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

Reference Number: CP.PHAR.574
Effective Date: 03.01.22
Last Review Date: 02.23
Line of Business: Commercial, HIM, Medicaid

Coding Implications
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.

It is the policy of health plans affiliated with Centene Corporation® that Fyarro and Hyftor are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor (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 lymphangioleiomyomatosis;
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 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: 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. Age 6 to 11 years: 600 mg (2 cm);
   b. Age ≥ 12 years: 800 mg (2.5 cm).

Approval duration: 3 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Currently receiving medication via Centene benefit, 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. Member meets one of the following (a or b):

a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*

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. Age 6 to 11 years: 600 mg (2 cm);
   b. Age ≥ 12 years: 800 mg (2.5 cm).

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid 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	Age 6 to 11 years: 600 mg (2 cm) Age ≥ 12 years: 800 mg (2.5 cm)

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 November 3, 2022.
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 November 3, 2022.
3. National Comprehensive Cancer Network. Soft Tissue Sarcoma Version 2.2022. Available at https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed November 3, 2022.
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 November 3, 2022.
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.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9331	Injection, sirolimus protein-bound particles (Fyarro), 1 mg

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
Added HCPCS code for Fyarro [J9331].	06.30.22	
Template changes applied to other diagnoses/indications and continued therapy section.	09.19.22	
1Q 2023 annual review: no significant changes; references reviewed and updated.	11.03.22	02.23

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering

benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.