

TITLE

A Rapamycin Method of Treatment and Composition

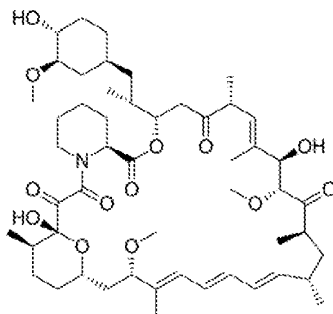
TECHNICAL FIELD

This invention relates to a Rapamycin composition for administration to humans and to a method of producing or using this.

BACKGROUND

Rapamycin was isolated in or around 1972 from samples of *Streptomyces hygroscopicus*. The compound was initially developed as an antifungal agent and its production is described in US patent No. 3929992 to Ayerst McKenna & Harrison.

Rapamycin has the following structural formula:



A problem with Rapamycin is that it often needs to be used for a prolonged period and over time can accumulate in the bloodstream in undesired levels, leading to adverse side effects such as stomatitis, pneumonitis, hyperlipidemia, anemia, thrombocytopenia, renal toxicity, joint pain and oedema. Further, Rapamycin is a United States FDA Category C drug for which animal studies have shown an adverse effect on a developing fetus, which is potentially an issue for women when pregnant with undesirable amounts of Rapamycin in their system.

OBJECT OF THE INVENTION

It is an object of a preferred embodiment of the invention to go at least some way towards addressing the above problem. While this applies to the preferred embodiment, it should be understood that the object of the invention per se is not so limited and is simply to provide the public with a useful choice. Therefore, any objects,

advantages or benefits of any preferred embodiment should not be inferred as limitations on any claims expressed more broadly.

DEFINITIONS

The term “comprising” or derivatives thereof, eg “comprises”, if and when used in this document in relation to a combination of features or steps should not be taken to rule out the option of there being additional features or steps that have not been mentioned. The term is therefore inclusive, not exclusive.

SUMMARY OF THE INVENTION

First Aspect – Method of Treatment

According to a first aspect, the invention is a method for treating a vascular abnormality of the skin of a human subject, comprising topically administering to the abnormality a composition comprising:

- a) Rapamycin;
- b) Monolaurin and Monomyristin as vehicle; and
- c) water;

once daily at a rate of:

- d) 4 -8 mg Rapamycin /cm²; and/or
- e) 1-6 mg Rapamycin.

Second Aspect – Use in Manufacturing

According to a first aspect, the invention is the use of

- a) Rapamycin;
- b) Monolaurin and Monomyristin as vehicle; and
- c) water;

in the manufacture of a composition for treating a vascular abnormality of the skin of a human subject by topically administering to the abnormality the composition once daily at a rate of:

- d) 4 -8 mg Rapamycin /cm²; and/or
- e) 1-6 mg Rapamycin.

Third Aspect – Composition for Treating

According to a third aspect, the invention is a composition comprising

- a) Rapamycin;
- b) Monolaurin and Monomyristin as vehicle; and
- c) water;

for treating a vascular abnormality of the skin of a human subject by topically administering the composition to the abnormality once daily at a rate of:

- d) 4 -8 mg Rapamycin /cm²; and/or
- e) 1-6 mg Rapamycin.

Fourth Aspect – Further Method of Treatment

According to a fourth aspect, the invention is a method of treating a vascular abnormality on the skin of a human subject, comprising topically applying to the abnormality, once daily for at least 1, 2, 3, 4, 5, or 6 months, a composition comprising:

- a) Rapamycin as active ingredient;
- b) vehicle comprising monolaurin and monomyristin, and
- c) water as a solvent;

such that at the conclusion of the at least 1, 2, 3, 4, 5, or 6 months the concentration of the rapamycin in the bloodstream of the subject, if any, does not exceed 1, 2, 3, 4 or 5 ng/mL (and preferably does not exceed 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8 or 0.9 mg/mL at the conclusion of one or more of the months). For the avoidance of doubt, any of the ng/mL figures here may apply for any said time period noted here.

Optional Features

The following optional features apply to all of the first, second, third and fourth aspects of the invention, in each case alone or in any combination with one or more of the following features or sets of features, except where they are mutually excluding.

Rate of Administration

The composition is administered, or is for administration, once daily at a rate of:

- a) 5 - 7 mg Rapamycin /cm²; or
- b) 2-5 mg Rapamycin.

The composition is administered, or is for administration, once daily at a rate of:

- c) about 6 mg Rapamycin /cm²; or
- d) 3-4 mg Rapamycin.

The composition is administered for at least 1, 2, 3, 4, 5 or 6 months.

The composition is administered, or is for administration, such that at the conclusion of at least 1, 2, 3, 4, 5, or 6 months the concentration of the Rapamycin in the bloodstream of the subject, if any, does not exceed 1, 2, 3, 4 or 5 ng/mL.

The composition is administered, or is for administration, such that at the conclusion of at least 1, 2, 3, 4, 5, or 6 months the concentration of the Rapamycin in the bloodstream of the subject, if any, does not exceed 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8 or 0.9 ng/mL.

Component Amounts

The composition comprises 0.5 - 5% wt Rapamycin.

The composition comprises 0.5 - 1% wt Rapamycin.

The composition comprises approximately 0.5% Rapamycin.

The composition comprises approximately 1% Rapamycin.

Conditions Treated

The vascular abnormality comprises angiofibroma.

The vascular abnormality comprises facial angiofibroma.

The vascular abnormality comprises a cutaneous vascular lesion.

The vascular abnormality comprises port wine stain.

The port wine stains are treated after laser treatment thereof.

Further Features

The composition comprises monolaurin at approximately 7 - 28% wt, or approximately 5% - 10% wt, or approximately 7% wt.

The composition comprises monomyristin at approximately 7%-28% wt or approximately 15%-25% wt, or approximately 21% wt.

The composition comprises:

- a) 5% - 9% wt Monolaurin + 19% – 23% wt Monomyristin; or
- b) 12% - 16% wt Monolaurin + 12 - 16% wt Monomyristin.

The composition comprises:

- a) about 7% wt Monolaurin + about 21% wt Monomyristin; or
- b) about 14% wt Monolaurin + about 14% wt Monomyristin.

Water Retainer

The composition comprises a water retainer.

The water retainer comprises polyoxyethylene stearate.

Softener

The composition comprises a softener.

The softener comprises one or more of propylene glycol, petrolatum, lanolin, mineral oil, glycerin, lecithin and sorbitol.

Buffer

The composition comprises a buffer.

The buffer comprises one or more of citric acid anhydrous, sodium bicarbonate and triethanolamine.

Sequestrant

The composition comprises a sequestrant.

The sequestrant comprises one or more of disodium edetate, citric acid and tetrasodium EDTA.

pH Adjuster

The composition comprises hydroxide for pH adjustment.

Preservative

The composition comprises a preservative.

The preservative comprises one or more of potassium sorbate, diazolidinyl urea, phenoxyethanol and sodium hydroxymethylglycinate.

Water

The composition comprises water at 58% - 72% wt.

Other Features

The composition comprises:

- a) 0.5 – 5% wt Rapamycin;
- b) vehicle comprising:
 - 7-28% wt monolaurin; and
 - 7-28% wt monomyristin; and
- c) water as a solvent.

The composition comprises 0.5 – 5% wt Rapamycin, 5% - 9% wt Monolaurin and 19% - 23% wt Monomyristin.

The composition comprises 0.5 – 5% wt Rapamycin, 7% wt Monolaurin and 21% wt Monomyristin.

The composition comprises 0.5% or 1% wt Rapamycin, 7% wt Monolaurin and 21% wt Monomyristin.

The composition comprises 0.5 – 5% wt Rapamycin, 12% - 16% wt Monolaurin and 12% – 16% wt Monomyristin.

The composition comprises 0.5 – 5% wt Rapamycin, 14% wt Monolaurin and 14% wt Monomyristin.

The composition comprises 0.5% or 1% wt Rapamycin, 14% wt Monolaurin and 14% wt Monomyristin.

The composition comprises 0.5 – 5% wt Rapamycin, 17.5% ($\pm 2\%$) wt Monolaurin and 10.5% ($\pm 2\%$) wt Monomyristin.

The composition comprises 0.5 – 5% wt Rapamycin, 17.5% wt Monolaurin and 10.5% wt Monomyristin.

The composition comprises 0.5% or 1% wt Rapamycin, 17.5% wt Monolaurin and 10.5% wt Monomyristin.

The composition comprises 0.5% or 1% wt Rapamycin, 21% wt Monolaurin and 7% wt Monomyristin.

The Monolaurin is glyceryl monolaurate and the Monomyristin is glyceryl monomyristate.

The composition comprises:

- a) 0.5 – 5% wt Rapamycin;
- b) vehicle comprising:
 - 10-18% wt monolaurin; and
 - 10-18% wt monomyristin; and
- c) water as a solvent.

All Statements

The composition components listed for any of the above aspects or options may be $\pm 5\%$ or $\pm 10\%$ of the values noted. For example 0.5% Rapamycin $\pm 5\%$ of this, or 1% Rapamycin $\pm 5\%$ of this.

IMAGES

Some preferred embodiments of the invention are illustrated by reference of the following images, of which-

- Figure 1** shows the results obtained from particle size analysis of a 1% Rapamycin composition for topical application;
- Figure 2** shows images of Rapamycin particles in the same 1% composition; and
- Figure 3** provides 'before and after' images for the skin of a person whose angiofibromas were treated according to an embodiment of the invention.

DETAILED DESCRIPTION

Example Formulations 1 & 2

Two preferred embodiments of the invention, namely Formulation 1 and Formulation 2, are for topical treatment of vascular abnormalities of the skin. Without limiting the scope of the invention, these diseases may comprise human angiofibromas, for example facial angiofibromas or cutaneous vascular lesions. The Formulations may also be used for treating port wine stains, for example after laser treatment to limit possible regrowth of the stain. They are composed substantially as shown in **Table 1** below-

Table 1			
Component	Function	Amount (% wt)	
		Formulation 1	Formulation 2
Rapamycin	Active ingredient	0.50	1.00
Monolaurin (Glyceryl monolaurate)	Vehicle	7.00	7.00
Monomyristin (Glyceryl Monomyristate)	Vehicle	21.00	21.00
Polyoxyethylene (100) stearate	Water retention	1.00	1.00

Propylene glycol	Softener	2.00	2.00
Citric acid anhydrous	Buffer	0.90	0.90
Disodium edetate	Sequestrant	0.05	0.05
Sodium hydroxide pellets	pH adjustment	0.18	0.18
Potassium sorbate	Preservative	0.20	0.20
Purified water	Solvent	67.17	66.67

Compositions according to the invention, including Formulations 1 and 2, may be produced according to the following method.

Production of a water phase pre-blend

A water phase pre-blend is prepared as follows:

- the Rapamycin and propylene glycol are combined and vortex mixed;
- the water is added with continued vortex mixing;
- the blend is then heated to 70°C ($\pm 5^\circ\text{C}$);
- citric acid, disodium EDTA and potassium sorbate are added with vortex mixing until dissolved;
- the temperature of the mixture is then regulated to 50°C; and
- the polyoxyethylene (100) stearate is added.

Production of an oil phase pre-blend

An oil phase pre-blend is prepared as follows:

- glyceryl monolaurate and glyceryl monomyristate are combined with slow speed vortex mixing and heating to 70°C ($\pm 5^\circ\text{C}$).

Final blend

The water and oil phase pre-blends, both at 70°C ($\pm 5^\circ\text{C}$), are combined and mixed thoroughly until homogenous. The mixture is then cooled slowly at a rate of 1°C per minute and vortex mixed until it forms into a smooth, white and iridescent cream.

When the cream had cooled to no more than 32°C it is packaged in 30mL aluminium tubes with polypropylene screw on caps.

Example Formulations 3 & 4

Formulations 3 and 4 were produced for the same purpose and in the same way described for Formulations 1 and 2. They are listed in **Table 2** below–

Table 2			
Component	Function	Amount (% wt)	
		Formulation 3	Formulation 4
Rapamycin	Active ingredient	0.10	5.00
Monolaurin (Glyceryl monolaurate)	Vehicle	7.00	7.00
Monomyristin (Glyceryl Monomyristate)	Vehicle	21.00	21.00
Polyoxyethylene (100) stearate	Water retention	1.00	1.00
Propylene glycol	Softener	2.00	2.00
Citric acid anhydrous	Buffer	0.90	0.90
Disodium edetate	Sequestrant	0.05	0.05
Sodium hydroxide pellets	pH adjustment	0.18	0.18
Potassium sorbate	Preservative	0.20	0.20
Purified water	Solvent	72	66.1

Particle Size Features

Figures 1 and 2 illustrate characteristics of the Rapamycin active ingredient for the 1% cream identified above as Formulation 2. The information was obtained by analysing the Formulation using a Malvern Morphologi GS3 image analyser. This is effectively an automated microscope that scanned the Formulation to detect 3D shape features of the Rapamycin particles.

Referring to Figure 1, the CE Diameter (‘circle equivalent diameter’) values represent particle size on a number weighted basis. In other words, it represents the particles as

2-dimensional shapes converted to the nearest applicable circle, for which the diameter is then calculated. Referring to the particular notation shown, $D[n,0.10](\mu\text{m})$: 3.17 means that 10% of the particles are $3.17\mu\text{m}$ or smaller on a number of particles basis; $D[n,0.16](\mu\text{m})$: means that 16% are smaller than $3.83\mu\text{m}$; and $D[n,0.50](\mu\text{m})$: means that 50% are smaller than $8.33\mu\text{m}$ on a number of particle basis, etc

Referring to Figure 2, the images are representative of the shape and relative size of Rapamycin particles in Formulation 2.

Figures 1 and 2 illustrate that the Rapamycin is not dissolved in the rest of the composition but rather sits suspended in the carrier or vehicle component.

Trials - Rapamycin Blood Concentration

Method

A multi-centre, double-blind, randomised, placebo-controlled, dose-response parallel study was run in compliance with the Declaration of Helsinki and the International Council for Harmonization Guidelines for Good Clinical Practice. Its purpose was to assess the efficacy in topically treating vascular abnormalities of the skin, including whether, and if so then to what extent, Rapamycin transfers into the bloodstream when applied topically via Formulation 1 or Formulation 2.

The study comprised 107 human participants aged 6 - 65 years diagnosed with facial angiofibromas associated with tuberous sclerosis complex. The facial angiofibromas were of mild or moderate severity. In other words, each subject had a score of 2 or 3 on an Investigator Global Assessment (IGA) scale.

The participants were randomised to one of three treatment groups, being Rapamycin 0.5% cream (Formulation 1; $n=36$), Rapamycin 1% cream (Formulation 2; $n = 33$), or placebo cream (ie the same excipients without the active ingredient; $n=38$).

The Formulations and placebo were applied to the angiofibromas topically, once daily, for 26 weeks at a Rapamycin rate of 6 mg/cm^2 of skin. Given that different participants had different sized areas of angiofibromas, they did not all receive the same amount of Formulation. However, the amount of Rapamycin administered per day averaged over the group was as shown in **Table 3** below-

Table 3 Formulations 1 & 2			
Age	Formulation	Mean amount of cream per person (mg/day)	Mean amount of Rapamycin per person (mg/day)
<12	1 (0.5%)	379	1.895
<12	2 (1%)	277	2.77
≥12	1 (0.5%)	460	2.3
≥12	2 (1%)	567	5.67

Safety and efficacy measures were assessed at days 14, 56, 98, 140 and 182 (Visits 1-5 respectively). The primary endpoint was based on IGA scores after 26 weeks of treatment.

Secondary assessment criteria included facial angiofibromas severity index (FASI) and subject and clinician-reported percentage-based improvement.

All treated participants were included in the final analysis.

Results

The degree of improvement at the end of the treatment period is indicated in **Table 4** as follows-

Table 4				
Number of Participants				
	Formulation 1 (0.5% Rapamycin) n=36	Formulation 2 (1% Rapamycin) n=33	Placebo n=38	Total n=107
Two-grade reduction in IGA score	4 (11.1%)	3 (9.1%)	2 (5.3%)	9 (8.4%)
One-grade reduction in IGA score	20 (55.6%)	20 (60.6%)	9 (23.7%)	49 (45.8%)

Participants that did not have an improved IGA score of at least 1 are not included in the results above.

An example of the reduction in facial angiofibromas achieved for one person in the trial that was treated as above with Formulation 2 is illustrated in **Figure 3**. This individual had an IGA Score of 3 at the beginning of the trial and an IGA Score of 2 at Visit 5.

Table 5 below reports the amount of Rapamycin found in the blood for the various participants. The value for “N” for the number of participants tested for each Visit is less than the number enrolled in each group because some did not provide a test sample. In some instances, this was due to reluctance by pediatric participants (children) to give blood at some test points. For example, for Rapamycin 1% at Visit 1, the number of subjects tested was N=26 compared with N=33 for the total number enrolled in the Trial for that group. However, no Rapamycin was detected for any participants that returned test samples at any test stage, except that at Test 1 (14 days) one participant in the 0.5% formulation group had 1.1 ng/ml Rapamycin in their blood.

Table 5				
Blood Rapamycin Concentration Changes Versus Baseline Over Time				
	Formulation 1 0.5 % Rapamycin	Formulation 2 1 % Rapamycin	Placebo	Total
Baseline value (N)	36	33	38	107
Visit 1				
1.1 ng/mL	1	0		
Nil	29	26	27	82
Change from baseline				
Nil to 1.1	1 (2.8%)	0 (0%)	0 (0%)	0.9 (0%)
Nil to Nil	29 (80.6%)	26 (78.8%)	27 (71.1%)	82 (76.6%)
Visit 2				
Nil	27	26	28	81
Change from baseline				
Nil to Nil	27 (75.0%)	26 (78.8%)	28 (73.7%)	81 (75.7%)

Visit 3				
Nil	29	27	23	69
Change from baseline				
Nil to Nil	29 (80.6%)	27 (78.8%)	23 (60.5%)	69 (64.5%)
Visit 4				
Nil	24	20	21	65
Change from baseline				
Nil to Nil	24 (66.7%)	20 (60.6%)	21 (55.3%)	65 (60.7%)
Visit 5				
Nil	30	27	34	91
Change from baseline				
Nil to Nil	30 (83.3%)	27 (81.8%)	34 (89.5%)	91 (85.0%)
Follow-up Visit				
Nil	23	20	20	63
Change from baseline				
Nil to Nil	23 (63.9%)	20 (60.6%)	20 (52.8%)	63 (58.9%)

In the trial, both of Formulations 1 and 2 were well tolerated and were effective in reducing facial angiofibromas in the majority of participants. Notably this was achieved without Rapamycin finding its way into the bloodstream, with the one exception indicated above for the 14 day test, but this did not recur at any later test stages / Visits. At 6 months, none of the participants that were tested were found to have any Rapamycin in their blood. These results are remarkable given that transfer of Rapamycin into the blood was expected, especially given the length of the period for which the drug was being taken and the amount administered.

By way of comparison, the commercial product HYFTOR™ Gel ¹ was tested. This is a topical gel containing 0.2% wt Rapamycin for treating tuberous sclerosis and similar diseases. The product was applied topically twice daily for 30 human participants at angiofibromas sites. The average total amount dosed per participant per day is shown in **Table 6** below –

¹ <https://www.hyftor.com>.

Table 6 HYFTOR™ Gel Dosage Rate		
Age	Mean amount of HYFTOR™ Gel per person (mg/day)	Mean amount of Rapamycin per person (mg/day)
<12	600	1.2
≥12	800	1.6

Tests were run to ascertain the amount of Rapamycin in the bloodstream over the period for which the HYFTOR™ Gel was taken, with results noted in **Table 7** as follows-

Table 7 HYFTOR™ Gel Blood Results				
	N	Number of patients with Rapamycin in their blood	Average amount of Rapamycin (ng/ml)	Maximum amount of Rapamycin (ng/ml)
Tested at 4 weeks				
All patients	30	27 (90%)	0.22	0.39
Pediatric patients	13	12 (92%)	0.19	0.29
Adults	17	15 (88%)	0.24	0.39
Tested at 12 weeks				
All patients	30	21 (70%)	0.24	0.50
Pediatric patients	13	10 (77%)	0.21	0.41
Adults	17	11 (65%)	0.27	0.50

Comparison

Formulations 1 & 2, versus HYFTOR™ Gel

As can be seen from Tables 3 and 6, with Formulations 1 and 2, more Rapamycin was administered to trial participants compared to HYFTOR™ Gel. In the case of Formulation 2 in particular, subjects who were ≥12 years of age received on average

5.67 mg /day Rapamycin compared to 1.6 mg/day for the subjects in the same age bracket for HYFTOR™ Gel.

Notwithstanding the greater amount of Rapamycin for Formulation 2, the Rapamycin was not found to collect in the system / blood stream, whereas with HYFTOR™ Gel it did. This suggests that formulations based on the monolaurin and monomyristin vehicles can be more safely used to deliver larger amounts of Rapamycin to patients in need of higher doses.

Further, the results indicate that even for people that only need lower amounts of Rapamycin, formulations based on monolaurin and monomyristin reduce the likelihood of Rapamycin collecting in the system / blood stream.

Disclosure

In terms of disclosure, this document hereby discloses each item, feature or step mentioned herein in combination with one or more of any of the other item, feature or step disclosed herein, in each case regardless of whether such combination is claimed.

Variations

While some preferred embodiments of the invention have been described by way of example, it should be understood that modifications and improvements can occur without departing from the scope of the following claims.

CLAIMS

1. A method for treating a vascular abnormality of the skin of a human subject, comprising topically administering to the abnormality a composition comprising:
 - a) Rapamycin;
 - b) Monolaurin and Monomyristin as vehicle; and
 - c) water;once daily at a rate of:
 - d) 4-8 mg Rapamycin /cm²; and/or
 - e) 1-6 mg Rapamycin.
2. A method according to claim 1, wherein the composition is administered once daily at a rate of:
 - a) 5 - 7 mg Rapamycin /cm²; and/or
 - b) 2-5 mg Rapamycin.
3. A method according to claim 1, wherein the composition is administered once daily at a rate of:
 - a) about 6 mg Rapamycin /cm²; and/or
 - b) 3-4 mg Rapamycin.
4. A method according to claim 1, 2 or 3, wherein the composition is administered for at least 1, 2, 3, 4, 5 or 6 months.
5. A method according to any one of claims 1-4, comprising administering the composition such that at the conclusion of at least 1, 2, 3, 4, 5, or 6 months of administration as stated the concentration of the Rapamycin in the bloodstream of the subject, if any, does not exceed 1, 2, 3, 4 or 5 ng/mL.
6. A method according to any one of claims 1-4, comprising administering the composition such that at the conclusion of at least 1, 2, 3, 4, 5, or 6 months of administration as stated the concentration of the Rapamycin in the bloodstream of the subject, if any, does not exceed 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8 or 0.9 ng/mL.
7. A method according to any one of the preceding claims, wherein the composition comprises 0.5 - 5% wt Rapamycin.

8. A method according to claim 7, wherein the composition comprises 0.5 - 1% wt Rapamycin.
9. A method according to claim 7, wherein the composition comprises approximately 0.5% Rapamycin.
10. A method according to claim 7, wherein the composition comprises approximately 1% Rapamycin.
11. A method according to any one of the preceding claims, wherein the vascular abnormality comprises angiofibroma.
12. A method according to any one of the preceding claims, wherein the vascular abnormality comprises facial angiofibroma.
13. A method according to any one of claims 1-11, wherein the vascular abnormality comprises a cutaneous vascular lesion.
14. A method according to any one of claims 1-11, wherein the vascular abnormality comprises port wine stain.
15. A method according to according to claim 14, wherein the port wine stain is treated after laser treatment thereof.
16. A method according to any one of the preceding claims, wherein the composition comprises monolaurin at approximately 7 - 28% wt, or approximately 5% - 10% wt, or approximately 7% wt.
17. A method according to any one of the preceding claims, wherein the composition comprises monomyristin at approximately 7%-28% wt or approximately 15%-25% wt, or approximately 21% wt.
18. A method according to any one of the preceding claims, wherein the composition comprises:
 - a) 5% - 9% wt Monolaurin + 19% – 23% wt Monomyristin; or

b) 12% - 16% wt Monolaurin + 12 - 16% wt Monomyristin.

19. A method according to any one of the preceding claims, wherein the composition comprises:

- a) about 7% wt Monolaurin + about 21% wt Monomyristin; or
- b) about 14% wt Monolaurin + about 14% wt Monomyristin.

20. A method according to claim 18 or 19, wherein the composition comprises Rapamycin at about 1% wt.

21. A method according to any one of the preceding claims, wherein composition comprises a water retainer.

22. A method according to claim 21, wherein the water retainer comprises polyoxyethylene stearate.

23. A method according to any one of the preceding claims, wherein the composition comprises a softener.

24. A method according to claim 23, wherein the softener comprises one or more of propylene glycol, petrolatum, lanolin, mineral oil, glycerin, lecithin and sorbitol.

25. A method according to any one of the preceding claims, wherein the composition comprises a buffer.

26. A method according to claim 25, wherein the buffer comprises one or more of citric acid anhydrous, sodium bicarbonate and triethanolamine.

27. A method according to any one of the preceding claims, wherein the composition comprises a sequestrant.

28. A method according to claim 26, wherein the sequestrant comprises one or more of disodium edetate, citric acid and tetrasodium EDTA.

29. A method according to any one of the preceding claims, wherein the composition comprises hydroxide for pH adjustment.

- 30.** A method according to any one of the preceding claims, wherein the composition comprises a preservative.
- 31.** A method according to claim 30, wherein the preservative comprises one or more of potassium sorbate, diazolidinyl urea, phenoxyethanol and sodium hydroxymethylglycinate.
- 32.** A method according to any one of the preceding claims, wherein the composition comprises water at 58% - 72% wt.
- 33.** A method according to any one of claims 1 to 7, wherein the composition comprises:
- a) 0.5 – 5% wt Rapamycin;
 - b) vehicle comprising:
 - 7-28% wt monolaurin; and
 - 7-28% wt monomyristin; and
 - c) water as a solvent.
- 34.** A method according to any one of claims 1-7, wherein the composition comprises 0.5 – 5% wt Rapamycin, 5% - 9% wt Monolaurin and 19% - 23% wt Monomyristin.
- 35.** A method according to claim 34, wherein the composition comprises 0.5 – 5% wt Rapamycin, 7% wt Monolaurin and 21% wt Monomyristin.
- 36.** A method according to claim 34, wherein the composition comprises 1% wt Rapamycin, 7% wt Monolaurin and 21% wt Monomyristin.
- 37.** A method according to any one of claims 1-7, wherein the composition comprises 0.5 – 5% wt Rapamycin, 12% - 16% wt Monolaurin and 12% – 16% wt Monomyristin.
- 38.** A method according to claim 38, wherein the composition comprises 0.5 – 5% wt Rapamycin, 14% wt Monolaurin and 14% wt Monomyristin.
- 39.** A method according to claim 38, wherein the composition comprises 0.5% or 1% wt Rapamycin, 14% wt Monolaurin and 14% wt Monomyristin.

40. A method according to any one of claims 1-7, wherein the composition comprises 0.5 – 5% wt Rapamycin, 17.5% ($\pm 2\%$) wt Monolaurin and 10.5% ($\pm 2\%$) wt Monomyristin.
41. A method according to any one of claims 1-7, wherein the composition comprises 0.5 – 5% wt Rapamycin, 17.5% wt Monolaurin and 10.5% wt Monomyristin.
42. A method according to any one of claims 1-7, wherein the composition comprises 0.5% or 1% wt Rapamycin, 17.5% wt Monolaurin and 10.5% wt Monomyristin.
43. A method according to any one of claims 1-7, wherein the composition comprises 0.5% or 1% wt Rapamycin, 21% wt Monolaurin and 7% wt Monomyristin.
44. A method according to any one of the preceding claims, wherein the Monolaurin is glyceryl monolaurate and the Monomyristin is glyceryl monomyristate.
45. A method according to any one of the preceding claims, wherein the vascular abnormality comprises angiofibroma, a cutaneous vascular lesion or a port wine stain.
46. A method according to any one of claims 1-7, wherein the composition comprises:
- a) 0.5 – 5% wt Rapamycin;
 - b) vehicle comprising:
 - 10-18% wt monolaurin; and
 - 10-18% wt monomyristin; and
 - c) water as a solvent.
47. The use of:
- a) Rapamycin;
 - b) Monolaurin and Monomyristin as vehicle; and
 - c) water;
- in the manufacture of a composition for treating a vascular abnormality of the skin of a human subject by topically administering to the abnormality the composition once daily at a rate of:
- d) 4 -8 mg Rapamycin /cm²; and/or
 - e) 1-6 mg Rapamycin.
48. A composition comprising:
- a) Rapamycin;

b) Monolaurin and Monomyristin as vehicle; and

c) water;

for treating a vascular abnormality of the skin of a human subject by topically administering to the abnormality the composition once daily at a rate of:

d) 4 -8 mg Rapamycin /cm²; and/or

e) 1-6 mg Rapamycin.

49. A method of treating a vascular abnormality on the skin of a human subject, comprising topically applying to the abnormality, once daily for at least 1, 2, 3, 4, 5, or 6 months, a composition comprising:

a) Rapamycin as active ingredient;

b) vehicle comprising monolaurin and monomyristin, and

c) water as a solvent;

such that at the conclusion of the at least 1, 2, 3, 4, 5, 6 months the concentration of the rapamycin in the bloodstream of the subject, if any, does not exceed 1, 2, 3, 4 or 5 ng/mL.