# NEW DRUG APPROVAL

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| **Brand Name** | Hyftor™ |
| **Generic Name** | sirolimus |
| **Drug Manufacturer** | Nobelpharma America, LLC |

## New Drug Approval

FDA Approval Date: March 22, 2022

Review Designation: Priority; Orphan

Review Type: Type 3 - New Dosage Form; New Drug Application (NDA): 213478

Dispensing Restrictions: N/A

## Place in Therapy

### DISEASE DESCRIPTION & EPIDEMIOLOGY

Tuberous sclerosis is a genetic disorder that is caused by mutations in tuberous sclerosis complex 1 (*TSC1*) gene, which encodes the protein hamartin, or the tuberous sclerosis complex 2 (*TSC2*) gene, which encodes the protein tuberin. The autosomal-dominant disease causes benign tumors to grow throughout the body primarily the brain, eyes, heart, kidneys, skin, and lungs. These proteins normally suppress the activation of the mechanistic of rapamycin (mTOR) pathway. However, when mutated, they can cause unregulated proliferation of cell growth forming multi-organ hamartomas, or facial skin lesions. mTOR is activated in the proliferating fibroblast-like cells within facial angiofibromas.

Facial angiofibromas present as pinkish or reddish bumps that are usually located on the cheeks, nose, and chin. They are seen in approximately 75%–80% of patients with TSC. Without treatment, they may cause significant disfiguration, bleeding, pruritus, erythema, and significant psychosocial consequences for affected patients. The tumor is benign and remains localized with no evidence of metastasis potential.

In the United States, approximately 50,000 people have TSC, and about 75%–80% (about 40,000) of patients with TSC have facial angiofibromas with most diagnosed as children. Facial angiofibromas are facial skin lesions caused by unregulated cell growth. Without treatment, these may cause significant disfiguration, bleeding, pruritus, and erythema. The estimated incidence of TSC is 1/6000 to 1/10,000 live births. Facial angiofibromas are considered one of the most obvious clinical presentations of TSC, a rare disorder that affects the skin, kidneys, heart, brain, and lungs. With TSC, angiofibromas typically arise on the face in childhood and early adulthood.

## Efficacy

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 (NCT02635789). 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. Overall, 28 subjects (45%) were male and 34 (55%) were female. A total of 25 subjects (40%) were between 6 and < 18 years of age. 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. The proportion of subjects assessed as 'Improved' or 'Markedly Improved' at Week 12 is presented in Table 1. 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.

**Table 1. Improvement in Facial Angiofibroma Associated with Tuberous Sclerosis in Patients Aged 6 Years and Older at Week 12**

| Proportion of Subjects Assessed by the Investigator As: | Hyftor™ (N = 30) | Vehicle (N = 32) |
|---|---|---|
| 'Improved' or 'Markedly improved' | 23% | 6% |
| 'Improved' | 13% | 3% |
| 'Markedly improved' | 10% | 3% |

In a 104-week, open-label safety trial, the most common adverse reactions associated with Hyftor™ application were application site irritation (31%), dry skin (28%), acne (20%), pruritus (9%), eye irritation (9%), erythema (7%), acneiform dermatitis (6%), contact dermatitis (5%), solar dermatitis (1%), and photosensitivity reaction (1%). Adverse reactions occurred with similar frequency in adult and pediatric subjects 6 years of age and older.

## Safety

### ADVERSE EVENTS

The most common adverse reactions reported by ≥1% of subjects treated with Hyftor™ and more frequently than in subjects treated with vehicle are presented in Table 2. Adverse reactions occurred with similar frequency in pediatric subjects 6 years of age and older.

**Table 2: Adverse Reactions in ≥1% of Subjects Aged 6 Years and Older with Facial Angiofibroma Associated with Tuberous Sclerosis Through Week 12**

| Preferred Term | Hyftor™ (N=30) | Vehicle (N= 32) |
|---|---|---|
| Dry skin[a] | 12 (40%) | 4 (13%) |
| Application site irritation | 11 (37%) | 9 (28%) |
| Pruritus | 5 (17%) | 4 (13%) |
| Acne | 2 (7%) | 0 (0%) |
| Acneiform dermatitis | 1 (3%) | 0 (0%) |
| Ocular hyperemia | 1 (3%) | 0 (0%) |
| Skin hemorrhage | 1 (3%) | 0 (0%) |
| Skin irritation | 1 (3%) | 0 (0%) |

### WARNINGS & PRECAUTIONS

- Hypersensitivity Reactions: Oral sirolimus has been associated with hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis. Discontinue Hyftor™ immediately if symptoms of hypersensitivity occur.
- Serious Infection: Serious infections, including opportunistic infections and latent viral infections, such as progressive multifocal leukoencephalopathy, have been reported with oral sirolimus. Discontinue Hyftor™ immediately if symptoms of infection occur.
- Malignancy: Oral sirolimus has been associated with malignancy, including lymphoma and skin cancer. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using Hyftor™.
- Hyperlipidemia: Oral sirolimus has been associated with increased serum cholesterol and triglycerides requiring treatment. Monitor for hyperlipidemia during treatment.
- Interstitial Lung Disease (ILD)/Non-infectious Pneumonitis: Oral sirolimus has been associated with ILD, sometimes fatal. Discontinue Hyftor™ if ILD symptoms occur.
- Immunizations: During treatment with Hyftor™ , vaccinations may be less effective. Avoid use of live vaccines during treatment with Hyftor™.
- Embryo-Fetal Toxicity: Based on animal studies, Hyftor™ can cause fetal harm. Use of effective contraception is recommended for females of reproductive potential prior to and throughout treatment, and for 12 weeks after final dose of Hyftor™.
- Male Infertility: Oral sirolimus has been associated with azoospermia and oligospermia. Advise males that Hyftor™ may impair fertility.

### CONTRAINDICATIONS

Hyftor™ is contraindicated in patients with a history of hypersensitivity to sirolimus or any other component of Hyftor™. Reactions to sirolimus have included anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis.

## Clinical Pharmacology

### MECHANISMS OF ACTION

The mechanism of action of sirolimus in the treatment of angiofibroma associated with tuberous sclerosis is unknown. Tuberous sclerosis is associated with genetic defects in TSC1 and TSC2 which leads to the constitutive activation of mammalian target of rapamycin (mTOR). Sirolimus inhibits mTOR activation.

## Dose & Administration

### ADULTS

800 mg (2.5 cm) for patients 12 years of age and older, apply to the skin of the face affected with angiofibroma twice daily.

### PEDIATRICS

600 mg (2 cm) for pediatric patients 6 to 11 years of age.

### GERIATRICS

Refer to adult dosing.

### RENAL IMPAIRMENT

No dosage adjustments required.

### HEPATIC IMPAIRMENT

No dosage adjustments required.

## Product Availability

### DOSAGE FORM(S) & STRENGTH(S)

Topical gel, 0.2%: 2 mg of sirolimus per gram.