# Clinical Policy: Sirolimus Protein-Bound Particles (Fyarro), Topical Gel (Hyftor)

Reference Number: ERX.SPA.466
Effective Date: 03.01.22
Last Review Date: 05.22
Line of Business: Commercial, Medicaid

Revision Log

**See Important Reminder at the end of this policy for important regulatory and legal information.**

**Description**
Sirolimus protein-bound particles (Fyarro™) and topical gel (Hyftor™) are mammalian target of rapamycin (mTOR) inhibitors.

**FDA Approved Indication(s)**
Fyarro is indicated for the treatment of adult patients with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor (PEComa).

Hyftor is indicated for the treatment of facial angiofibroma associated with tuberous sclerosis in adults and pediatric patients 6 years of age and older.

**Policy/Criteria**
*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

*Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.*

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Fyarro and Hyftor are **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**

**A. Perivascular Epithelioid Cell Tumor** (must meet all)**:**

1. Diagnosis of locally advanced unresectable or metastatic malignant PEComa;
2. Request is for Fyarro;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. Use as a single agent;
6. Member does not have PEComa type lymphagioleiomyomatosis;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 100 mg/m² IV on Days 1 and 8 of each 21-day cycle;
   b. Dose is supported by practice guideline or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration: 6 months**

**B. Facial Angiofibroma Associated with Tuberous Sclerosis** (must meet all)**:**

1. Diagnosis of facial angiofibroma associated with tuberous sclerosis;
2. Request is for Hyftor;
3. Prescribed by or in consultation with an oncologist, neurologist, or dermatologist;
4. Age ≥ 6 years;
5. Dose does not exceed one of the following (a or b):
   a. 600 mg (2 cm) for members 6 to 11 years of age;
   b. 800 mg (2.5 cm) for members 12 years of age and older.

**Approval duration: 3 months**

**C. Other diagnoses/indications**
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**II. Continued Therapy**

**A. Perivascular Epithelioid Cell Tumor** (must meet all):
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, or documentation supports that member is currently receiving Fyarro for a covered indication and has received this medication for at least 30 days;
2. Request is for Fyarro;
3. Member is responding positively to therapy;
4. If request is for a dose increase, request meets one of the following (a or b):*
   a. Both of the following (i and ii):
      i. New dose does not exceed 100 mg/m² IV on Days 1 and 8 of each 21-day cycle;
      ii. Dose is at least 45 mg/m² IV on Days 1 and 8 of each 21-day cycle;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration: 12 months**

**B. Facial Angiofibroma Associated with Tuberous Sclerosis** (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Request is for Hyftor;
3. Member is responding positively to therapy as evidenced by, including but not limited to, a reduction in the size and/or redness of facial angiofibroma;
4. If request is for a dose increase, new dose does not exceed one of the following (a or b):
   a. 600 mg (2 cm) for patients 6 to 11 years of age;
   b. 800 mg (2.5 cm) for patients 12 years of age and older.

**Approval duration: 12 months**

**C. Other diagnoses/indications** (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   **Approval duration: Duration of request or 6 months (whichever is less)**; or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**III. Diagnoses/Indications for which coverage is NOT authorized:**

**A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

FDA: Food and Drug Administration
NCCN: National Comprehensive Cancer Network
PEComa: perivascular epithelioid cell tumor

*Appendix B: Therapeutic Alternatives*

Not applicable

*Appendix C: Contraindications/Boxed Warnings*

- Contraindication(s): history of severe hypersensitivity to sirolimus, other rapamycin derivatives, or albumin.

- Boxed warning(s): none reported

## V. Dosage and Administration

| Drug Name | Indication | Dosing Regimen | Maximum Dose |
|---|---|---|---|
| Sirolimus protein-bound particles (Fyarro) | Locally advanced unresectable or metastatic malignant PEComa | 100 mg/m² administered as an IV infusion over 30 minutes on Days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity | 100 mg/m² administered as an IV infusion over 30 minutes on Days 1 and 8 of each 21-day cycle |
| Sirolimus topical gel (Hyftor) | Facial angiofibroma associated with tuberous sclerosis | Apply to the skin of the face affected with angiofibroma twice daily | 600 mg (2 cm) for patients 6 to 11 years of age;<br>800 mg (2.5 cm) for patients 12 years of age and older |

## VI. Product Availability

| Drug Name | Availability |
|---|---|
| Sirolimus protein-bound particles (Fyarro) | Lyophilized powder for infusion: 100 mg of sirolimus formulated as albumin-bound particles in single-dose vial for reconstitution |
| Sirolimus topical gel (Hyftor) | Topical gel, 0.2%: 2 mg of sirolimus per gram |

## VII. References

1. Fyarro Prescribing Information. Pacific Palisades, CA. Aadi Bioscience, Inc; November 2021. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213312Orig1s000Corrected_lbl.pdf. Accessed December 8, 2021.
2. Hyftor Prescribing Information. Bathesda, MD. Nobelpharma America, LLC; March 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213478s000lbl.pdf. Accessed April 14, 2022.
3. National Comprehensive Cancer Network. Soft Tissue Sarcoma Version 2.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed December 8, 2021.
4. ClinicalTrials.gov. A Phase 2 Study of ABI-009 in Patients with Advanced Malignant PEComa (AMPECT). Available at https://www.clinicaltrials.gov/ct2/show/NCT02494570. Accessed December 8, 2021.
5. Bissler JJ, McCormack FX, Young LR et al. Sirolimus for Angiomyolipoma in Tuberous Sclerosis complex or Lymphangioleiomyomatosis. The New England Journal of Medicine. 2008; 358:140-51.
6. Wagner AJ, Malinowska-Kolodziej I, Morgan JA et al. Clinical Activity of mTOR Inhibition with Sirolimus in Malignant Perivascular Epithelioid Cell Tumors: Targeting the Pathogenic Activation of mTORC1 in Tumors. Journal of Clinical Oncology. 2010; DOI: 10.1200/JCO.2009.25.2981.
7. 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 1;154(7):781-788.
8. Northrup H, Aronow ME, Bebin EM, et al. International Tuberous Sclerosis Complex Consensus Group. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatr Neurol. 2021 Oct;123:50-66.

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| Policy created. | 12.14.21 | 02.22 |
| RT4: added Hyftor to policy. | 04.14.22 | 05.22 |

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.