**Sirolimus** (facial angiofibroma associated with tuberous sclerosis complex, ≥ 6 years)

Resolution of: 21 March 2024 valid until: unlimited
Entry into force on: 21 March 2024
Federal Gazette, BAnz AT 08 05 2024 B2

**Therapeutic indication (according to the marketing authorisation of 15 May 2023):**

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

**Therapeutic indication of the resolution (resolution of 21 March 2024):**

See therapeutic indication according to marketing authorisation.

## 1. Extent of the additional benefit and significance of the evidence

Sirolimus is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

<u>Adults and paediatric patients aged 6 years and older with facial angiofibroma associated with tuberous sclerosis complex</u>

**Extent of the additional benefit and significance of the evidence of sirolimus:**

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

**Study results according to endpoints:**[1]

Adults and paediatric patients aged 6 years and older with facial angiofibroma associated with tuberous sclerosis complex

**Summary of results for relevant clinical endpoints**

| Endpoint category | Direction of effect/ risk of bias | Summary |
|---|---|---|
| Mortality | ↔ | No deaths occurred. |
| Morbidity | ↑ | Advantage in the improvement of angiofibromas. |
| Health-related quality of life | ↔ | No relevant differences for the benefit assessment. |
| Side effects | ↔ | No relevant differences for the benefit assessment. |
| Explanations:<br>↑: statistically significant and relevant positive effect with low/unclear reliability of data<br>↓: statistically significant and relevant negative effect with low/unclear reliability of data<br>↑↑: statistically significant and relevant positive effect with high reliability of data<br>↓↓: statistically significant and relevant negative effect with high reliability of data<br>↔: no statistically significant or relevant difference<br>∅: No data available.<br>n.a.: not assessable | | |

**NPC-12G-1 study:** pivotal approval study, phase III RCT, sirolimus vs placebo, 12 weeks, data cut-off: 21 October 2016

**OSD-001-001 study:** Dose escalation study in a parallel group design, RCT, sirolimus (cohort with the dosage of 0.2% compliant with the marketing authorisation) vs placebo, 12 weeks, data cut-off: 30.09.2014

**NPC-12G-2 study:** single-arm long-term study, open-label, uncontrolled, data cut-off: 26.09.2018 (presented additionally)

**Mortality**

No deaths occurred.

[1] Data from the dossier assessment of the G-BA (published on 2. January 2024), and from the amendment to the dossier assessment from 13 February 2024, unless otherwise indicated.

## Morbidity

| ***NPC-12G-1 study*** **Endpoint** | **Sirolimus** | | **Placebo** | | **Sirolimus vs placebo** |
|---|---|---|---|---|---|
| | N[a] | Patients with event n (%) | N[a] | Patients with event n (%) | RR [95% CI][b] p value |
| **Improvement in angiofibromas according to IFA at week 12** | | | | | |
| Improvement by ≥ 3 points[c] | 30 | 21 (70.0) | 32 | 1 (3.1) | 22.40 [3.21; 156.39] 0.0017 |

| ***NPC-12G-1 study*** **Endpoint** | **Sirolimus** | | **Placebo** | | **Sirolimus vs placebo** |
|---|---|---|---|---|---|
| | N[a] | Patients with event n (%) | N[a] | Patients with event n (%) | RR [95% CI][b] p value |
| ***Combined improvement[d] in angiofibromas at week 12 according to IRC (presented additionally)*** | | | | | |
| *3 = significantly improved* | *30* | *18 (60.0)* | *32* | *0 (0.0)* | *39.43 [2.48; 626.22]; 0.01* |
| *2 = improved* | | | | | |

| ***OSD-001-001 study*** **Endpoint** | **Sirolimus** | | **Placebo** | | **Sirolimus vs placebo** |
|---|---|---|---|---|---|
| | N[a] | Patients with event n (%) | N[a] | Patients with event n (%) | RR [95% CI][b] p value |
| ***Combined improvement[e] in angiofibromas at week 12 (presented additionally)*** | | | | | |
| *Score of 1.5 or higher* | *8* | *8 (100)* | *12* | *3 (25.0)* | *3.57 [1.47; 8.69]; 0.005* |

| ***NPC-12G-2 study (presented additionally)*** ***Endpoint*** | ***Sirolimus*** | |
|---|---|---|
| | ***N[a]*** | ***Patients with event n (%)*** |
| *Combined improvement in angiofibromas at week 52 according to IRC[f] (presented additionally)* | *93* | *68 (73.1)* |

## Health-related quality of life

| ***NPC-12G-1 study*** **Endpoint** | **Sirolimus N = 30** | **Placebo N = 32** | **Sirolimus vs placebo** |
|---|---|---|---|

| | N[a] | Baseline *MV (SD)* | Change from baseline *MV (SD)* | N[a] | Baseline *MV (SD)* | Change from baseline *MV (SD)* | *p value*[g] |
|---|---|---|---|---|---|---|---|
| **Subjects < 16 years[h] (CDLQI)** | | | | | | | |
| CDLQI total score[i] (Change at week 12) | 10 | 1.2 (1.55) | -0.4 (2.07) | 10 | 0.8 (0.92) | 0.1 (1.91) | 0.639 |
| **Subjects ≥ 16 years[h] (DLQI)** | | | | | | | |
| DLQI total score[i] (Change at week 12) | 16 | 2.1 (4.65) | -0.1 (3.43) | 18 | 2.4 (3.16) | -0.9 (2.49) | 0.076 |

| ***NPC-12G-2 study (presented additionally) Endpoint*** | ***Sirolimus*** | | | |
|---|---|---|---|---|
| | *N[j]* | *Baseline MV (SD)* | *N[k]* | *Change at week 52 MV (SD)* |
| ***DLQI and CDLQI total score[h,l]*** | | | | |
| *< 16 years (CDLQI)[m]* | *37* | *0.7 (1.08)* | *33* | *0.0 (1.52)* |
| *≥ 16 years (DLQI)[m]* | *46* | *1.4 (2.67)* | *40* | *-0.5 (2.19)* |

## Side effects

| **Endpoint** Study | **Sirolimus** | | **Placebo** | | **Sirolimus vs placebo** |
|---|---|---|---|---|---|
| | N[a] | Patients with event n (%) | N[a] | Patients with event n (%) | RR [95% CI] p value |
| **AE** | | | | | |
| NPC-12G-1 study | 30 | 27 (90.0) | 32 | 22 (68.8) | - |
| OSD-001-001 study[n] | 8 | 7 (87.5) | 12 | 7 (58.3) | - |
| **Severe AEs** | | | | | |
| NPC-12G-1 study | 30 | 0 | 32 | 0 | - |
| OSD-001-001 study[n] | 8 | 1 (12.5) | 12 | 0 | 4.41 [0.20; 95.97]; 0.34 |
| Meta-analysis[o] | 38 | 1 (2.6) | 44 | 0 | 4.33 [0.20; 94.83]; 0.35 |
| **SAE** | | | | | |
| NPC-12G-1 study | 30 | 1 (3.3) | 32 | 0 | 3.20 |

| **Endpoint**<br>Study | **Sirolimus** | | **Placebo** | | **Sirolimus vs placebo** |
|---|---|---|---|---|---|
| | N[a] | Patients with event n (%) | N[a] | Patients with event n (%) | RR [95% CI] p value |
| | | | | | [0.14; 75.52]; 0.47 |
| OSD-001-001 study[n] | 8 | 1 (12.5) | 12 | 1 (8.3) | 1.50 [0.11; 20.68]; 0.76 |
| Meta-analysis[o] | 38 | 2 (5.3) | 44 | 1 (2.3) | 2.79 [0.25; 31.33]; 0.41 |
| **AEs which led to the discontinuation of the study medication** | | | | | |
| NPC-12G-1 study | 30 | 0 | 32 | 0 | - |
| OSD-001-001 study[n] | 8 | 0 | 12 | 0 | - |
| Meta-analysis[o] | 38 | 0 | 44 | 0 | - |
| **Severe adverse events according to MedDRA** (with incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT) | | | | | |
| NPC-12G-1 study | No severe AEs occurred | | | | |
| OSD-001-001 study[n] | No significant differences | | | | |
| **SAEs according to MedDRA** (with incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT) | | | | | |
| NPC-12G-1 study | No significant differences | | | | |
| OSD-001-001 study[n] | No significant differences | | | | |
| **Adverse events of special interest** (with statistically significant difference between the treatment arms) | | | | | |
| Symptoms of skin irritations[p] | | | | | |
| NPC-12G-1 study | 30 | 24 (80.0) | 32 | 15 (46.9) | 1.71 [1.13; 2.57]; 0.01 |
| OSD-001-001 study[n] | 8 | 7 (87.5) | 12 | 3 (25.0) | 3.50 [1.27; 9.65]; 0.02 |

| ***NPC-12G-2 study[l,q] (presented additionally)***<br>***Endpoint*** | ***Sirolimus*** | |
|---|---|---|
| | ***N*** | ***Patients with event n (%)*** |
| *Severe AEs* | *94* | *6 (6.4)* |
| *SAE* | *94* | *9 (9.6)* |

| | | |
|---|---|---|
| *AEs which led to the discontinuation of the study medication* | *94* | *2 (2.1)* |

a. Number of subjects in the evaluation.
b. Calculated using the Cochran-Mantel-Haenszel method with zero cell correction.
c. The total value results from the addition of the individual values and can be between 0 and 20 (higher values = severe disease burden). 3 points and more therefore correspond to a response threshold of at least 15%.
d. Improvement is assessed compared to the start of study and is defined as achieving a score of 2 (improved) or 3 (significantly improved).
e. In the dossier, module 4, the pharmaceutical company specifies post hoc that the improvement at week 12 compared to the start of study is assessed as achieving a score of 1.5 (improved) or higher.
f. Data from the dossier, module 4.
g. Wilcoxon rank sum test
h. Age at the time of the first visit (screening).
i. DLQI and CLDQI total score (0-30 points) is calculated by totalling the points achieved in each domain. A higher value corresponds to a higher impairment of the quality of life.
j. Number of subjects with baseline data.
k. Number of subjects in the evaluation at week 52.
l. 4 children between 3 and 5 years of age, who are not included in the therapeutic indication according to the marketing authorisation, were enrolled in the study.
m. Age at the time of the declaration of consent.
n. Information from the dossier, module 4. No information could be identified in the study documents.
o. Assumption of a model with fixed effects. The Mantel-Haenszel method was used as a pooling method without continuity correction.
p. AESI: Symptoms of skin irritation (e.g. erythema, papules, blisters, erosions and oedema, etc.)
q. Evaluation takes place in SAS. Results refer to the median survey period of 792 days (min.; max.: 6; 951)

Abbreviations used:
AESI: adverse event of special interest; CDLQI: Children's Dermatology Life Quality Index; DLQI: Dermatology Life Quality Index; IFA: Index for Facial Angiofibromas; IRC: Independent Review Committee; n.d.: no data available; CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; MV: mean value; n.a.: not assessable; RR: relative risk; SAS: safety analysis set; SD: standard deviation; (S)AE: (serious) adverse event.

## 2. Number of patients or demarcation of patient groups eligible for treatment

Adults and paediatric patients aged 6 years and older with facial angiofibroma associated with tuberous sclerosis complex

approx. 1,500 – 5,000 patients

## 3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Hyftor (active ingredient: sirolimus) at the following publicly accessible link (last access: 13 March 2024):

https://www.ema.europa.eu/en/documents/product-information/hyftor-epar-product-information_en.pdf

If there is no effect of treatment, the use of sirolimus must be discontinued after 12 weeks.

## 4. Treatment costs

**Annual treatment costs:**

Adults and paediatric patients aged 6 years and older with facial angiofibroma associated with tuberous sclerosis complex

| Designation of the therapy | Annual treatment costs/ patient |
|---|---|
| Medicinal product to be assessed: | |
| Sirolimus | € 8,505.12 - € 19,103.81 |

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 March 2024)

Costs for additionally required SHI services: not applicable

## 5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Adults and paediatric patients aged 6 years and older with facial angiofibroma associated with tuberous sclerosis complex

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.