 10-15% of patients with TSC meeting clinical diagnostic criteria have no mutation identified by conventional genetic testing. Therefore, failure to identify a pathogenic variant in *TSC1* or *TSC2* does not exclude a diagnosis of TSC. Clinical diagnostic criteria indicate a definitive TSC diagnosis if 2 major features or 1 major feature with 2 minor features are met. Major features are: hypomelanotic macules (greater than or equal to 3, at least 5 mm diameter), angiofibroma (greater than or equal to 3) or fibrous cephalic plaque, ungual fibromas (greater than or equal to 2), shagreen patch, multiple retinal hamartomas, multiple cortical tubers and/or radial migration lines, subependymal nodule (greater than or equal to 2), subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangiomyomatosis, angiomyolipomas (greater than or equal to 2); note that a combination of LAM and angiomyolipomas, without other features, does not meet the criteria for a definite diagnosis. Minor features are: "confetti" skin lesions, dental enamel pits (greater than or equal to 3), intraoral fibromas (greater than or equal to 2), retinal achromic patch, multiple renal cysts, nonrenal hamartomas, sclerotic bone lesions.(6) There is no significant risk of malignant transformation of skin lesions associated with TSC. When not prominent, the skin lesions do not require treatment. However, closer

	surveillance and intervention is recommended for skin lesions that rapidly change in size or number, and for those that cause pain, bleeding, functional impairment, or social problems. Procedures to improve the appearance of skin lesions include dermabrasion, laser therapy, or surgical removal (excision) of a lesion.(2,3,6) These procedures are not effective, however, in preventing early lesions and therefore have less than satisfactory outcomes. Sirolimus topical gel is FDA approved for the treatment of facial angiofibroma associated with TSC in patients age 6 years and older. Although there is rapid response in practically all patients, the possibility of recurrence is quite high. For severely disfiguring facial angiofibromas, a combination of laser therapy or dermabrasion in conjunction with topical sirolimus can be very useful.(2,3)
Efficacy	Tuberous sclerosis complex (TSC) is associated with genetic defects in the *TSC1* and *TSC2* genes which results in overactivation of the mTOR pathway and benign tumor formation in multiple organs. Sirolimus inhibits mTOR activation.(1,4,5) A single, randomized, double-blind, vehicle-controlled, multicenter, Phase 3 trial evaluated Hyftor for the treatment of adults and pediatric patients 6 years of age and older with facial angiofibroma associated with definite TSC. The response rates of angiofibromas at weeks 4, 8, and 12 of treatment were 0 each in the placebo group in contrast to 20% (95% CI, 8%-39%; p = .01), 43% (95% CI, 26%-63%; p less than .001), and 60% (95% CI, 41%-77%; p less than .001), respectively, in the sirolimus group.(1,5) In another evaluation of 33 patients with facial angiofibromas associated with TSC, sirolimus gel treatment improved FA associated with TSC in 23 of the 33 (70%) patients after 3 months of treatment. None of the patients discontinued the treatment due to adverse events.(4)
Safety(1)	HYFTOR is contraindicated in patients with a history of hypersensitivity to sirolimus or any other component of HYFTOR.

REFERENCES

Number	Reference
1	HYFTOR prescribing information. Nobelpharma America, LLC. March 2022.
2	DiMario FJ, et al. Tuberous Sclerosis. National Organization for Rare Disorders (NORD). Last updated May 2023. Available at https://rarediseases.org/rare-diseases/tuberous-sclerosis/.
3	Randle S, et al. Tuberous Sclerosis Complex: Management and Prognosis. Literature review current through June 2023. Last updated August 2022.
4	Hatano T, Ohno Y, Imai Y, et al. Improved Health-Related Quality of Life in Patients Treated with Topical Sirolimus for Facial Angiofibroma Associated with Tuberous Sclerosis Complex. Orphanet J Rare Dis. 2020 Jun;15:133.
5	Wataya-Kaneda M, Ohno Y, Fujita Y, et al. Sirolimus Gel Treatment vs Placebo for Facial Angiofibromas in Patients with Tuberous Sclerosis Complex. JAMA Dermatology. 2018 Jul;154(7):781-788.
6	Northrup H, Aronow ME, Bebin EM, et al. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatr Neurol. 2021 Oct;123:50-66.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Hyftor	sirolimus gel	0.2 %	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Hyftor	Sirolimus Gel	0.2 %	7	Tubes	84	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Hyftor	sirolimus gel	0.2 %	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Hyftor	Sirolimus Gel	0.2 %	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of tuberous sclerosis complex (TSC) confirmed by ONE of the following: A. The patient has two major features OR one major and two minor features of TSC clinical diagnostic criteria (Major features: hypomelanotic macules [greater than or equal to 3, at least 5 mm diameter], angiofibroma [greater than or equal to 3] or fibrous cephalic plaque, ungual fibromas [greater than or equal to 2], shagreen patch, multiple retinal hamartomas, multiple cortical tubers and/or radial migration lines, subependymal nodule [greater than or equal to 2], subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangiomyomatosis (LAM)*, angiomyolipomas* [greater than or equal to 2]; note that a combination of LAM and angiomyolipomas, without other features, does not meet the criteria for a definite diagnosis. Minor features: "confetti" skin lesions, dental enamel pits [greater than or equal to 3], intraoral fibromas [greater than or equal to 2], retinal achromic patch, multiple renal cysts, nonrenal hamartomas, sclerotic bone lesions) **OR** B. The patient has a pathogenic variant in the TSC1 gene or TSC2 gene confirmed by genetic testing **AND** 2. The patient has three or more facial angiofibromas **AND** 3. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**

Module	Clinical Criteria for Approval
	B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., dermatologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 weeks NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., dermatologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** Initial 12 weeks; Renewal 12 months