EU Risk Management Plan for Hyftor 2 mg/g Gel (sirolimus)

RMP version to be assessed as part of this application:

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QPPV name: Evangelia Tsakiraki

QPPV signature:

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Sirolimus
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, selective immunosuppressants, ATC code: L04AA
Marketing Authorisation Applicant	Plusultra pharma GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Hyftor 2 mg/g gel
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: macrocyclic lactone
	Summary of mode of action: In tuberous sclerosis complex (TSC), a germline mutation of the *TSC1* or *TSC2* gene, leading to activation of the mammalian Target Of Rapamycin (mTOR) pathway, accounts for the pathogenesis of TSC-associated angiofibroma. The exact mechanism of action of sirolimus in the treatment of angiofibroma in the TSC 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.
	Important information about its composition: Sirolimus is a macrocyclic lactone fermentation product produced by *Streptomyces hygroscopicus*.
Hyperlink to the Product Information	Hyftor 2 mg/g gel Product Information
Indication(s) in the EEA	Current: Treatment of facial angiofibroma associated with tuberous sclerosis complex in adults and paediatric patients aged 6 years and older
	Proposed (if applicable): Not applicable

Dosage in the EEA	Current: Hyftor 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 Hyftor (1.2 mg sirolimus), corresponding to approximately 2 cm gel strand per day. •Patients aged ≥ 12 years should apply up to 800 mg Hyftor (1.6 mg sirolimus), corresponding to approximately 2.5 cm gel strand per day. The dose should be equally divided for two administrations.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): Gel for cutaneous use. 1 tube contains 10 g of gel. Each gram of gel contains 2 mg of sirolimus.
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Hyftor 2 mg/g Gel (Hyftor) is indicated for the treatment of facial angiofibroma associated with tuberous sclerosis complex in adults and paediatric patients aged 6 years and older

Incidence and prevalence: Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder, with penetrance reaching 95% (Rosset 2017). Prevalence in Europe is estimated as 1 in 25,000 to 1 in 11,300 (National Organization for Rare Disorders, NORD 2019).

Demographics of the population in the proposed indication –age, gender, racial and/or ethnic origin and risk factors for the disease: TSC is an autosomal-dominant genetic disease caused by mutations in either the *TSC1* or *TSC2* genes. The onset of signs and symptoms of TSC is typically shortly after birth. TSC occurs in males and females and in all races. Angiofibroma (AF), presenting as small papules or red spots primarily on the face, may first appear in patients aged 3 to 5 years. The lesions increase in size and number over time and through adolescence, and then tend to grow more slowly during adulthood (NORD 2019; Darling 2018).

The main existing treatment options: Topical sirolimus was started to be used for the treatment of AF after early reports on improvements in AF as 'side-effect' of oral sirolimus treatment. In one of the first reports, immunosuppressive treatment with oral sirolimus in a TSC patient with extensive angiomyolipoma leading to bilateral nephrectomy and renal transplantation was also shown to dramatically reduce facial AF (Hofbauer 2008). Some authors have noted greater improvement in childhood, when AF lesions are at an early stage of formation (e.g. Tanaka 2013; Viswanath 2016; Amin 2017; Lee 2018), prompting recommendations that patients be treated early. It is not known whether prolonged therapy during childhood will minimise the formation of new lesions or whether lesions will grow less rapidly in adulthood even after stopping topical treatment (Darling 2018). So far, sirolimus treatment has shown sustained clinical benefit during long-term treatment, and there is no evidence for the development of resistance in AFs (Darling 2018).

Given that no commercialised topical sirolimus preparations exist in Europe or North America, compounds of different concentrations have generally been developed by crushing and sifting commercially available sirolimus tablets (Rapamune), later also by using sirolimus in powder form (Salido-Vallejo 2014).

Apart from mTOR inhibitor use, the existing treatment options are invasive and painful and include dermabrasion, laser therapy, excision of lesions (NORD 2019), radiofrequency ablation, and electrocoagulation (Salido-Vallejo 2014). These modalities can yield good results, especially with severe facial AFs, but they also carry the risk of complications from general anaesthesia, as well as hypertrophic scars, pigmentation disorders, and postoperative infections (Salido-Vallejo 2014). AF tends to recur after treatment cessation (Schwartz 2007).

Natural history of the indicated condition in the <untreated> population, including mortality and morbidity: AF presents as small papules or red spots primarily on the face, often in a butterfly pattern, and may first appear in patients aged 3 to 5 years. Untreated, the lesions increase in size and number over time and through adolescence (NORD 2019). In adulthood, the lesions tend to be stable or to grow more slowly (Darling 2018). Histological data suggest a significantly greater degree of increased

small blood vasculature in paediatric AFs compared to adult AFs, while adult AFs are characterised by more thickened collagen fibres in the dermis (Lee 2018).

Published clinical experience suggests that in most patients, facial AFs do not affect physiological functioning. However, case studies of patients with serious disfigurement and impaired physiological functions of breathing, eating, speaking, or vision, have been reported (e.g. Earnest 2003; Kacerovska 2012; Biondo 2014).

Thus, although facial AFs are benign they may have a considerable psychological impact on patients (Knöpfel 2014), causing emotional distress and social isolation/marginalisation (Biondo 2014), as well as physiological impact in some patients. In a cross-sectional cohort survey study in paediatric patients with TSC with facial AFs (Crall 2016), the presence of AF and the lack of treatment of AF significantly impacted the quality of life (QOL) of patients and caregivers alike, as measured by different validated QOL questionnaires.

Important co-morbidities: TSC may affect any organ system where hamartomas can form. Due to their benign nature, the tumours do not metastasise; they can, however, through continued growth, damage the affected tissues or organs. The signs, symptoms, and severity of TSC vary greatly between patients, in part depending on which organ systems are affected and how strongly (NORD 2019), from symptomless patients to patients in whom hamartomas lead to organ obstruction and haemorrhage and affect organ function.

Central nervous system tumours, which are frequent in TSC, can cause pressure and obstruction within the brain, and most patients with TSC develop seizures (epilepsy) at some point during their life. Patients may experience developmental delays; they may have some degree of intellectual disability and may develop neuropsychiatric disorders (NORD 2019). Other organ systems frequently affected by hamartomas are the kidneys, lungs, heart, and eyes (Salido-Vallejo 2014). Some women with TSC develop lymphangioleiomyomatosis (LAM), characterised by cystic lung destruction. Nearly all patients with TSC develop skin abnormalities, which, in addition to AFs, also include hypomelanotic macules, shagreen patches, fibrous plaques, and ungual fibromas (NORD 2019).

Part II: Module SII - Non-clinical part of the safety specification

Sirolimus gel is a topical formulation of sirolimus for the treatment of facial AF associated with TS. In order to support the safe chronic use of sirolimus gel in patients with AF associated with TS, one single dose toxicity study was conducted in rats and a number of dermal repeat-dose toxicities were conducted in rats and cynomolgus monkeys. Further studies performed with sirolimus gel included a medium-term carcinogenicity study in mice, local tolerance studies including skin irritation, eye irritation and skin sensitization studies, as well as photosafety studies evaluating phototoxicity and photoallergy.

In addition to the studies conducted with sirolimus gel, the Applicant relies on non-clinical data for the EU-approved medicinal product Rapamune (the reference product, EU/1/01/171) and on information in the published literature to support a hybrid Marketing Authorization Application (MAA) according to Article 10(3) of Directive 2001/83/EC.

Two formulations of sirolimus gel, OSD-001 Gel and NPC-12G Gel, were used in the nonclinical development program. Both the OSD-001 Gel and the NPC-12G Gel formulations were used in clinical trials of sirolimus gel, 0.2%. The OSD-001 Gel contained trometamol as pH modifier which was later replaced by triethanolamine (trolamine) in the NPC-12G Gel. NPC-12G Gel (formulation 2) was used in the Phase III study NPC-12G-1 and in the first half of the long-term safety study NPC-12G-2. During the second half of the long-term safety study and in preparation for commercialization, the composition of the NPC-12G Gel formulation was changed to formulation 3 by replacement of ethanol by anhydrous ethanol. The net quantity of ethanol and water is the same in formulation 2 and formulation 3. Therefore, it can be assumed that the toxicological properties remain the same for the two formulations and that no further toxicity studies were required. The commercial formulation for the EU market (formulation 4) includes a 3% drug substance overage.

Key safety findings from non-clinical findings with sirolimus gel and from systemic studies with sirolimus are presented in Table SII.

Table SII - Key safety findings from non-clinical studies and relevance to human usage:

Key Safety Findings from Non-Clinical Studies	**Relevance to Human Use**
Key issues identified from acute or repeat-dose toxicity studies: Studies conducted by the Applicant: The Applicant conducted repeat-dose toxicity studies in rats following percutaneous administration of sirolimus gel, one of which had an oral Rapamune control administered at an immunosuppressive dose (NPC-12G Gel and OSD-001 Gel) for 3 months and repeat-dose toxicity studies using percutaneous administration of sirolimus gel in cynomolgus monkeys (NPC-12G Gel) for 3 and 9 months.	The observed signs of toxicity are likely related to a systemic effect via percutaneous absorption of sirolimus. No adverse reactions due to systemic immunosuppression were observed after topical administration in clinical studies. In addition, from the available sparse PK measurements included in the clinical trials and the fact that only the face will be treated in humans, systemic exposure in humans is expected to be considerably lower than in the animals.

In rats, decreased thymus weights and increases in macrophages, diffuse atrophy, and necrosis of lymphocytes in the thymus were noted following topical BID treatment with 0.8% sirolimus gel for 13 weeks (8 mg/kg/day) and increases in foamy macrophages in submandibular lymph nodes and mesenteric lymph nodes were observed following BID treatment with 0.05%, 0.2% and 0.8% sirolimus gel for 13 weeks (0.5, 2 and 8 mg/kg/day) to 10% of the total body surface area. These changes were considered to be a result of the systemic immunosuppressant activity of sirolimus (European Public Assessment Report [EPAR] Rapamune). Histopathology revealed increases in foamy macrophages in submandibular lymph nodes and mesenteric lymph nodes and alveolar macrophage aggregation in the lungs of animals treated with 0.5, 2 and 8 mg/kg/day, and increases in fine vacuoles in the zona glomerulosa in the adrenals in animals treated with 8 mg/kg/day sirolimus. Thymus and submandibular and mesenteric lymph nodes: In rats, decreased cellularity and or macrophage accumulation was noted. Increased lung weights and aggregation of alveolar macrophages in the lungs were noted in males and females treated topically BID for 13 weeks with 0.05%, 2% and 0.8% sirolimus gel (0.5, 2 and 8 mg/kg/day). Pulmonary alveolar macrophages that gained characteristics common to phospholipidosis are described for rats treated systemically with sirolimus (EPAR Rapamune). In monkeys, while 13 weeks of topical BID dosing of sirolimus gel at strengths of 0.01, 0.05, 0.2, and 0.8% (0.05, 0.25, 1.0 and 4.0 mg/kg/day) to 5% of the total body surface area did not induce any signs of toxicity, chronic topical BID dosing of sirolimus gel at 0.05%, 0.2%, and 0.8% (0.25, 1.0 and 4.0 mg/kg/day) to 5% of the total body surface area was associated with a deterioration of the general condition and premature sacrifice of one male at 4.0 mg/kg/day and one female at 1.0 mg/kg/day. Histopathological examination revealed typhlitis, colitis and rectitis as described for monkeys receiving systemic treatment with sirolimus (EPAR Rapamune). In addition, signs of nephrotoxicity in the form of vacuolation of proximal tubular epithelium, dilation of distal	

tubule and collecting ducts were present in both animals. Histopathological findings in the kidney in the form of eosinophilic/brown granules in the proximal tubular epithelium were also noted in surviving males and females at 4.0 mg/kg/day and in females at 1.0 mg/kg/day. Studies referred to: Adverse reactions seen in animals at exposure levels similar to clinical exposure levels following systemic administration of sirolimus and with possible relevance to clinical use, were as follows: pancreatic islet cell vacuolation, testicular tubular degeneration, gastrointestinal ulceration, bone fractures and calluses, hepatic haematopoiesis, and pulmonary phospholipidosis.	None, as these adverse reactions were not observed after topical administration in clinical studies
<u>Genotoxicity:</u> Genotoxicity studies conducted for the systemic use of sirolimus are referred to (Rapamune Summary of Product Characteristics [SmPC]; EPAR Rapamune): Sirolimus was not mutagenic in in vitro bacterial reverse mutation assays, a Chinese Hamster Ovary cell chromosomal aberration assay, a mouse lymphoma cell forward mutation assay, or an in vivo mouse micronucleus assay (Rapamune SmPC).	None
<u>Carcinogenicity:</u> Studies conducted by the Applicant: The Applicant investigated the potential skin carcinogenic effect of sirolimus gel (NPC-12G Gel) in mice using a two-stage skin carcinogenesis bioassay with the initiator 7,12-dimethylbenz[a]anthracene (DMBA). Topical study with sirolimus gel: A two-stage skin carcinogenesis bioassay in mice showed no development of skin masses following treatment with 0.2% or 0.8% sirolimus gel indicating that sirolimus gel does not promote skin carcinogenesis when administered after initiation with DMBA. Studies referred to: Long-term oral carcinogenicity studies in mice and rats for sirolimus are referred to (Rapamune SmPC; EPAR Rapamune): In mice, increased incidences of lymphomas	None It is known that malignancies (lymphoma) secondary to chronic use of immunosuppressive agents can occur. Hyftor should not be used in immunosuppressed patients.

(males and females), hepatocellular adenoma and carcinoma (males) and granulocytic leukaemia (females) were observed. In rats, testicular interstitial cell adenomas were observed. These were likely indicative of a species-dependent response to lutenising hormone levels and are usually considered of limited clinical relevance (Rapamune SmPC).	
Reproductive and developmental toxicity: Reproductive and developmental toxicity studies conducted for the systemic use of sirolimus are referred to (Rapamune SmPC; EPAR Rapamune): 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).	Due to the low systemic exposure after topical administration observed in AF patients, the risk of reproductive and developmental toxicity during treatment with Hyftor is considered low, however it is preferable to avoid use of Hyftor when pregnant.
Local tolerance: Dermal tolerance: NPC-12G Gel was not skin irritating in rabbits at concentrations up to 0.2%. Ocular tolerance: NPC-12G Gel 0.01%, 0.05% and 0.2% sirolimus gels were classified as "moderately irritant" according to the Draize scale. Since irritant effects were also caused by the gel base, the effects were considered to be mostly due to an ingredient of the gel base. Skin Sensitization: The skin sensitizing potential of OSD-001 Gel was evaluated in guinea pigs using the adjuvant and patch test method. Under the conditions of this study, OSD-001 Gel had no skin sensitizing potential.	Contact with eyes or mucous membranes (mouth, nose) should be avoided.
Juvenile toxicity: The Applicant conducted a 4-week toxicity study in juvenile SD rats and a 7-week toxicity study in juvenile HWY/Slc rats. A similar toxicological	The available blood concentration data in humans do not suggest an age effect on systemic sirolimus concentrations following topical

profile of sirolimus and similar exposure levels in juvenile rats was seen in the adult rats.	treatment with sirolimus gel, 02%. In particular, the available data do not show a systematic difference between younger and older paediatric patients in sirolimus blood concentrations.
Photosafety Evaluation: Phototoxicity: Sirolimus was not phototoxic in an in vitro phototoxicity study in 3T3 cells. Skin photosensitization: Photosensitivity-like reactions were observed in local tolerance studies in guinea pigs. Photosensitive disease-like skin reactions were dose-dependent. Sunscreen had protective effects when applied at challenge.	Exposure to ultraviolet light (e.g. natural sunlight, tanning salon) should be avoided, even as part of phototherapy.

Where appropriate, recommendations for use were included in the relevant section of Hyftor SmPC. There were no findings in the non-clinical testing which warrant inclusion among the summary of safety concerns.

Part II: Module SIII - Clinical trial exposure

The marketing authorization application for Hyftor is a hybrid application according to Article 10(3) of Directive 2001/83/EC. The reference medicinal product is Rapamune (EU/1/01/171).

Rapamune is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant (in combination with ciclosporin microemulsion and corticosteroids, or as maintenance therapy with corticosteroids), and for the treatment of patients with sporadic LAM with moderate lung disease or declining lung function (Rapamune SmPC).

Four clinical studies were performed with sirolimus gel in the AF development programme (Table SIII.1): a randomised, placebo-controlled Phase III study (NPC-12G-1), an uncontrolled, open-label long-term study (NPC-12G-2), a Phase I/II dose escalation study (OSD-001-001), all in Japanese AF patients; and a Phase I study in Caucasian healthy volunteers (NPC-12G-4/US).

Cumulative exposure, including person time, for patients in studies with AF is provided in Table SIII.2 and breakdowns by age and gender and by ethnicity are provided in Table SIII.3 and Table SIII.4, respectively. All but 16 of the 148 patients with AF were exposed to sirolimus gel at a concentration of 0.2%. Therefore, no stratification has been provided by dose. Across the studies in the AF development programme, a total of 148 AF patients were exposed to sirolimus gel. All patients from study NPC-12G-1 rolled after study completion over to NPC-12G-2. Furthermore, due to lack of unique identifying information, it was not possible to track the number of patients from study OSD-001-001 through enrolment into other studies, and it is assumed that patients from OSD-001-001 also participated in NPC-12G-1 and NPC-12G-2. Therefore, the number of unique AF patients exposed to sirolimus gel is likely lower than 148.

Sirolimus gel is also developed in neurofibromatosis type 1 (NF1). An investigator-initiated, randomised, double-blind, placebo-controlled Phase II study (OSD-001-003) and investigator-initiated, randomised, double-blind, placebo-controlled Phase II/III study (OSD-001-004) have been completed. As in the AF study programme, individual patients could have been enrolled in several of the NF1

studies, so that the number of unique NF1 patients is lower than the sum of patients from the individual trials. The pilot study (OSD-001-003) and the dose-ranging study OSD-001-004 investigated 2 doses of sirolimus gel, i.e. 0.2% and 0.4%.

Table SIII.1. Studies contributing to the evaluation of the PK, efficacy, and safety of sirolimus gel, 0.2% for the treatment of AF associated with TSC

Study ID	Study objectives	Study design	Treatment	Population	Patients[2], n
Studies in AF patients, interventional					
NPC-12G-1	E, S, PK	R, DB, PBO-controlled	12-w dosing bid, 0.2% sirolimus	AF pts	S0.2%: 30 Placebo: 32
NPC-12G-2	E, S, PK	OL, UC	Continued[1] dosing bid, 0.2% sirolimus	AF pts	Total: 94
OSD-001-001	E, S, PK, dose finding	R, DB, PBO-controlled	12-w dosing bid, 0.05, 0.1, 0.2% sirolimus	AF pts	Sirolimus: 24 Placebo: 12
Studies in HVs, interventional					
NPC-12G-4/US	PK	OL, fixed-sequence, 2-period	Single dose of sirolimus gel, 0.2% containing 1.6 mg sirolimus; Rapamune 2 mg tablet	HV	Total: 12
Studies in other indications, interventional					
OSD-001-003	E, S	R, DB, PBO-controlled	24-w dosing bid, 0.2%, 0.4% sirolimus; placebo	NF1 pts	Total: 18 S0.2%: 6 S0.4%: 6 Placebo: 6
OSD-001-004	E, S	R, DB, PBO-controlled	52-w dosing bid, 0.2%, 0.4% sirolimus; placebo	NF1 pts	Total: 76 S0.2%: 25 S0.4%: 24 Placebo: 27

Abbreviations: AF pts= angiofibroma patients; bid= twice daily; E= efficacy; FS= fixed sequence; HV= healthy volunteers; NF1= neurofibromatosis type 1; OL= open-label; PK= pharmacokinetics; S= safety; w= week

[1] Until study completion or approval

[2] Actual patient number in completed studies, planned number in ongoing studies

Table SIII.2: Duration of exposure in interventional studies in patients with angiofibroma (NPC-12G-1, NPC-12G-2, and OSD-001-001)

Cumulative exposure for patients with angiofibroma (person time)		
Duration of exposure	**Number of Patients[a]**	**Person time (years)**
<1 month	2	0.036
1 to <3 months	5	1.081
3 to <6 months	24	6.133
6 to <12 months	28	13.273
≥12 months	89	187.255
Total person time	148	207.778

[a] after study completion, all patients from study NPC-12G-1 rolled over to NPC-12G-2. Furthermore, due to lack of unique identifying information, it was not possible to track the number of patients from study OSD-001-001 through enrolment into other studies, and it is assumed that patients from OSD-001-001 also participated in NPC-12G-1 and NPC-12G-2. Therefore, the number of unique AF patients exposed to sirolimus gel is lower than 148.

Table SIII.3: Exposure by age group and gender in interventional studies in patients with angiofibroma (NPC-12G-1, NPC-12G-2, and OSD-001-001)

Age group	**Number of Patients[a]**		**Person time (years)**	
	M	F	M	F
Children (3 to 11 years)	23	16	38.084	23.086
Adolescents (12 to 18 years)	14	22	16.676	36.991
Adults (19 to 64 years)	28	45	33.180	59.762
Elderly patients (65 years or older)	0	0	-	-
Total	65	83	87.940	119.838

[a] after study completion, all patients from study NPC-12G-1 rolled over to NPC-12G-2. Furthermore, due to lack of unique identifying information, it was not possible to track the number of patients from study OSD-001-001 through enrolment into other studies, and it is assumed that patients from OSD-001-001 also participated in NPC-12G-1 and NPC-12G-2. Therefore, the number of unique AF patients exposed to sirolimus gel is lower than 148.
F= Female, M= Male

Table SIII.4: Exposure by ethnic origin in interventional studies in patients with angiofibroma (NPC-12G-1, NPC-12G-2, and OSD-001-001)

Ethnic origin	**Number of Patients[a]**	**Person time (years)**
Asian	148	207.778

[a] after study completion, all patients from study NPC-12G-1 rolled over to NPC-12G-2. Furthermore, due to lack of unique identifying information, it was not possible to track the number of patients from study OSD-001-001 through enrolment into other studies, and it is assumed that patients from OSD-001-001 also participated in NPC-12G-1 and NPC-12G-2. Therefore, the number of unique AF patients exposed to sirolimus gel is lower than 148.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria in the pivotal study, NPC-12G-1, are discussed below.

1) Patients who have difficulty applying the study medication according to the prescribed regimen by themselves or legally accepted representative.

2) Patients with clinical findings such as erosion, ulcer and eruption on or around the lesion of AF, which may affect assessment of safety or efficacy.

3) Patients for whom it is considered impossible to adequately take pictures of their skin lesions for the reasons such as the incapability of following the instruction to keep still.

Reason for exclusion: Difficulties with application of the gel or with the assessment of the skin lesions or clinical findings on or around the lesion of AF would have interfered with the evaluation of safety and efficacy.

Is it considered to be included as missing information?: No

Rationale: Exclusion criteria 1-3 were to avoid confounding factors affecting safety and efficacy assessments and not due to a concern for a particular safety concern.

4) Patients with a history of hypersensitivity to alcohol or allergy to sirolimus.

Reason for exclusion: Patients with a known history of hypersensitivity to the active substance or any of the excipients were excluded as a safety measure to avoid such reactions in these patients.

Is it considered to be included as missing information?: No

Rationale: Hypersensitivity to the active substance or to any of the excipients is a contraindication for use.

5) Patients who have complications of malignant tumor, infectious disease, serious heart disease, hepatic function disorder, renal function disorder or blood disorders (determined by the investigator or subinvestigator with reference to grade 2 or more serious disease defined in the Standards for Classification of Seriousness of Adverse Drug Reactions of Pharmaceuticals.)

Reason for exclusion: This broad exclusion criterion was to avoid confounding safety and efficacy assessments.

Is it considered to be included as missing information?: No

Rationale: The exclusion criterion was to avoid confounding factors affecting safety and efficacy assessments and not due to a particular safety concern, in particular due to the low expected systemic absorption of topical sirolimus. The decision to use Hyftor is to be made by the healthcare provider taking the product information into consideration. This is considered sufficient.

6) Patients who have complications such as diseases unsuitable for the study participation, for examples, uncontrolled diabetes (fasting blood glucose level >140 mg/dL or postprandial blood glucose level > 200 mg/dL), dyslipidemia (cholesterol level > 300 mg/dL or > 7.75 mmol/L, triglycerides level > 300 mg/dL or > 3.42 mmol/L).

Reason for exclusion: This broad exclusion criterion was to avoid confounding safety and efficacy assessments.

Is it considered to be included as missing information?: No

Rationale: The exclusion criterion was to avoid confounding factors affecting safety and efficacy assessments and not due to a particular safety concern, in particular due to the low expected systemic absorption of topical sirolimus. The decision to use Hyftor is to be made by the healthcare provider taking the product information into consideration. This is considered sufficient.

7) Patients who have used any drugs that has mTOR inhibitory activity, such as sirolimus, everolimus or temsirolimus within 12 months before the provisional registration.

Reason for exclusion: These exclusion criteria were to avoid confounding factors affecting safety and efficacy assessments.

Is it considered to be included as missing information?: No

Rationale: Concomitant use of systemic mTOR inhibitors was not permitted in the pivotal study NPC-12G-1 to avoid influencing the efficacy and safety evaluation of sirolimus gel. However, data on such concomitant use is available from the long-term study NPC-12G-2, in which 19 patients (20.4%) were concomitantly prescribed systemic mTOR inhibitors, and from post-marketing surveillance in the form of the Rapalimus® Gel general drug-use survey, in which 174 (20.0%) of the 871 patients evaluable for safety were concomitantly treated with systemic mTOR inhibitors. Based on the analysis of adverse event data from these studies by the presence or absence of oral mTOR inhibitor, it was concluded that concomitant administration of oral mTOR inhibitors did not impact the safety or efficacy of sirolimus gel in patients with facial angiofibroma and hence, did not influence the overall benefit/risk ratio of this product and thus there is no need to include concomitant mTOR use under missing information.

8) Patients who have used topical tacrolimus on the lesion of AF within 3 months before the provisional registration.

9) Patients who have received laser therapy or surgery (including liquid nitrogen therapy and phototherapy) to the lesion of AF within 6 months before the provisional registration.

Reason for exclusion: These exclusion criteria were to avoid confounding factors affecting safety and efficacy assessments.

Is it considered to be included as missing information?: No

Rationale: These exclusion criteria were to avoid confounding safety and efficacy assessments and not due to a particular safety concern.

10) Female patients who are pregnant, may become pregnant, or are lactating.

11) Patients who do not agree to take appropriate measures of contraception until completion of the post observation or the follow up after withdrawal from informed consent.

Reason for exclusion: 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 SmPC, section 5.3). Available pharmacokinetic data in rats have shown excretion of systemically administered sirolimus in milk (SmPC, section 4.6). It is unknown whether sirolimus is excreted in human milk, although clinical data have shown that the systemic exposure with sirolimus is low following administration of Hyftor.

Is it considered to be included as missing information?: No

Rationale: As communicated in the product information, Hyftor should not be used during pregnancy unless the clinical condition of the woman requires treatment with sirolimus (SmPC, section 4.6). This is considered sufficient.

12) Patients who have participated in any other clinical study and have taken a study drug within 6 months before the provisional registration.

13) Patients who are considered by the investigator as unsuitable for participation in the study.

Reason for exclusion: These broad exclusion criteria were to avoid confounding factors affecting safety and efficacy assessments.

Is it considered to be included as missing information?: No

Rationale: These broad exclusion criteria were to avoid confounding factors affecting safety and efficacy assessments, and not due to a particular safety concern.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme for Hyftor is unlikely to detect certain types of adverse reactions such as rare adverse reactions or adverse reactions with a long latency.

Safety data in patients with AF are available from 2 studies of 12 weeks' duration each, with 30 and 24 patients treated, respectively, and from a long-term study in 94 patients with a mean treatment duration of about 2 years. In addition, post-marketing safety data is available since approval of Rapalimus® Gel 0.2% in March 2018 in Japan.

The limitations to detect adverse reactions should further be considered in the context of this hybrid application. The safety of sirolimus gel is supported by the long availability of oral sirolimus (first approved in the EU in 2001) and the wide-spread topical use of compounded oral sirolimus tablets in the treatment of AF.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Patients with hepatic or renal impairment were not included in the Hyftor clinical development program. In the pivotal study, hepatic or renal impairment was determined by the investigator or subinvestigator with reference to grade 2 or more serious disease defined in the Standards for Classification of Seriousness of Adverse Drug Reactions of Pharmaceuticals. Patients with serious heart disease were not included in the Hyftor clinical development program. In the pivotal study, serious heart disease was determined by the investigator or subinvestigator with reference to grade 2 or more serious disease defined in the Standards for Classification of Seriousness of Adverse Drug Reactions of Pharmaceuticals. Immunocompromised patients were not included in the Hyftor clinical development program. With regard to disease severity, patients with three or more reddish papules of AF (≥2 mm in diameter) on the face at screening tests were eligible to enter the Phase III study in AF (NPC-12G-1).
Population with relevant different ethnic origin	All studies in patients with AF were in Japanese (Asian) patients (Table SIII.4). A relative bioavailability study was performed in Caucasian patients (n = 12; NPC-12G-4/US).
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Other	Not applicable

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

No post-authorisation exposure is available for Hyftor in the EEA. Available post-authorization exposure data available for sirolimus gel, 0.2%, approved in Japan on 23 March 2018 under the brand name Rapalimus® Gel 0.2%, are provided below.

SV.1.1 Method used to calculate exposure

Nobelpharma conducted an all-case, post-marketing survey from 06 June 2018 to 31 March 2022 as part of the conditions for approval of Rapalimus® Gel 0.2% in Japan. All patients treated with Rapalimus® Gel, 0.2% were to be captured in a central registration system. A case report form was required for each patient entered into the survey, which collected demographic, drug-use, safety and efficacy data. Please note, the regulatory inspection via reexamination by the Pharmaceuticals and Medical Devices Agency (PMDA) of this survey has not been conducted yet.

SV.1.2 Exposure

Between 06 June 2018 and 31 March 2022, 933 patients were registered in the all-case, post-marketing survey. Of these, 871 patients were included in the safety analysis, meaning that they visited after the date of prescription and received treatment (PSUR for Rapalimus® Gel 0.2% for Japan no. 6, 2022). Table SV.1.1 and Table SV.1.2 show the patient characteristics (sex and age) and Rapalimus® Gel, 0.2% exposure (duration and total dose) for patients evaluable for safety in the post-marketing surveillance all-case survey in Japan, respectively.

Table SIV.1.1: Patient Characteristics of Patients Exposed to Rapalimus® gel, 0.2% Post-marketing Surveillance in Japan (Safety Analysis; Data cut-off 31 March 2022)

Baseline case characteristics		**Number of Cases**	**Percentage**
Number of cases for analysis		871	-
Sex	Male	405	46.50%
	Female	466	53.50%
Age	Less than 15 years	288	33.07%
	15 years to less than 65 years	575	66.02%
	65 years or older	8	0.92%
	Number of cases	871	
	Mean ± SD	23.0±14.40	
	Median	20.0	
	Minimum and maximum values	0/84	

Source: Table 2.2.3-1, Report on Rapalimus® Gel 0.2% General Drug Use-Results Survey (All-Case Survey) (01 June 2022)

Table SV.1.2: Use of Rapalimus® Gel, 0.2% in Patients Evaluable for Safety in Post-marketing Surveillance in Japan (Safety Analysis; Data cut-off 31 March 2022)

Baseline case characteristics		Number of Cases	Percentage
Number of cases for analysis		871	-
Duration of Exposure	Less than 30 days	24	2.76%
	30 days to less than 90 days	75	8.61%
	90 days to less than 180 days	67	7.69%
	180 days to less than 270 days	50	5.74%
	270 days to 364 days or less	631	72.45%
	Unknown or undescribed	24	2.76%
	Number of cases	847	
	Mean ± SD	296.5±115.57	
	Median	364.0	
	Minimum and maximum values	2/364	
Total Dose	Less than 20 g	306	35.13%
	20 g to less than 60g	328	37.66%
	60 g and less than 120g	116	13.32%
	120 g and less than 180g	65	7.46%
	180 g and less than 240g	27	3.10%
	240 g or more	24	2.76%
	Unknown or undescribed	5	0.57%
	Number of cases	866	
	Mean ± SD	50.2±65.98	
	Median	20.0	
	Minimum and maximum values	1.4/490	

Source: Table 2.2.4-1, Report on Rapalimus® Gel 0.2% General Drug Use-Results Survey (All-Case Survey) (01 June 2022)

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Based on its mechanism of action and safety profile, Hyftor is not considered to have misuse potential for illegal purposes in the targeted indication.

Part II: Module SVII - Identified and potential risks

Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression with oral sirolimus (Rapamune SmPC) and malignancy is an important identified risk for the "reference medicine", Rapamune (Summary of RMP for Rapamune, 2018).

The Applicant does not consider malignancy to be an identified risk for Hyftor due to lack of adequate evidence of an association between the topical administration of Hyftor and malignancy. Among

patients treated topically with sirolimus gel in the AF studies, 7 patients had neoplasms, including 3 patients with skin papilloma (verbatim: verruca vulgaris, or common warts), 2 patients had kidney angiomyolipoma, and one patient each had lymphangioma and neoplasm skin. None of these events was judged as being drug-related. The patients with skin neoplasm, lymphangioma, and kidney angiomyolipoma had medical history suggesting that the neoplasms had been present before initiation of sirolimus treatment. Lymphangioma and kidney angiomyolipoma belong to the hamartomas that are a hallmark of TSC (Krueger 2013). Patients with skin papilloma had no relevant medical history. However, it is important to note that all 3 were paediatric patients. Verruca vulgaris is particularly common in children and adolescents, and the prevalence of cutaneous warts increases during childhood and peaks in adolescence, declining again at later ages (Fabbrocini 2009). Given the limited systemic exposure obtained with local application of sirolimus and the safety profile observed in the clinical development programme, malignancy has been included as an important potential risk for Hyftor, rather than an important identified risk in this RMP.

The absence of clinically relevant safety observations is considered to be due to the low systemic absorption of topically administered sirolimus. However, as a precaution, Hyftor should not be used in immunocompromised patients and exposure to natural and artificial sunlight should be avoided (SmPC, section 4.4.).

The long-term safety in patients with sporadic LAM is not applicable as missing information for Hyftor as it falls outside of the intended indication for this topical formulation.

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated) by system organ class and preferred term:

- 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.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Potential Risk: Malignancy

Malignancy has been reported with the systemic use of immunosuppressant medications such as sirolimus. However, given the limited systemic exposure obtained with local application of sirolimus, malignancy is considered to be an important potential risk for Hyftor, rather than an important identified risk.

Risk-benefit impact: No drug-related reports of skin malignancies have been received and, given the limited systemic exposure obtained with local application of sirolimus, it is not expected that regular use of Hyftor will cause clinically-relevant immunosuppression. However, the occurrence of systemic adverse reactions after treatment with sirolimus cannot be ruled out.

The recommendations in the product information regarding concomitant immunosuppression and exposure to natural or artificial sunlight are considered adequate to mitigate the risk of malignancy, and therefore, the risk-benefit balance remains favourable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Potential Risk: Malignancy

Potential mechanisms:

Immunosuppressant medications, such as sirolimus, have been associated with malignancy, which has been attributed to their influence on the immune system.

Evidence source(s) and strength of evidence:

Malignancy has been reported with the systemic use of immunosuppressant medications such as sirolimus. However, given the limited systemic exposure obtained with local application of sirolimus, malignancy is included as an important potential risk for Hyftor, rather than as an important identified risk.

Characterisation of the risk:

Among patients treated topically with sirolimus gel in the AF studies, neoplasms were reported for 7 patients, including 3 patients with skin papilloma (verbatim in all: verruca vulgaris), 2 patients with kidney angiomyolipoma, one patient with lymphangioma, and one patient with neoplasm skin. None of these events was judged as being drug-related. The patients with lymphangioma, kidney angiomyolipoma, and skin neoplasm had relevant medical history. Both lymphangioma and kidney angiomyolipoma belong to the hamartomas that are the hallmark of TSC.

There have been no reports of skin malignancies from post-marketing sources in Japan (Rapalimus® Gel, 0.2% PSUR no. 6).

Risk factors and risk groups:

Patients on immunosuppressant agents may be at an increased risk of malignancy.

Preventability:

Avoid use in immunosuppressed patients.

Even though systemic exposure is much lower during treatment with Hyftor, as precaution patients should minimise or avoid exposure to natural or artificial sunlight while using Hyftor. 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.

Impact on the risk-benefit balance of the product:

No drug-related reports of skin malignancies have been received. The warning to avoid exposure to sunlight is considered appropriate to minimize the risk of skin malignancies. Given the limited systemic exposure obtained with local application of sirolimus, it is not expected that regular use of Hyftor will cause clinically-relevant immunosuppression. However, the occurrence of systemic adverse reactions after treatment with sirolimus cannot be ruled out. The recommendations in the product information regarding concomitant immunosuppression and exposure to sunlight are considered adequate to mitigate the risk of malignancy, and therefore, the risk-benefit balance remains favourable.

Public health impact:

Malignancy is not considered to have a major impact on public health.

SVII.3.2. Presentation of the missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Malignancy
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for malignancy: none

Other forms of routine pharmacovigilance activities for malignancy: none

III.2 Additional pharmacovigilance activities

Not applicable.

III.3 Summary table of additional Pharmacovigilance activities

Not applicable. There are no ongoing or planned additional pharmacovigilance activities for Hyftor.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Malignancy	Routine risk communication: SmPC Section 4.4 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: 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 (SmPC Section 4.4) Other routine risk minimisation measures beyond the Product Information: Legal status: medical prescription

V.2. Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Malignancy	Routine risk communication: SmPC Section 4.4 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: 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 (SmPC Section 4.4)	None

Part VI: Summary of the risk management plan

Summary of risk management plan for Hyftor 2 mg/g Gel (sirolimus)

This is a summary of the risk management plan (RMP) for Hyftor 2 mg/g Gel (Hyftor). The RMP details important risks of Hyftor and how more information will be obtained about Hyftor's risks and uncertainties (missing information).

Hyftor's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Hyftor should be used.

This summary of the RMP for Hyftor should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Hyftor's RMP.

I. The medicine and what it is used for

Hyftor is authorised for treatment of facial angiofibroma associated with tuberous sclerosis complex in adults and paediatric patients aged 6 years and older (see SmPC for the full indication). It contains sirolimus as the active substance and it is given by the cutaneous route.

Further information about the evaluation of Hyftor's benefits can be found in Hyftor's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Hyftor, together with measures to minimise such risks and the proposed studies for learning more about Hyftor's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Hyftor are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Hyftor. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	Malignancy
Missing information	None

II.B Summary of important risks

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	Malignancy has been reported with the systemic use of immunosuppressant medications such as sirolimus. However, given the limited systemic exposure obtained with local application of sirolimus, malignancy is included as an important potential risk for Hyftor, rather than as an important identified risk.
Risk factors and risk groups	Patients on immunosuppressant agents may be at an increased risk of malignancy
Risk minimisation measures	Routine risk communication: SmPC Section 4.4 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: 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 (SmPC Section 4.4)

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Hyftor.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Hyftor.

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Annex 4 - Specific adverse drug reaction follow-up forms

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Annex 7 - Other supporting data (including referenced material)

Annex 8 – Summary of changes to the risk management plan over time

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.