

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Hyftor 2 mg/g gel

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of gel contains 2 mg of sirolimus.

Excipient with known effect

Each gram of gel contains 458 mg of ethanol.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Gel

Colourless transparent gel.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

#### Posology

This medicinal product should be applied to the affected area twice daily (in the morning and at bedtime). The application should be limited to skin areas with angiofibroma.

A dose of 125 mg gel (or 0.5 cm gel, corresponding to 0.25 mg sirolimus) should be administered per 50 cm<sup>2</sup> lesion in the face.

The maximum recommended daily dose in the face is:

- Patients aged 6-11 years should apply up to 600 mg gel (1.2 mg sirolimus), corresponding to approximately 2 cm gel strand per day.
- Patients aged  $\geq$  12 years should apply up to 800 mg gel (1.6 mg sirolimus), corresponding to approximately 2.5 cm gel strand per day.

The dose should be equally divided for two administrations.

#### Missed dose

If the first dose was missed in the morning, the application should be done immediately upon realisation of the fact provided this was before dinner of the same day. Otherwise only the application in the evening should be administered on that day. If the application in the evening was missed this should not be taken at a later point in time.

### Special populations

#### *Elderly*

No dose adjustment is required in elderly patients ( $\geq 65$  years) (see section 5.2).

#### *Renal impairment*

No formal studies have been performed in patients with renal impairment. However, no dose adjustment is required in this population since systemic exposure to sirolimus is low in individuals using Hyftor.

#### *Hepatic impairment*

No formal studies have been performed in patients with hepatic impairment. However, no dose adjustment is required in this population since systemic exposure to sirolimus is low in individuals using Hyftor (see section 4.4).

#### *Paediatric population*

The posology is the same in adults and children aged 12 years and older (up to a total of 800 mg gel per day).

The maximum dose for patients aged 6-11 years is a total of 600 mg gel per day.

The safety and efficacy of Hyftor in children less than 6 years has not been established. Currently available data are presented in section 5.2 but no recommendation on a posology can be made.

### Method of administration

For cutaneous use only.

Application should be limited to areas of facial angiofibroma lesions (see section 4.4.).

A thin layer of gel should be administered to the affected skin and rubbed in gently.

The application site should not be occluded.

The gel should not be applied around the eyes and on the eyelids (see section 4.4).

In case no treatment effect appears, administration with Hyftor should be discontinued after 12 weeks.

Hands should be washed carefully before and after administration of the gel to ensure that no gel remains on the hands that may be accidentally ingested or trigger exposure to sirolimus of any other part of the body or other persons.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Immunosuppressed patients

Although systemic exposure is much lower following topical treatment with Hyftor than after systemic treatment with sirolimus, the gel should not be used in immunocompromised adults and children as a precautionary measure.

#### Mucous membranes and damaged skin

Hyftor should not be used on wounds, irritated skin or skin with a clinically confirmed diagnosis of infection as well as in patients with known skin barrier defects.

Contact with eyes or mucous membranes (mouth, nose) should be avoided. Therefore, the gel should not be applied around the eyes and on the eyelids.

### Photosensitivity

Photosensitivity reactions have been observed in patients treated with Hyftor (see sections 4.8 and 5.3). Therefore, patients should avoid exposure to natural or artificial sunlight during the treatment period. Physicians should advise patients on appropriate sun protection methods, such as minimisation of the time in the sun, use of a sunscreen product and covering of the skin with appropriate clothing and/or headgear.

### Skin cancer

Skin cancer has been observed after long-term treatment with oral sirolimus in preclinical studies (see section 5.3) and in patients treated systemically for immunosuppression. Although systemic exposure is much lower during treatment with sirolimus gel than with systemically administered sirolimus, patients should minimise or avoid exposure to natural or artificial sunlight during therapy using the same measures as mentioned above, to prevent photosensitivity.

### Lymphoproliferative disorders

Lymphoproliferative disorders secondary to chronic systemic use of immunosuppressive agents have been reported in patients.

### Severe hepatic impairment

Sirolimus is metabolised in the liver and blood concentrations are low following topical administration. As a precautionary measure in patients with severe hepatic impairment, treatment should be discontinued in case any potential systemic side effects are observed.

### Hyperlipidaemia

Increased serum levels of cholesterol or triglycerides have been observed during treatment with sirolimus, in particular after oral administration. Patients with established hyperlipidaemia should regularly monitor lipid blood levels during treatment with sirolimus gel.

### Excipients with known effect

#### Ethanol

This medicinal product contains 458 mg ethanol in each gram. This may cause burning sensation on damaged skin.

## **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed.

Sirolimus is extensively metabolised by the CYP3A4 isoenzyme, and it is a substrate for the multidrug efflux pump P-glycoprotein (P-gp). In addition, sirolimus has been shown to inhibit human liver microsomal cytochrome P450 CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 *in vitro*. In the light of the low systemic exposure after topical administration it is not expected that clinical relevant interactions will occur, but Hyftor should be used with caution in patients taking respective concomitant medicinal products. Potential adverse reactions should be monitored and in case observed, treatment should be interrupted.

Except for sunscreens, no other topical treatments should be used on the facial angiofibroma lesions while treatment is ongoing.

## Vaccination

During treatment with Hyftor, vaccinations may be less effective. Vaccination with live vaccines should be avoided during treatment.

## Oral contraceptives

No interactions studies with Hyftor and oral contraceptives have been performed. Low systemic exposure to sirolimus during topical treatment with Hyftor makes pharmacokinetic drug interactions unlikely. The possibility of changes in the pharmacokinetics that might affect the efficacy of the oral contraceptive during long-term treatment with Hyftor cannot be fully excluded. For this reason, patients should be advised to use non-hormonal contraceptive measures during treatment.

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

There are no or limited amount of data from the use of Hyftor in pregnant women. Studies in animals have shown reproductive toxicity following systemic administration (see section 5.3). Hyftor should not be used during pregnancy, unless the clinical condition of the woman requires treatment with sirolimus.

### Breast-feeding

Available pharmacokinetic data in rats have shown excretion of systemically administered sirolimus in milk. It is unknown whether sirolimus is excreted in human milk, although clinical data have shown that systemic exposure is low following administration of Hyftor.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Hyftor therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

### Fertility

Impairments of sperm parameters have been observed among some patients treated systemically with sirolimus. These effects were reversible upon discontinuation of systemic sirolimus treatment in most cases.

## **4.7 Effects on ability to drive and use machines**

Hyftor has no or negligible influence on the ability to drive and use machines.

## **4.8 Undesirable effects**

### Summary of the safety profile

The most commonly reported adverse reactions were skin irritation events, including application site irritation (34.7%), dry skin (33.7%), acne (19.4%), and pruritus (11.2%). These events were generally mild or moderate in intensity, nonserious, and did not lead to treatment discontinuation.

### Tabulated list of adverse reactions

Adverse reactions reported from the clinical studies are listed in table 1 by system organ class and frequency using the following convention: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1\ 000$  to  $< 1/100$ ), rare ( $\geq 1/10\ 000$  to  $< 1/1\ 000$ ), very rare ( $< 1/10\ 000$ ), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Table 1: Adverse reactions**

<b>System Organ Class</b>	<b>Very common</b>	<b>Common</b>
Infections and Infestations		Conjunctivitis; Folliculitis Furuncle; Tinea versicolour
Eye disorders		Eye irritation; Erythema of eyelid; Ocular hyperaemia
Respiratory, thoracic and mediastinal disorders		Nasal discomfort
Gastrointestinal disorders		Stomatitis
Skin and subcutaneous tissue disorders	Dry skin; Pruritus Acne	Asteatosis; Dermatitis; Dermatitis contact; Dermatitis acneiform; Dermal cyst; Eczema Papule Photosensitivity reaction; Rash pruritic; Seborrhoeic dermatitis Solar dermatitis; Urticaria; Xeroderma Erythema; Rash; Skin exfoliation; Skin irritation; Skin haemorrhage
General disorders and administration site conditions	Application site irritation	Application site haemorrhage; Application site paraesthesia; Application site swelling
Injury, poisoning and procedural complications		Skin abrasion

Description of selected adverse reactionsApplication site irritation

Application site irritation of mild or moderate intensity occurred in 34.7% of patients treated with sirolimus gel in clinical studies. Application site irritation did not require discontinuation of treatment with the medicinal product.

Dry skin

Dry skin of mild or moderate intensity occurred in 33.7% of patients treated with sirolimus gel in clinical studies. Dry skin did not require discontinuation of treatment with the medicinal product.

Acne

Acne was reported in 19.4% of patients overall treated with sirolimus gel in clinical studies. Acne was of mild or moderate intensity; no severe acne was reported. Acne/dermatitis acneiform did not require discontinuation of treatment with the medicinal product.

## Pruritus

Mild or moderate intensity pruritus occurred in 11.2% of patients treated with sirolimus gel in clinical studies. Pruritus did not require discontinuation of treatment with the medicinal product.

## Paediatric population

In clinical development, no difference was seen in the safety between paediatric patients aged 6 years and older and adult patients included in a Phase III study including 27 patients  $\leq$  18 years (Hyftor: n=13) and a long-term study including 50 patients  $\leq$  18 years (Hyftor: all).

## Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## **4.9 Overdose**

If accidentally ingested, general supportive measures may be appropriate. Due to the poor aqueous solubility and high erythrocyte and plasma protein binding, sirolimus will not be dialysable to a significant extent.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: Not yet assigned

#### Mechanism of action

The exact mechanism of action of sirolimus in the treatment of angiofibroma in the tuberous sclerosis complex is not exactly known.

In general, sirolimus inhibits activation of mTOR which is a serine/threonine protein kinase that belongs to the phosphatidylinositol-3-kinase (PI3K)-related kinase family and regulates cellular metabolism, growth and proliferation. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. This complex binds to and inhibits the activation of mTOR.

#### Clinical efficacy and safety

Sirolimus gel was evaluated in a Phase III, randomised, double-blind, placebo-controlled study (NPC-12G-1).

In this study, patients enrolled were aged  $\geq$  6 years with a diagnosis of tuberous sclerosis complex with  $\geq$  3 facial, red angiofibroma (AF) lesions  $\geq$  2 mm in diameter, and who had not received prior laser therapy or surgery. Patients with clinical findings such as erosion, ulcer and eruption on or around the lesion of angiofibroma, which may affect assessment of safety or efficacy, were excluded.

Sirolimus gel (or matching placebo) was applied to facial AF lesions twice daily for 12 weeks, with a Hyftor gel amount of 125 mg (corresponding to 0.25 mg sirolimus) per 50 cm<sup>2</sup> affected skin area. No other medicinal products with an anticipated treatment effect on AF associated with tuberous sclerosis complex were allowed.

A total of 62 patients were enrolled (30 in the sirolimus gel group and 32 in the placebo group). The mean age was 21.6 years in the sirolimus gel group and 23.3 years in the placebo group and paediatric patients accounted for 44% overall trial population.

The results of the study showed a statistically significant increase in composite AF improvement (defined as concomitant improvement in AF size and AF redness) at 12 weeks with sirolimus gel treatment, compared with placebo treatment, based on independent review committee (IRC) assessment. The responder rate, defined as patients with improvement or markedly improvement, was 60% with sirolimus gel versus 0% with placebo (see Table 2).

**Table 2: Efficacy results in study NPC-12G-1: composite AF improvement by IRC at week 12**

	Sirolimus gel	Placebo
Patients, n (%)	30 (100.0)	32 (100.0)
Markedly improved	5 (16.7)	0
Improved	13 (43.3)	0
Slightly improved	11 (36.7)	5 (15.6)
Unchanged	1 (3.3)	26 (81.3)
Slightly exacerbated	0	0
Exacerbated	0	0
Not evaluated	0	1 (3.1)
p-value (Wilcoxon rank sum test)	<0.001	

Change in AF size at Week 12 compared to baseline was markedly improved or improved in 60% (95% Confidence Interval (CI): 41%-77%) of patients receiving sirolimus gel vs 3% (95% CI: 0%-11%) of patients receiving placebo. Change in AF redness at Week 12 compared to baseline (by IRC) was markedly improved or improved in 40% (95% CI: 23%-59%) of patients receiving sirolimus gel vs 0% (95% CI: 0%-11%) of patients receiving placebo. Table 3 summarises efficacy in different age groups.

**Table 3: Efficacy results in study NPC-12G-1: composite AF improvement by IRC at week 12, stratified by age. Data presented indicated the outcome “markedly improved” and “improved”.**

	Sirolimus gel	Placebo	p-value*
6-11 years	5/6 (83.3%)	0/6 (0.0%)	0.004
12-17 years	6/7 (85.7%)	0/6 (0.0%)	0.010
≥ 18 years	7/17 (41.2%)	0/20 (0.0%)	0.000

\* Wilcoxon 2-sample test

## 5.2 Pharmacokinetic properties

### Absorption

In the phase III study in patients treated for angiofibroma, 70% of patients had measurable sirolimus plasma concentrations after 12 weeks of treatment (range 0.11-0.50 ng/ml). Blood samples were obtained in the 52-week long-term -study at pre-defined time points and the maximum sirolimus concentration measured at any time in adult patients was 3.27 ng/ml and the maximum sirolimus concentration measured at any time in paediatric patients was 1.80 ng/ml.

### Distribution

For systemically administered sirolimus, terminal half-life in stable renal transplant patients after multiple oral doses was 62±16 hours.

The blood to plasma ratio of 36 indicates that sirolimus is extensively partitioned into formed blood elements.



### Biotransformation

Sirolimus is a substrate for both, cytochrome CYP3A4 and P-gp. Sirolimus is extensively metabolised by O-demethylation and/or hydroxylation. Seven major metabolites, including hydroxyl, demethyl, and hydroxydemethyl, are identifiable in whole blood. Sirolimus is the major component in human whole blood and contributes to greater than 90% of the immunosuppressive activity.

### Elimination

Excretion of sirolimus is mainly via the hepatic/faecal route. After a single oral dose of [<sup>14</sup>C]-sirolimus in healthy volunteers, the greatest amount (91.1%) of radioactivity was recovered from the faeces, and only a minor amount (2.2%) was excreted in urine.

### Special populations

#### Elderly

There are no pharmacokinetic data available after administration of sirolimus gel to patients aged 65 years and older since studies performed with sirolimus gel did not include patients of this age (see sections 4.2).

#### Renal impairment

Pharmacokinetic data from patients with renal impairment are not available.

#### Hepatic impairment

Pharmacokinetic data from patients with hepatic impairment are not available.

#### Paediatric population

Descriptive statistics of sirolimus blood concentrations revealed no relevant differences in post-dose samples taken after 4 and 12 weeks of treatment between adult and paediatric patients aged 6-11 years and 12-17 years.

## **5.3 Preclinical safety data**

### Repeated dose toxicity and local tolerance

In cynomolgus monkeys treated twice daily with 2 mg/g and 8 mg/g sirolimus gel for 9 months toxic effects were observed in one male at 8 mg/g gel and one female at 2 mg/g gel at exposure levels similar to clinical exposure levels following systemic administration of sirolimus and with possible relevance to clinical use, were as follows: typhlitis, colitis, and rectitis, vacuolation of the renal proximal tubular epithelium, dilation of distal tubule and collecting ducts, enlargement of the adrenal glands and hypertrophy/eosinophilia of the zona fasciculata, hypocellularity of the bone marrow, atrophy of thymus, lymph nodes and white pulp of the spleen, acinar atrophy of the exocrine pancreas and submandibular gland.

Following systemic treatment with sirolimus, pancreatic islet cell vacuolation, testicular tubular degeneration, gastrointestinal ulceration, bone fractures and calluses, hepatic haematopoiesis, and pulmonary phospholipidosis were observed.

Photosensitivity-like reactions were observed in local tolerance studies in guinea pigs.

## Mutagenicity

Sirolimus was not mutagenic in the *in vitro* bacterial reverse mutation assays, the Chinese hamster ovary cell chromosomal aberration assay, the mouse lymphoma cell forward mutation assay, or the *in vivo* mouse micronucleus assay.

## Carcinogenicity

Long-term carcinogenicity studies conducted in mouse and rat using systemic administration of sirolimus showed increased incidences of lymphomas (male and female mouse), hepatocellular adenoma and carcinoma (male mouse) and granulocytic leukaemia (female mouse). In mouse, chronic ulcerative skin lesions were increased. The changes may be related to chronic immunosuppression. In rat, testicular interstitial cell adenomas were noted.

A two-stage skin carcinogenesis bioassay in mice showed no development of skin masses following treatment with 2 mg/g or 8 mg/g sirolimus gel indicating that sirolimus gel does not promote skin carcinogenesis when administered after initiation with dimethylbenz[a]anthracene (DMBA).

## Reproduction toxicity

In reproduction toxicity studies using systemic administration of sirolimus, decreased fertility in male rats was observed. Partly reversible reductions in sperm counts were reported in a 13-week rat study. Reductions in testicular weights and/or histological lesions (e.g. tubular atrophy and tubular giant cells) were observed in rats and in a monkey study. In rats, sirolimus caused embryo/foetotoxicity that was manifested as mortality and reduced foetal weights (with associated delays in skeletal ossification).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Carbomer  
Anhydrous ethanol  
Trolamine  
Purified water

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

15 months

Shelf life after first opening: 4 weeks.

### **6.4 Special precautions for storage**

Store in a refrigerator (2°C – 8°C).

Store in the original package in order to protect from light.

Keep away from fire.

#### **6.5 Nature and contents of container**

Aluminium tube with high density polyethylene closure.

Pack size: 1 tube containing 10 g of gel.

#### **6.6 Special precautions for disposal**

Any remaining medicinal product, as well as the materials used for its administration, must be destroyed in accordance with the procedure applicable for cytotoxic agent and in compliance with current legislation relating to the elimination of hazardous waste.

### **7. MARKETING AUTHORISATION HOLDER**

Plusultra pharma GmbH,  
Fritz-Vomfelde-Str. 36  
40547 Düsseldorf  
Germany

### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/23/1723/001

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation:

### **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) responsible for batch release

MSK Pharmalogistic GmbH  
Donnersbergstraße 4  
64646 Heppenheim  
Germany

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to medical prescription.

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Hyftor 2 mg/g gel  
sirolimus

**2. STATEMENT OF ACTIVE SUBSTANCE**

Each gram of gel contains 2 mg sirolimus.

**3. LIST OF EXCIPIENTS**

Excipients: Carbomer, anhydrous ethanol, trolamine and purified water.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Gel  
10 g

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For cutaneous use only.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

Discard the tube 4 weeks after first opening.

Open date:  
Discard date:

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.



Store in the original package in order to protect from light.  
Keep away from fire.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Plusultra pharma GmbH,  
Fritz-Vomfelde-Straße. 36,  
40547 Düsseldorf  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/23/1723/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Hyftor

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**MINIMUM PARTICULARS TO APPEAR ON SMALL PACKAGING UNITS**

**TUBE**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION**

Hyftor 2 mg/g gel  
sirolimus  
For cutaneous use only.

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

Discard the tube 4 weeks after first opening.

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT**

10 g

**6. OTHER**

Store in a refrigerator

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the user

### Hyftor 2 mg/g gel sirolimus

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Hyftor is and what it is used for
2. What you need to know before you use Hyftor
3. How to use Hyftor
4. Possible side effects
5. How to store Hyftor
6. Contents of the pack and other information

#### **1. What Hyftor is and what it is used for**

Hyftor contains the active substance sirolimus, which is a medicine that reduces the activity of the immune system.

In patients with tuberous sclerosis complex a protein that regulates the immune system, m-TOR, is overactive. By blocking the activity of m-TOR, Hyftor regulates cell growth and reduces the number or size of angiofibromas.

Hyftor is a medicine used to treat adults and children from 6 years of age with angiofibroma on the face resulting from tuberous sclerosis complex. Tuberous sclerosis complex is a rare genetic disease causing non-cancerous tumours to grow in different organs of the body, including the brain and skin. The disease causes facial angiofibromas, non-cancerous lesions (growths) of the skin and mucous membranes (moist body surfaces, such as the lining of the mouth) in the face, in many patients.

#### **2. What you need to know before you use Hyftor**

**Do not use Hyftor** if you are allergic to sirolimus or any of the other ingredients of this medicine (listed in section 6)

#### **Warnings and precautions**

Talk to your doctor before using Hyftor if you have:

- a weakened immune system
- severely reduced liver function

Avoid contact of Hyftor with the eyes, the lining of the mouth and nose, or wounds. Similarly, it should not be used on irritated skin or skin that is infected or otherwise damaged.

In case of accidental contact it is recommended to immediately wash the gel off.

Avoid exposing skin treated with Hyftor to direct sunlight since it may cause side effects on the skin. This includes both natural and artificial (for example in the solarium) sunlight. Your doctor will advise you about appropriate sun protection, like the use of sunscreen and clothing to cover the skin or wearing headgear.

**Children**

Hyftor is not recommended for children under 6 years since the product has not been sufficiently studied in this age group.

**Other medicines and Hyftor**

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Do not apply other medicines to the area of skin treated with Hyftor.

**Pregnancy and breast-feeding**

Hyftor is not recommended during pregnancy unless your doctor thinks that the benefits of treatment are greater than the risks. There is no information on the use of Hyftor in pregnant women.

Women of childbearing potential should use safe contraception during treatment with Hyftor.

It is not known, whether sirolimus is excreted into human milk after treatment with Hyftor. You and your doctor should make a decision whether to discontinue breast-feeding or to discontinue/abstain from Hyftor therapy taking into account the benefit of breast feeding for your child and the benefit of therapy for you.

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

**Driving and using machines**

This medicine is not expected to affect the ability to drive or use machines.

**Hyftor contains alcohol**

This medicine contains 458 mg alcohol (ethanol) in each gram. It may cause a burning sensation when applied to damaged skin.

**3. How to use Hyftor**

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

**The recommended dose is**

Your doctor or pharmacist will show you how much gel you should use.

About 0.5 cm of the gel strand twice daily is recommended for a lesion of around 7 by 7 cm (50 cm<sup>2</sup>).

The maximum recommended dose on the face is:

- children 6 to 11 years: no more than 1 cm gel strand twice daily
- adults and children from 12 years: no more than 1.25 cm gel strand twice daily

**How to apply the gel**

Apply a thin layer of Hyftor twice daily (morning and evening) to the affected skin area and rub in gently. The application should be done once in the morning and once in the evening before going to bed. Limit the use to skin areas affected by angiofibroma. Do not cover the affected skin after application of Hyftor.

Wash your hands carefully before and immediately after using the gel to avoid any unintentional spread or ingestion.

**Duration of use**

Your doctor will tell you how long you should use Hyftor for.

**If you use more Hyftor than you should**

Hyftor is applied to the skin and absorption into the body is minimal. This makes overdose very unlikely.

If you apply too much gel to a lesion, carefully wipe off the excess gel with a paper towel and throw away the towel.

If you or anybody else accidentally swallows some gel, contact your doctor immediately.

**If you forget to use Hyftor**

If you forget to use the medicine in the morning, apply the gel as soon as you remember immediately before your meal in the evening of the same day. After your meal in the evening, only administer Hyftor at bedtime on that day. If you forget to use the medicine at bedtime, skip that dose. Do not apply more gel to make up for a missed dose.

**If you stop using Hyftor**

Your doctor will tell you how long you should use Hyftor and when you can stop treatment. Do not stop using it without consulting your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

**4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Very common** (may affect more than 1 in 10 people)

- dry skin
- itching skin
- acne
- irritation at the application site, such as reddening, burning stinging, itching, swelling and/or numbness

**Common** (may affect up to 1 in 10 people)

- bleeding at application site
- abnormal sensation, including at the application site, such as numbness, prickling, tingling and itchiness
- application site swelling
- eczema characterised by changes that occur when skin becomes abnormally dry, red, itchy and cracked
- dermal cyst (a cyst containing solid tissue or structures such as hair)
- rash, itchy rash
- peeling of skin
- skin irritation
- reddening
- bleeding of the skin
- dermatitis (inflammation of the skin), including contact dermatitis (inflammation of the skin after contact with the medicine), acneiform dermatitis (inflammation of the skin with small acne-like bumps), seborrhoeic dermatitis (skin condition affecting the head with scaly and red skin), solar dermatitis (inflammation of the skin after exposure to sunlight)
- dry, hard and scaly skin
- hives
- nodules
- boils
- tinea versicolour (a fungal infection of the skin)
- inflammation of the lining of the mouth
- increased sensitivity to light
- reddening of the eyelid

- red eye
- eye irritation
- conjunctivitis (redness and discomfort in the eye)
- inflammation of hair follicles
- sensations like numbness, tingling and pins and needles
- nasal discomfort

### **Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Hyftor**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the tube after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

Store in the original tube in order to protect from light.

Keep away from fire.

Throw away the tube and any remaining gel 4 weeks after opening.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Hyftor contains**

- The active substance is sirolimus. Each gram of gel contains 2 mg of sirolimus
- The other ingredients are carbomer, anhydrous ethanol, trolamine and purified water (see section 2 “Hyftor contains alcohol”).

### **What Hyftor looks like and contents of the pack**

Hyftor is a transparent, colourless gel. It is supplied in an aluminium tube containing 10 g of gel.

Pack size: 1 tube

### **Marketing Authorisation Holder**

Plusultra pharma GmbH  
Fritz-Vomfelde-Str. 36  
40547 Düsseldorf  
Germany

### **Manufacturer**

MSK Pharmalogistic GmbH.  
Donnersbergstraße 4  
64646 Heppenheim  
Germany

**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency website:  
<http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.