TITLE

Treatment for Hemangioma

FIELD OF INVENTION

This invention relates to a treatment for hemangioma, including but not limited to infantile hemangioma, using Fosinopril and Propranolol in particular proportions.

BACKGROUND

Haemangiomas are complex growths which develop as the result of proliferation of endothelial cells surrounding blood-filled cavities. They can occur anywhere on the body, but most commonly appear on the face, scalp, chest or back. Haemangiomas generally fade over time, and most do not require treatment. However, they can be cosmetically disfiguring, psychologically disturbing, and can cause functional disability depending on the location of lesions. For example, they can cause blindness if lesions occur in the tissue surrounding the eye. Infantile haemangioma in particular affects up to 10% of children. It is the most common type of hemangioma and is characterised by an initial rapid proliferation phase, followed by a slow spontaneous involution over 5 to 10 years, which may lead to a fibro-fatty residuum[1].

The patent publication WO 2021/154102[2] discloses the use of certain ACE Inhibitors (ACEis) and beta blockers for the treatment of infantile hemangioma. In the WO document the inventors' focus was on situations where the molar ratio of the ACEi is significantly higher than that of the beta blocker. The document does not provide particularised ratio, dosage or application rate data for Fosinopril + Propranolol, or for Fosinopril alone.

The inventors of the current invention have found that for an ACEi + Propranolol combination for treating haemangiomas, the ACEi should be present in a substantially lessor molar amount than the Propranolol. This was unexpected and enables the formulation of treatments with a relative lower amount of ACEi, and therefore assists to reduce the risk of undesirable systemic absorption thereof.

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[1] *Itinteang et al., Plast. Reconstr. Surg*. 2011; 128, 499-507.
[2] *Davis, MacKay, Patterson, Tan and Tan*, 5 Aug 2021.

DEFINITIONS

The term “comprises” or “has”, if/when used in this document in relation to one or more features, should not be seen as excluding the option of additional unmentioned features. The same applies to derivative terms such as “comprising” and “having”.

References to Propranolol and Fosinopril should be taken to include these molecules per se and all pharmaceutically acceptable salts thereof. In the event that weight amounts are given for Propranolol and Fosinopril, the weight amounts cited should be taken as scaled up when considering salts so as to account for the extra mass of the salt component, ie to give the same amount of the base.

For example, 1 mol of Propranolol weighs 259.3 g, and may be taken as substantially equivalent to 1 mol of Propranolol hydrochloride which weighs 295.8 g. Accordingly, a claim for 1% wt “Propranolol” should be taken as broad enough to cover 1.14 % wt Propranolol hydrochloride, etc.

By way of further example, 1 mol of Fosinopril weighs 563.7 g, and may be taken as substantially equivalent to 1 mol of Fosinopril sodium which weighs 585.6 g. Accordingly, a claim for 1% wt “Fosinopril” should be taken as broad enough to cover 1.04 % wt Fosinopril sodium, etc.

Unless the context requires otherwise, references in this specification to hemangioma mean all forms of the condition. The term includes, but is not limited to limited to, infantile hemangioma, cutaneous hemangioma, capillary hemangioma, lobular capillary hemangioma, pyogenic granuloma, cavernous hemangioma, retinal hemangioma (including for example, retinal cavernous hemangioma, retinal capillary hemangioma, choroidal hemangioma, cavernous hemangioma of the orbit), and/or periocular hemangioma.

The term topical treatment as used in this document preferably indicates application to the skin, but can optionally mean application to the eye, for example as an ointment or an eye drop.

The terms “approximately” or “about” when used to qualify a numerical value in the ‘Summary of Invention’ or ‘Claims Sections’ hereof mean of the value stated ± 0%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9% or 10%.

SUMMARY OF THE INVENTION

First Aspect – A Medicament

According to a first aspect of the invention there is a medicament for use in topically treating hemangioma, comprising Propranolol and Fosinopril in a molar ratio of 2 to 0.9 - 1.3 respectively.

Optionally the molar ratio of Propranolol to Fosinopril is 2 to 1 – 1.2 respectively.

Optionally the molar ratio of Propranolol to Fosinopril is 2 to approximately 1 respectively.

Optionally the molar ratio of Propranolol to Fosinopril is 2 to 1 respectively.

Optionally the medicament comprises approximately 0.1% to approximately 5% by weight of Propranolol and approximately 0.1% to approximately 5% by weight of Fosinopril.

Optionally the medicament comprises approximately 0.5% to approximately 5% by weight of Propranolol and approximately 0.5% to approximately 5% by weight of Fosinopril.

Optionally the medicament comprises approximately 1% to approximately 5% by weight of Propranolol and approximately 1% to approximately 5% by weight of Fosinopril.

Optionally the medicament comprises approximately 1% by weight of Propranolol and approximately 1.1% by weight of Fosinopril.

Optionally the medicament comprises approximately 1.5% to approximately 4.5% by weight of Propranolol and approximately 1.5% to approximately 4.5% by weight of Fosinopril.

Optionally the medicament comprises approximately 2% to approximately 4% by weight of Propranolol and approximately 2% to approximately 4% by weight of Fosinopril.

Optionally the medicament comprises approximately 2.5% to approximately 3.5% by weight of Propranolol and approximately 2.5% to approximately 3.5% by weight of Fosinopril.

Optionally the medicament comprises approximately 3% by weight of Propranolol and approximately 3% by weight of Fosinopril.

Optionally the medicament comprises approximately 0.9% by weight of Propranolol and approximately 1% by weight of Fosinopril.

Optionally the medicament comprises approximately 1% by weight of Propranolol hydrochloride and approximately 1% by weight of Fosinopril sodium.

Optionally the medicament is in the form of a topical lotion, cream, ointment or gel.

Optionally the medicament comprises carrier, emulsifier and preservative.

Optionally the medicament comprises a cream having the following ingredients:

a) Propranolol hydrochloride;
b) Fosinopril sodium;
c) Emollient;
d) Emulsifier;
e) Buffer;
f) Humectant;
g) Preservative;
h) Chelating agent; and
i) Water.

Optionally the medicament comprises a cream having the following ingredients:

a) Propranolol hydrochloride
b) Fosinopril sodium
c) Liquid paraffin
d) Cetyl alcohol

e) Isopropyl myristate

f) Sorbitol (70%)

g) Glyceryl Stearate

h) PEG-40 Stearate

i) Citric Acid

j) Potassium Sorbate

k) Sodium Hydroxide

l) Disodium EDTA

m) Water

Optionally the medicament comprises a cream having the following ingredients and amounts –

Ingredient	**% wt**
Propranolol hydrochloride	1
Fosinopril sodium	1
Liquid paraffin	8.5
Cetyl alcohol	5
Isopropyl myristate	5
Sorbitol (70%)	5
Glyceryl Stearate	2
PEG-100 Stearate	2
PEG-40 Stearate	2
Citric Acid	0.2
Potassium Sorbate	0.2
Sodium Hydroxide	0.125
Disodium EDTA	0.05
Water	Make up to 100%

Optionally the medicament comprises the following ingredients:

a) Propranolol hydrochloride;

b) Fosinopril sodium;

c) Vitamin E;

d) Isopropyl palmitate;

e) Liquid paraffin;

f) White beeswax;

g) White petroleum jelly;

Optionally the medicament consists of any of the following three sets of ingredients:

Ingredient	**% wt** (approximately)		
Fosinopril sodium	1	2.5	5
Propranolol hydrochloride	1	2.5	5
Vitamin E	0.05	0.05	0.05
Isopropyl palmitate	5	5	5
Liquid paraffin	10	10	10
White beeswax	5	5	5
White petroleum jelly	77.95	74.95	69.95

Optionally the medicament is not of necessity for topical treatment and/or is not of necessity for treating hemangioma.

The options for the First Aspect above may be implemented alone or in any combination thereof.

Second Aspect - Use in Manufacturing

According to a second aspect, the invention comprises the use of Propranolol and Fosinopril in the manufacture of a medicament according to any one of the medicament statements for the First Aspect noted above, for topical administration to a human patient for treating hemangioma.

Optionally the hemangioma comprises infantile hemangioma.

Optionally the medicament is for application to the hemangioma at a rate of 150 mg to 1,500 mg Propranolol, and 150 mg to 1,500 mg Fosinopril, per dosage event.

Optionally the medicament is for application to the hemangioma at a rate of, or equivalent to, one or more of:

a) 1 FTU for the face and neck;

b) 1 FTU for an arm and hand;

c) 1.5 FTUs for a leg and foot;

d) 1 FTU for the chest and stomach; and

e) 1.5 FTUs for the back and buttocks.

The options for the Second Aspect above may be implemented alone or in any combination thereof.

Third Aspect - Method of Treatment

According to a third aspect, the invention is a method of treating hemangioma in a human subject, comprising topically applying to the hemangioma a medicament according to any one of the medicament statements for the First Aspect above.

Optionally the hemangioma comprises infantile hemangioma.

Optionally the medicament is applied to the hemangioma at a rate of 150 mg to 1,500 mg Propranolol, and 150 mg to 1,500 mg Fosinopril, per dosage event.

Optionally the medicament is applied to the hemangioma at a rate of, or equivalent to, one or more of:

a) 1 FTU for the face and neck;

b) 1 FTU for an arm and hand;

c) 1.5 FTUs for a leg and foot;

d) 1 FTU for the chest and stomach; and

e) 1.5 FTUs for the back and buttocks.

The options for the First Aspect above may be implemented alone or in any combination thereof.

Fourth Aspect

According to a fourth aspect, the invention is a pharmaceutical composition for topical use comprising Propranolol and Fosinopril in a molar ratio or a weight amount as noted for the First Aspect.

DRAWINGS / GRAPHS

Some preferred embodiments of the invention will now be described by way of example and with reference to the accompanying drawings/graphs, of which-

Figure 1 is a graphical representation of the results of efficacy and cytotoxicity tests for various ACEis used against infantile hemangioma cell lines;

Figure 2 is a graphical representation of the results of efficacy tests for various ACEis at high concentrations when used against infantile hemangioma cell lines;

Figure 3 is a graphical representation of the results of efficacy tests for Propranolol when used with the ACEi Fosinopril in a 2:1 molar ratio against hemangioma cell lines, together with a comparison for the combination versus the two active agents alone;

Figure 4 is a graphical representation of efficacy results for various ratios of Propranolol + Fosinopril used against infantile haemangioma cell lines;

Figure 5 is a graphical representation of the results of skin permeation tests showing the percentage of Fosinopril in formulations comprising salts of Fosinopril and Propranolol.

Figure 6 is a graphical representation of the results of skin permeation tests showing the weight amount of Fosinopril in formulations comprising salts of Fosinopril and Propranolol.

Figure 7 is a graphical representation of the results of skin permeation tests showing the percentage of Propranolol in formulations comprising salts of Fosinopril and Propranolol.

Figure 8 is a graphical representation of the results of skin permeation tests showing the weight amount of Propranolol in formulations comprising salts of Fosinopril and Propranolol.

DETAILED DESCRIPTION

Comparison of Fosinopril with Other ACEis

A series of studies were run to develop a drug combination for topically treating hemangioma, for example infantile hemangioma, in human subjects. The studies involved an MTS cell proliferation assay-model with patient-derived primary hemangioma cell lines to assess both suppression of cell proliferation and cytotoxicity.

The studies were conducted *in vitro* using primary hemangioma cell lines derived from excised human patient tissues (n=14). All the tissues were obtained during the proliferating phase of infantile hemangioma as assessed by a pathologist, and each cell line was assessed/characterised to confirm it was of a hemangioma phenotype as indicated by the expression of surface CD31, a marker of endothelial cells.

The tests further involved growing cells isolated from the infantile hemangioma patients. The cells were passaged to a maximum of 6 times *in vitro*. To test drug efficacy, the cells were grown in Biolamin 521 coated tissue culture flasks and then placed into Biolaminin coated 96 well plates. The assay was performed by either adding 1 dose of drug at the beginning of the culture process, or daily for up to 3 days, and the cell growth rate was measured on day 3 using MTS, comparing the suppression of cellular growth (as measured by metabolic output) in the cultures compared to the growth in the well that contained no drug or active pharmaceutical ingredients.

The assay initially tested the effectiveness of the following drugs:

a) Captopril;

b) Ramipril;

c) Lisinopril;

d) Trandolapril;

e) Quinapril;

f) Fosinopril; and

g) Captopril.

Referring to **Figures 1 & 2**, apart from Lisinopril, all the ACEis were found able to suppress hemangioma cell growth. However, Fosinopril was found to be surprisingly more efficacious than the others, with negligible cytotoxicity, resulting in actual or near to 100% suppression even when used at significantly lower concentrations than the other ACEis. Fosinopril also showed surprising efficacy compared to Propranolol, which is often viewed as the 'standard of care' for the disease. The MTT data was further assessed where, as illustrated in Figure 2, even at high concentrations the ACEi's Ramipril, Lisinopril, Trandolapril, and Quinapril did not perform as well as Fosinopril did at low concentrations.

Optimal Ratios for Propranolol + ACEi

The inventors also used MTS[3] data to explore the efficacy of Propranolol in combination with ACEis at various dosages/ratios. In this regard primary hemangioma cell lines were dosed with Propranolol at 0-150 µM and an ACEi selected from Fosinopril, Trandolapril, Ramipril, or Quinapril at 0-600 µM. It was determined from the results that for each pairing, the following ratios worked best, with substantially equivalent efficacy.

ACE-I: Propranolol	**Ratio (molar)**	**ACE-I Prodrug**	**Phosphate Containing**
Ramipril	5:1	Yes	No
Trandolopril	3.75:1	Yes	No
Quinapril	5:1	Yes	No
Fosinopril	1:2	Yes	Yes
Captopril	Not studied due to significant cytotoxicity	No	No
Lisinopril	Not studied due to lack of effect.	No	No

[3] An assay similar to MTT without the need to solubilise the crystals before readout.

As indicated, in contrast to the other ACEis, Fosinopril surprisingly gave the best results when there is significantly less ACEi compared to Propranolol. For the other ACEis the ratio relationship was the inverse of this.

While not wishing to be bound by theory, it is hypothesised that the superior result for Fosinopril when combined with Propranolol relates to Fosinopril having a phosphate group. Notably, none of the other ACEis tested have a phosphate group.

2:1 Propranolol + Fosinopril

Referring to **Figure 3**, The 2:1 ratio of Propranolol to Fosinopril was further tested using an MTS assay with the same 14 individual patient-derived infantile hemangioma cell lines, comparing the 2:1 molar combination of Propranolol and Fosinopril with the active ingredients individually.

As indicated, the molar ratio of 2:1 Propranolol to Fosinopril was significantly more effective than the equivalent dose of Fosinopril alone and was even more significantly effective than the equivalent dose of propranolol alone.

This indicates that by using a 2:1 Propranolol-Fosinopril combination there is less risk, compared to at least several ACEis, of systemic and cytotoxic adverse events by reason of only needing a lessor amount of ACEi. The lower amount of ACEi also has manufacturing benefits in terms of handling and costs. Further, the ability to use less ACEi helps to lower the potential for adverse patient events in terms of cytotoxicity and cardiovascular health.

Other Ratios of Propranolol + Fosinopril

For comparison the inventors ran further MTS tests to investigate alternative molar ratios of Propranolol + Fosinopril. The results are shown in **Figure 4**. It illustrates the zone in which the combination of Propranolol and Fosinopril is most synergistic and the boundary at which the synergy drops off.

As illustrated, the optimum molar ratio range was found to be a Propranolol : Fosinopril molar ratio of 3.3 : 1 to 2 : 1. And more preferably, the optimum Propranolol to Fosinopril molar ratio range was found to be from about 2.5 : 1 to about 2 : 1.

Formulation Excipients

In preferred embodiments of the invention, the medicament is in the form of a lotion, cream, ointment or gel for topical application to human skin affected by hemangioma, having the Propranolol and Fosinopril in the same formulation.

The medicament may include as a solvent or carrier one or more of water and liquid paraffin.

The medicament may include as a skin conditioner or emollient one or more of liquid paraffin and isopropyl myristate.

The medicament may include as an emulsifier one or more of Cetyl alcohol, Glyceryl stearate, PEG 100 stearate and PEG 40 stearate.

The medicament may include as a preservative, Potassium sorbate.

The medicament may include as a humectant, Sorbitol.

The medicament may include as a buffering agent, one or more of citric acid and Sodium hydroxide.

The medicament may include as a chelating agent, Disodium EDTA.

It is not essential that all of the above excipients be used and those that are used may be in any combination. Preferably all excipients used, and the resulting formation, are suitable for paediatric use.

A preferred embodiment of the invention comprises a topical formulation as follows -

Ingredient	**Function**	**% wt**
Propranolol hydrochloride	Active agent	1
Fosinopril sodium	Active agent	1
Liquid paraffin	Skin conditioner and Emollient	8.5
Cetyl alcohol	Emulsifier	5

Isopropyl myristate	Skin conditioner and Emollient	5
Sorbitol (70%)	Humectant	5
Glyceryl Stearate	Emulsifier	2
PEG-100 Stearate	Emulsifier	2
PEG-40 Stearate	Emulsifier	2
Citric Acid	Buffering agent	0.2
Potassium Sorbate	Preservative	0.15
Sodium Hydroxide	Buffering agent / pH modifier	0.125
Disodium EDTA	Chelating agent	0.05
Water	Solvent	Make up to 100%

For the above formulation, for optimal results, the active ingredients were mixed into oil-based ingredients before adding water.

While it is preferred that the Propranolol and Fosinopril are in the same lotion, cream or gel, in other embodiments the medicament may have them as separate lotions, creams or gels, for example in the same pack.

Administration Amounts

Optionally the medicament comprises approximately 0.1% to approximately 5% by weight of Propranolol and approximately 0.1% to approximately 5% by weight of Fosinopril, provided that the molar ratio for is approximately 2 Propranolol to 0.9 – 1.3 Fosinopril.

Preferably the medicament is applied to the hemangioma at a rate of 150 mg to 1,500 mg Propranolol, and 150 mg to 1,500 mg Fosinopril, per dosage event.

Optionally the medicament is applied to the hemangioma, particularly in the case of an infant/child, at a rate of, or equivalent to, one or more of:

a) 1 FTU for the face and neck;

b) 1 FTU for an arm and hand;

c) 1.5 FTUs for a leg and foot;

d) 1 FTU for the chest and stomach; and

e) 1.5 FTUs for the back and buttocks.

The term FTU denotes “finger tip unit”, or in other words the amount of medicament normally carried on an adult finger tip when the finger tip is comfortably laden with medicament. One FTU comprises approximately 450 mg to 550 mg of medicament, and preferably about 500 mg of medicament.

Skin Permeation Tests

The following formulations were prepared for the purpose of in vitro skin permeation tests.

Component	**Function**	**Formulation**		
		A **% wt**	**B** **% wt**	**C** **% wt**
Fosinopril sodium	Active	1	2.5	5
Propranolol hydrochloride	Active	1	2.5	5
Vitamin E	Antioxidant	0.05	0.05	0.05
Isopropyl palmitate	Emollient	5	5	5
Mineral oil (liquid paraffin)	Emollient	10	10	10
White beeswax pastilles (pellets)	Ointment base	5	5	5
White petroleum ultima (white petroleum jelly)	Ointment base	77.95	74.95	69.95
Total		100	100	100

The viscosity each formulation at room temperature, and the particle size profile for the combination of the two actives in each case, was as follows:

Formulation	Viscosity	Particle size profile
A	30,900 cP	D10: 1.1 µm D50: 2.5 µm D90: 8.0 µm
B	18,960 cP	D10: 1.2 µm D50: 2.8 µm D90: 10.0 µm
C	34,920 cP	D10: 1.1 µm D50: 2.8 µm D90: 9.7 µm

Skin samples were obtained from a black male donor aged 69 and were subjected to permeation testing following ICH Guidelines, using a LOGAN Dry Heating Transdermal Diffusion System according to the following parameters.

System	LOGAN Dry Heating Transdermal Diffusion System
Stir Speed	600 RPM
Skin Surface Temperature	32 ± 1° C
Receptor Medium	PBS buffer +1% Brij-20 + 0.02% NaN3
Dosage Duration	Wipe off sample at 6-hour
Sample Collection	Time point withdraw at 0 hr, 3 hr, 6 hr, 9 hr, 20 hr and 24 hr.
Stratum Corneum Sampling	Strip skin surface 5 times with stripping tapes after 24-hour run. Soak the stripping tapes in Receptor Medium (RM).
Epidermis Sampling	Separate epidermis from the skin piece after stripping, then soak it in RM
Dermis Sampling	Cut the epidermis-removed skin into small pieces, soak it in RM.

The tests were conducted to determine the ability of the formulations to deposit and retain the active ingredients in the skin where they needed for optimal treatment of hemangioma, ie without allowing an undue amount of the actives to penetrate the skin

and enter the blood stream. As will be appreciated, it is generally undesirable for an ACEi (eg Fosinopril) or a beta blocker (eg Propranolol) to enter the bloodstream to the extent that they can adversely impact cardiac or other functions of the body.

Referring to **Figure 5 & 6**, these show, for each formulation, the percentage and the weight amount of Fosinopril respectively that was able to pass through the skin as well that which remained in the various layers of skin. **Figures 7 & 8** provide similar data in a similar fashion but for the propranolol. For optimal therapy of hemangioma it is preferred that the actives be located within the epidermis and dermis (the key layers).

As shown in Figures 5 and 6, a much higher proportion of the Fosinopril was found in the key layers of the skin for the low concentration 1% formulations (A and D) compared with the higher 2.5% and 5% formulations (B and C). For example, the 1% Formulation A delivered about 89% as much Fosinopril to the key layers as the 2% Formulation B, notwithstanding that Formulation A was only half as concentrated. Further, the 1% Formulation A delivered about 54% as much Fosinopril to the key layers as the 5% Formulation C, notwithstanding that Formulation A was only one fifth as concentrated.

As shown in Figures 7 and 8, a much higher proportion of the Propranolol was found in the key layers of the skin for the low concentration 1% formulation A compared with the higher 2.5% and 5% formulations (B and C). For example, the 1% Formulation A delivered about 81% as much Propranolol to the key layers as the 2% Formulation B, notwithstanding that Formulation A was only half as concentrated. Further, the 1% Formulation A delivered about 80% as much Propranolol to the key layers as the 5% Formulation C, notwithstanding that Formulation A was only one fifth as concentrated.

The results show that the combinations in a 1:1 molar ratio can be formulated at lower concentrations without compromising the ability of the Fosinopril and Propranolol to reach key layers in sufficient quantities. This assists to avoid the risk of unnecessarily high amounts of the actives reaching the bloodstream to cause adverse effects.

Misc

While some forms of the invention have been described by way of example, it should be appreciated that modifications and improvements can be made without departing from the scope of the following claims.

In terms of disclosure, this document envisages and hereby posits any feature mentioned herein in combination with itself (eg two of the same) or any other feature or features mentioned herein, even if the combination is not claimed below.

CLAIMS

1. A medicament for use in topically treating hemangioma, comprising Propranolol and Fosinopril in a molar ratio of 2 to 0.9 - 1.3 respectively.

2. A medicament according to claim 1, wherein the molar ratio of Propranolol to Fosinopril is 2 to 1 – 1.2 respectively.

3. A medicament according to claim 1, wherein the molar ratio of Propranolol to Fosinopril is 2 to approximately 1 respectively.

4. A medicament according to claim 1, wherein the molar ratio of Propranolol to Fosinopril is 2 to 1 respectively.

5. A medicament according to any one of the preceding claims, comprising approximately 0.1% to approximately 5% by weight of Propranolol and approximately 0.1% to approximately 5% by weight of Fosinopril.

6. A medicament according to any one of the preceding claims, comprising approximately 0.5% to approximately 5% by weight of Propranolol and approximately 0.5% to approximately 5% by weight of Fosinopril.

7. A medicament according to any one of the preceding claims, comprising approximately 1% to approximately 5% by weight of Propranolol and approximately 1% to approximately 5% by weight of Fosinopril.

8. A medicament according to any one of claims 1 to 4, comprising approximately 1.5% to approximately 4.5% by weight of Propranolol and approximately 1.5% to approximately 4.5% by weight of Fosinopril.

9. A medicament according to any one of claims 1 to 4, comprising approximately 2% to approximately 4% by weight of Propranolol and approximately 2% to approximately 4% by weight of Fosinopril.

10. A medicament according to any one of claims 1 to 4, comprising approximately 2.5% to approximately 3.5% by weight of Propranolol and approximately 2.5% to approximately 3.5% by weight of Fosinopril.

11. A medicament according to any one of claims 1 to 4, comprising approximately 3% by weight of Propranolol and approximately 3% by weight of Fosinopril.

12. A medicament according to any one of claims 1 to 4, comprising approximately 0.9% by weight of Propranolol and approximately 1% by weight of Fosinopril.

13. A medicament according to any one of claims 1 to 4, comprising approximately 1% by weight of Propranolol and approximately 1.1% by weight of Fosinopril.

14. A medicament according to any one of claims 1 to 4, comprising approximately 1% by weight of Propranolol hydrochloride and approximately 1% by weight of Fosinopril sodium.

15. A medicament according to any one of the preceding claims, in the form of a topical lotion, cream, ointment or gel.

16. A medicament according to any one of the preceding claims, comprising carrier, emulsifier and preservative.

17. A medicament according to claim 1, comprising a cream having the following ingredients:

a) Propranolol hydrochloride;

b) Fosinopril sodium;

c) Emollient;

d) Emulsifier;

e) Buffer;

f) Humectant;

g) Preservative;

h) Chelating agent; and

i) Water.

18. A medicament according to claim 1, comprising a cream having the following ingredients:

a) Propranolol hydrochloride;

b) Fosinopril sodium;

c) Liquid paraffin;

d) Cetyl alcohol;

e) Isopropyl myristate;

f) Sorbitol (70%);

g) Glyceryl Stearate;

h) PEG-40 Stearate;

i) Citric Acid;

j) Potassium Sorbate;

k) Sodium Hydroxide;

l) Disodium EDTA;

m) Water.

19. A medicament according to claim 1, comprising a cream having the following ingredients and amounts –

Ingredient	**% wt**
Propranolol hydrochloride	1
Fosinopril sodium	1
Liquid paraffin	8.5
Cetyl alcohol	5
Isopropyl myristate	5
Sorbitol (70%)	5
Glyceryl Stearate	2
PEG-100 Stearate	2
PEG-40 Stearate	2
Citric Acid	0.2
Potassium Sorbate	0.2
Sodium Hydroxide	0.125
Disodium EDTA	0.05

Water	Make up to 100%

20. A medicament according to claim 1, comprising the following ingredients:

a) Propranolol hydrochloride;

b) Fosinopril sodium;

c) Vitamin E;

d) Isopropyl palmitate;

e) Liquid paraffin;

f) White beeswax;

g) White petroleum jelly;

21. A medicament according to claim 1 consisting of any of the following three sets of ingredients:

Ingredient	**% wt** (approximately)		
	Option A	Option B	Option C
Fosinopril sodium	1	2.5	5
Propranolol hydrochloride	1	2.5	5
Vitamin E	0.05	0.05	0.05
Isopropyl palmitate	5	5	5
Liquid paraffin	10	10	10
White beeswax	5	5	5
White petroleum jelly	77.95	74.95	69.95

22. The use of Propranolol and Fosinopril in the manufacture of a medicament according to any one of the preceding claims, for the treatment of hemangioma by topically administering the medicament.

23. The use according to claim 22, wherein the hemangioma comprises infantile hemangioma.

24. The use according to claim 22 or 23, wherein the medicament is for application to the hemangioma at a rate of, or equivalent to, one or more of:

a) 1 FTU for the face and neck;

b) 1 FTU for an arm and hand;

c) 1.5 FTUs for a leg and foot;

d) 1 FTU for the chest and stomach; and

e) 1.5 FTUs for the back and buttocks.

25. A method of treating hemangioma in a human subject, comprising topically applying to the hemangioma a medicament according to any one of claims 1 to 21.

26. A method according to claim 25, wherein the hemangioma comprises infantile hemangioma.

27. A method according to claim 25 or 26, wherein the medicament is applied to the hemangioma at a rate of, or equivalent to, one or more of:

a) 1 FTU for the face and neck;

b) 1 FTU for an arm and hand;

c) 1.5 FTUs for a leg and foot;

d) 1 FTU for the chest and stomach; and

e) 1.5 FTUs for the back and buttocks.