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^2 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 ≥ 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 (≥ 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 800 mg administered twice daily).

The maximum dose for patients aged 6-11 years is 600 mg administered twice daily.

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 accidentially 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

Immunosupressed 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 administred 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 (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 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

System Organ Class	Very common	Common
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

System Organ Class	Very common	Common
		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 reactions

Application 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 ≤ 18 years (Hyftor: n=13) and a long-term study including 50 patients ≤ 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 theYellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the **Google Play** or **Apple App Store**. By reporting side effects, you can help provide more information on the safety of this medicine.

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: Protein kinase inhibitors, mammalian target of rapamycin (mTOR) kinase inhibitors, ATC code: L01EG04

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 ≥ 6 years with a diagnosis of tuberous sclerosis complex with ≥ 3 facial, red angiofibroma (AF) lesions ≥ 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^2 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 [^{14}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

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