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NOTICE OF ENTITLEMENT

We, **AMERICAN HOME PRODUCTS CORPORATION** of Five Giralda Farms, Madison, New Jersey 07940-0874, United States of America state the following in connection with Australian Application No. 39391/93:

1. We are the nominated person.
2. The nominated person is the assignee of the actual inventors.
3. The nominated person is the assignee of the applicants of the basic application listed in the declaration under Article 8 of the PCT.
4. The basic application is the application first made in a Convention country in respect of the invention.

Dated: 26 September 1994

By **PHILLIPS ORMONDE & FITZPATRICK**
Patent Attorneys for the Applicant

By:

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To: The Commissioner of Patents

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- (57) Claim

1. An aqueous, injectable rapamycin solution obtainable by a process comprising mixing.
 - (a) 0.1 to 10 weight percent of a concentrate solution of rapamycin in N,N-dimethylacetamide, the concentration of rapamycin in the concentrated solution ranging from 0.5mg/ml to 100mg/ml;
with
 - (b) a diluent solution 0.1 to 10 weight percent of one or more polyoxyethylene sorbitan esters, 10 to 60 weight percent of either polyethylene glycol 200 or 300 or both and 36 to 90 volume percent water; wherein the concentration of rapamycin in the combined solution ranges from 0.05mg/ml to 5.0mg/ml.

2. A product containing a concentrate solution of rapamycin in a suitable container together with a diluent in the suitable container for mixing prior to IV injection to give a solution having a concentration of rapamycin in the range 0.05mg/ml to 5.0mg/ml; said concentrate solution comprising

(11) AU-B-39391/93
(10) 681579

-2-

rapamycin N,N-dimethylacetamide in the range 0.5mg/ml to 100mg/ml, the diluent solution comprising 0.1 to 10 weight percent of one or more polyoxyethylene sorbitan esters, 10 to 60 weight percent of either polyethylene glycol 200 or 300 or both, 36 to 90 volume percent water.

19. A process for preparing an aqueous, injectable rapamycin solution which comprises mixing;
 - (a) 0.1 to 10 percent by weight of a concentrate solution of rapamycin in N,N-dimethylacetamide, the concentration of rapamycin in the concentrated solution ranging from 0.5mg/ml to 100mg/ml; with
 - (b) a diluent solution comprising 0.1 to 10 weight percent of one or more polyoxyethylene sorbitan esters, 10 to 60 weight percent of either polyethylene glycol 200 or 300 or both and 36 to 90 volume percent water; wherein the concentration of rapamycin in the combined solution ranges from 0.05mg/ml to 5.0mg/ml.

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(54) Title: RAPAMYCIN FORMULATION FOR IV INJECTION

(57) Abstract

Disclosed herein is an aqueous, injectable rapamycin solution obtainable by a process comprising mixing 0.1 to 10 weight percent of a concentrate solution of rapamycin in N,N-dimethylacetamide, at concentrations of rapamycin ranging from 0.25 mg/ml to 100 mg/ml, with a diluent solution comprising 0.1 to 10 weight percent of one or more polyoxyethylene sorbitan esters, 10 to 60 weight percent of either polyethylene glycol 200 or 300 or both and 36 to 90 volume percent water, wherein the concentration of rapamycin in the combined solution ranges from 0.05 mg/ml to 5.0 mg/ml.

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RAPAMYCIN FORMULATION FOR IV INJECTION

5 The invention disclosed herein provides an aqueous formulation of rapamycin for intravenous injection (iv). In one aspect the invention comprises a concentrate solution of rapamycin in N,N-dimethylacetamide, in combination with a diluent consisting of a polyoxyethylene sorbitan ester, polyethylene glycol 300 and water, all in given proportions as described below.

10 Background of the Invention

Rapamycin is a macrolide antibiotic produced by *Streptomyces hygroscopicus* which was discovered first for its properties as an antifungal agent. It adversely affects the growth of fungi such as *Candida albicans* and *Microsporum gypseum*. Rapamycin, 15 its preparation and its antibiotic activity were described in U.S. Patent No. 3,929,992, issued December 30, 1975 to Surendra Sehgal et al. In 1977 Martel, R. R. et al. reported on immunosuppressive properties of rapamycin against experimental allergic encephalitis and adjuvant arthritis in the Canadian Journal of Physiological Pharmacology, 55, 48-51 (1977). In 1989, Calne, R. Y. et al. in Lancet, 1989, no. 2, 20 p. 227 and Morris, R. E. and Meiser, B. M. in Medicinal Science Research, 1989, No. 17, P. 609-10, separately reported on the effectiveness of rapamycin in inhibiting rejection *in vivo* in allograft transplantation. Numerous articles have followed describing the immunosuppressive and rejection inhibiting properties of rapamycin, and clinical investigation has begun for the use of rapamycin in inhibiting rejection in 25 transplantation in man.

Rapamycin is insoluble in water and is only slightly soluble in solubilizers, such as propylene glycol, glycerin and PEG 400, commonly used in preparing parenteral formulations. It is only sparingly soluble in PEG 200 and 300 and is insoluble or very slightly soluble in commonly used aqueous injectable co-solvent 30 systems, such as, 20% ethanol/water, 10% DMA/water, 20% Cremophar EL®/water and 20% polysorbate 80/water. For these reasons commercially acceptable injectable formulations of rapamycin have been difficult to make. An injectable composition of rapamycin is described in European Patent Publication No. 0041795, published December 16, 1981. In this injectable formulation rapamycin is first dissolved in a low 35 boiling point organic solvent, namely, acetone, methanol or ethanol. This solution is then mixed with a nonionic surfactant selected from polyoxyethylated fatty acids;

- 2 -

polyoxyethylated fatty alcohols; and polyoxyethylated glycerin hydroxy fatty acid esters, e.g. polyoxyethylated castor oil, exemplified by Cremophor® EL and polyoxyethylated hydrogenated castor oil, exemplified by Cremophor® RH 40 and Cremophor® RH 60. Cremophor® EL is the primary nonionic surfactant used in the examples.

The primary immunosuppressive agent presently used for inhibiting rejection in the allograft transplantation of organs in man is cyclosporine (Sandimmune®). Cyclosporine is a cyclic polypeptide consisting of 11 amino acids. The intravenous injectable formulation of Sandimmune® (IV) is a sterile ampul containing, per ml, 50 mg of cyclosporine, 650 mg of Cremophor® EL and alcohol Ph Helv. (32.9% by volume) (under nitrogen). For administration this mixture is diluted further with 0.9 % Sodium Chloride Injection or 5% Dextrose Injection before use. (Physicians' Desk Reference, 45th ed., 1991, pp. 1962-64, Medical Economics Company, Inc.) The macrolide molecule designated FK506, which has certain structural similarities to rapamycin, is also currently undergoing clinical investigation for inhibiting rejection in allograft organ transplantation in man. FK506 is isolated from *Streptomyces tsuskubaensis* and is described in U.S. Patent No. 4,894,366 to Okuhara et al., issued January 16, 1990. R. Venkataramanan et al., in *Transplantation Proceedings*, 22, No. 1, Suppl., 1 pp 52-56 (February 1990), report that the intravenous injectable formulation of FK506 is provided as a 10 mg/ml solution of FK506 in polyoxyethylated castor oil (HCO-60, a surfactant) and alcohol. The intravenous preparation must be diluted with saline or dextrose and administered as an infusion for 1 to 2 hours.

Detailed Description of the Invention

One aspect of this invention is an aqueous-based, injectable rapamycin solution comprising a concentrate solution of rapamycin in N,N-dimethylacetamide (DMA) in combination with a diluent solution comprising a polyoxyethylene sorbitan ester, polyethylene glycol 300 and water. Specifically, Applicants' invention is an aqueous, injectable rapamycin solution comprising 0.1 to 10 weight percent of a concentrate solution of rapamycin in N,N-dimethylacetamide, at concentrations of rapamycin ranging from 0.25 mg/ml to 100 mg/ml, in combination with a diluent solution consisting of 0.1 to 10 weight percent of one or more polyoxyethylene sorbitan esters, 10 to 60 weight percent of either polyethylene glycol 200 or 300 or both and at least about 36 volume percent water, (eg. about 40 to 90%) wherein the concentration of

- 3 -

rapamycin in the combined solution ranges from 0.05 mg/ml to 5.0 mg/ml. Preferred aqueous, injectable rapamycin solutions are those wherein one polyoxyethylene sorbitan ester is present and the polyethylene glycol present is polyethylene glycol 300.

Preferred aqueous, injectable rapamycin solutions of this aspect of the invention
5 are those in which the concentration of rapamycin in the N,N-dimethylacetamide concentrate ranges from 0.5 mg/ml to 50 mg/ml. More preferred are those in which the concentration of rapamycin in the N,N-dimethylacetamide concentrate ranges from 5.0 mg/ml to 50 mg/ml. Also preferred aqueous, injectable rapamycin solutions of the invention are those in which the concentration of rapamycin in the combination solution
10 ranges from 0.1 mg/ml to 4 mg/ml and those wherein the N,N-dimethylacetamide concentrate of rapamycin comprises 0.2 to 8 weight percent of the total solution.

Further preferred aqueous, injectable rapamycin solutions of the invention are those in which the diluent consists of 1.0 to 8 weight percent polyoxyethylene sorbitan ester, 10 to 50 weight percent polyethylene glycol 300, and 40 to 90 volume percent of
15 water. Also preferred are aqueous, injectable rapamycin solutions of the invention in which 30 to 90 percent by volume of the total solution is water.

Especially preferred aqueous, injectable rapamycin solutions according to this aspect of the invention comprise 0.2 to 8 weight percent of a concentrate solution of rapamycin in N,N-dimethylacetamide, at concentrations of rapamycin ranging from 5
20 mg/ml to 50 mg/ml, in combination with a diluent solution consisting of 1.0 to 8 weight percent of a polyoxyethylene sorbitan ester, 10 to 50 weight percent polyethylene glycol 300 and 40 to 90 volume percent water, wherein the concentration of rapamycin in the combined solution ranges from 0.1 mg/ml to 4.0 mg/ml.

A second aspect of this invention is an aqueous, injectable solution of
25 rapamycin, said solution comprising rapamycin in 0.1 to 10 weight percent N,N-dimethylacetamide, 0.09 to 7.5 weight percent of one or more polyoxyethylene sorbitan esters, 9 to 60 weight percent of either polyethylene glycol 200 or 300 or both and 30 to 90 volume percent of water, wherein the concentration of rapamycin in the solution ranges from 0.05 mg/ml to 5.0 mg/ml. Preferred aqueous, injectable rapamycin
30 solutions are those wherein one polyoxyethylene sorbitan ester is present and the polyethylene glycol present is polyethylene glycol 300.

Preferred aqueous, injectable rapamycin solutions of this aspect of the invention are those wherein the concentration of rapamycin in the solution ranges from 0.1 mg/ml to 4 mg/ml. Also preferred, independently, are those wherein the N,N-
35 dimethylacetamide comprises 0.2 to 8 weight percent of the solution, the polyoxyethylene sorbitan ester comprises 2 to 7.5 percent by weight, the polyethylene

glycol 300 comprises 10 to 50 weight percent of the solution, and water comprises 30 to 90 percent by volume of the total solution.

Especially preferred aqueous, injectable solutions of rapamycin, of this aspect of the invention comprise rapamycin in 2 to 8 weight percent N,N-dimethylacetamide, 2 to 7.5 weight percent of a polyoxyethylene sorbitan ester, 10 to 50 weight percent polyethylene glycol 300 and 36 to 86 volume percent of water, wherein the concentration of rapamycin in the solution ranges from 0.1 mg/ml to 4.0 mg/ml.

The aqueous, injectable rapamycin solutions of the invention are preferred for administration by bolus injection, rather than by infusion, particularly for such solutions where the concentration of rapamycin in the combined solution is greater than 0.1 mg/ml. An infusion period of less than 24 hours is preferred. An infusion period of one-quarter hour to 6 hours is particularly preferred.

This invention also provides a process for preparing an aqueous, injectable rapamycin solution, which comprises mixing 0.1 to 10 percent by weight of a concentrate solution of rapamycin in N,N-dimethylacetamide, the concentration of rapamycin ranging from 0.25 mg/ml to 100 mg/ml, with a diluent solution comprising of 0.1 to 10 weight percent of one or more polyoxyethylene sorbitan esters, 10 to 60 weight percent of either polyethylene glycol 200 or 300 or both and 36 to 90 volume percent water, wherein the concentration of rapamycin in the combined solution ranges from 0.05 mg/ml to 5.0 mg/ml.

This invention also provides a product containing a concentrate solution of rapamycin and a diluent solution, as a combined preparation for mixing prior to IV injection to give a solution having a concentration of rapamycin in the range 0.05 mg/ml to 5.0 mg/ml; said concentrate solution comprising rapamycin in N,N-dimethylacetamide in the range 0.25 mg/ml to 100 mg/ml, the diluent solution comprising 0.1 to 10 weight percent of one or more polyoxyethylene sorbitan esters, 10 to 60 weight percent of either polyethylene glycol 200 or 300 or both, 36 to 90 volume percent water.

The manufacture of rapamycin iv concentrate comprises adding the rapamycin to the DMA and mixing until a solution results, which may be accomplished at room temperatures. The solution is then filtered in a known manner for sterility. Appropriate volumes of the concentrate solution are filled into ampules which are then sealed in a known manner. In accordance with standard manufacturing procedures for injectables, sterile conditions are maintained throughout the filtering, filling and sealing operations. The product rapamycin concentrate is best stored under refrigeration.

The manufacture of each of the rapamycin iv diluent systems comprises weighing the polysorbate 80 into a suitable container, adding the appropriate amounts of PEG 300 and water for injection and mixing until a solution results. Appropriate volumes of diluent are filled into vials which are then stoppered, sealed and autoclaved.

5 The completed rapamycin diluent solution may be stored at room temperature or under refrigeration.

The procedure for constituting the final formulas for administration comprises injecting an aliquot of rapamycin iv concentrate into a vial containing the rapamycin iv diluent, shaking for approximately one minute or until a clear solution results. The constituted solution should be administered within the stated use period. The use period of constituted rapamycin injectable solutions is the period of time during which the constituted solution remains clear and colorless. The use period may range up to 4 hours, but a use period of 1 hour is preferred.

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Preferred polyoxyethylene sorbitan esters are polysorbate 20, 60 or 80, of which polysorbate 80 is particularly preferred. DMA, polysorbate 80 and PEG 300 are readily available commercial products for use in pharmaceutical manufacturing. DMA may be obtained from EM Science of Gibbstown, New Jersey. PEG 300 may be obtained from J.T. Baker Inc. of Phillipsburg, New Jersey, and polysorbate 80 may be obtained from ICI America, Inc of Wilmington, Delaware.

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The following examples further illustrate the practice of the invention.

Example 1

Preparation of Rapamycin IV Concentrate in Dimethylacetamide (50 mg/ml)

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Rapamycin IV Concentrate in Dimethylacetamide (50 mg/ml)

Formula (Density - 0.944 g/ml):

	<u>Ingredients</u>		<u>Amount</u>
	Rapamycin @ 100%		5.0 gm
30	Dimethylacetamide (DMA)	qs	100 ml or 94.4 gm

Procedure:

1. Weigh the rapamycin into a suitably calibrated container.
2. Adjust volume to 100 ml with DMA.
3. Mix until a uniform solution results.
- 35 4. Sterile filter the solution.
5. Package into ampules and seal.

Example 2Preparation of Rapamycin IV solution at 2.0 mg/ml.

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A. Diluent for Rapamycin IV at 2.0 mg/ml

Formula (Density - 1.081 gm/ml):

	<u>Ingredients</u>	<u>Amount</u>
	Polysorbate 80, NF	4.0 gm
10	Polyethylene Glycol 300, NF	50.0 gm
	Water for Injection, USP qs	100 ml or 108.1 gm

Procedure:

- 15 1. Weigh the Polysorbate 80 into a suitably calibrated container.
 2. Add the Polyethylene Glycol 300 to the container in Step #1.
 3. Adjust to final volume with Water for Injection, USP.
 4. Mix until uniform.
 5. Filter the resulting solution.
 20 6. Fill 12.0 ml \pm 0.1 ml into each 20 ml flint vial, seal and crimp.
 7. Autoclave to achieve sterility.

B. Rapamycin IV solution at 2.0 mg/ml (constituted)

Formula (Density - 1.077 gm/ml):

	<u>Ingredients</u>	<u>Amount</u>
25	Rapamycin IV Concentrate @ 50 mg/ml	0.5 ml
	Diluent for IV-Rapamycin	12.0 ml

Procedure:

1. Inject 0.5 ml of Rapamycin IV Concentrate at 50 mg/ml into a vial containing
 12.0 ml of diluent for IV-Rapamycin using good sterile technique.
 30 2. Shake until a clear solution results.

Example 3

Preparation of Rapamycin IV solution at 4.0 mg/ml.

- A. Diluent for Rapamycin IV at 4.0 mg/ml
 5 Formula (Density - 1.077 gm/ml):

	<u>Ingredients</u>	<u>Amount</u>
	Polysorbate 80, NF	8.0 gm
	Polyethylene Glycol 300, NF	50.0 gm
10	Water for Injection, USP qs	100 ml or 107.7 gm

Procedure:

1. Weigh the Polysorbate 80 into a suitably calibrated container.
2. Add the Polyethylene Glycol 300 to the container in Step #1.
- 15 3. Adjust to final volume with Water for Injection, USP.
4. Mix until uniform.
5. Filter the resulting solution.
6. Fill 5.75 ml \pm 0.1 ml into each 10 ml flint vial, seal and crimp.
7. Autoclave to achieve sterility.

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- B. Rapamycin IV solution at 4.0 mg/ml (constituted)
Formula (Density - 1.072 gm/ml):

	<u>Ingredients</u>	<u>Amount</u>
	Rapamycin IV Concentrate @ 50 mg/ml	0.5 ml
25	Diluent for IV-Rapamycin	5.75 ml

Procedure:

1. Inject 0.5 ml of Rapamycin IV Concentrate at 50 mg/ml into a vial containing 5.75 ml of diluent for IV-Rapamycin using good sterile technique.
- 30 2. Shake until a clear solution results.

Example 4

The examples herein represent the batch production of ampules of rapamycin concentrate and vials of diluent for use in obtaining 0.1, 0.5, 2.0 and 4.0 mg/mL. The

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rapamycin iv solutions may be constituted for injection in the same manner as in Examples 2B and 3B.

5	A. <u>Rapamycin IV Concentrate 50 mg/ml</u>			Representative Batch Formula <u>10,000 Ampules</u>
	<u>Active Ingredient</u>	<u>Claim/mL</u>	<u>Input/Ampule</u>	
	Rapamycin @ 100%	0.050 g	0.0325 g	0.325 kg
10	<u>Inactive Ingredients:</u>			
	Dimethylacetamide qs ad		0.65 mL or 0.61 g	6.50 L or 6.14 kg
15	Density = 0.944 g/mL			
20	B. <u>Diluent for Rapamycin IV at 0.1 mg/mL</u>			Representative Batch Formula <u>10,000 Vials</u>
	<u>Active Ingredient</u>		<u>Input/Vial</u>	
	Polysorbate 80, NF		4.00 g	40.0 kg
	Polyethylene Glycol 300, NF		50.0 g	500 kg
25	Water for Injection, USP qs ad		100 mL or 108 g	1000 L or 1081 kg
	Density - 1.081 g/mL			
30	C. <u>Diluent for Rapamycin IV at 0.5 mg/mL</u>			Representative Batch Formula <u>10,000 Vials</u>
	<u>Active Ingredient</u>		<u>Input/Vial</u>	
	Polysorbate 80, NF		2.00 g	20.0 kg
35	Polyethylene Glycol 300, NF		23.0 g	250 kg
	Water for Injection, USP qs ad		50.0 mL or 54.1 g	500 L or 541 kg
	Density - 1.081 g/mL			
40	D. <u>Diluent for Rapamycin IV at 2 mg/mL</u>			Representative Batch Formula <u>10,000 Vials</u>
	<u>Active Ingredient</u>		<u>Input/Vial</u>	
	Polysorbate 80, NF		0.480 g	4.80 kg
45	Polyethylene Glycol 300, NF		6.00 g	60.0 kg
	Water for Injection, USP qs ad		12.0 mL or 13.0 g	120 L or 150 kg
	Density - 1.081 g/mL			

E. Diluent for Rapamycin IV at 4 mg/mL

	<u>Active Ingredient</u>	<u>Input/Vial</u>	<u>Representative Batch Formula 10,000 Vials</u>
5	Polysorbate 80, NF	0.460 g	4.60 kg
	Polyethylene Glycol 300, NF	2.88 g	28.8 kg
	Water for Injection, USP qs ad	5.75 mL or	57.5 L or
		6.19 g	61.9 kg
10	Density - 1.077 g/mL		

Note: A-E If the potency of rapamycin is less than 100%, the input must be adjusted to give claim potency.

Procedures for preparations A-E.

A. Rapamycin IV Concentrate at 50 mg/ml Procedure:

- 15 1. Weigh the rapamycin into a suitably calibrated container.
2. Add Dimethylacetamide to achieve the appropriate volume or weight
3. Mix until a solution results.
4. Maintain sterile conditions throughout filtering, filling and sealing.
5. Filter the solution from Step #3 through a 0.2 micron filter.
- 20 6. Fill 0.65 ml ± 0.05 ml (0.61 g + 0.05 g) of the solution from Step #5 into each 1 ml amber ampule and seal
7. Store under refrigeration.

B. Rapamycin IV Diluent at 0.1 mg/ml Procedure:

1. Weigh the Polysorbate 80 into a suitable container.
- 25 2. Add the appropriate weight of the Polyethylene Glycol 300 to the container in Step #1.
3. Add Water for Injection to achieve the appropriate volume or weight.
4. Mix until a solution results.
5. Filter the solution from Step #4 through a 0.2 micron filter.
- 30 6. Fill 100 mL ± 2 mL (108 g ± 2.7 g) of the solution from Step #5 into each 100 mL flint vial, seal with a barrier faced stopper and crimp with an aluminum seal.
7. Sterilize by steam autoclave.
8. Store at room temperature or under refrigeration.

C. Rapamycin IV Diluent at 0.5 mg/ml Procedure:

- 35 1. Weigh the Polysorbate 80 into a suitable container.
2. Add the appropriate weight of the Polyethylene Glycol 300 to the container in Step #1.
3. Add Water for Injection to achieve the appropriate volume or weight.

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4. Mix until a solution results.
 5. Filter the solution from Step #4 through a 0.2 micron filter.
 6. Fill 50 mL \pm 1 mL (54 g \pm 1.1 g) of the solution from Step #5 into each 100 mL flint vial, seal with a barrier faced stopper and crimp with an aluminum seal.
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7. Sterilize by steam autoclave.
 8. Store at room temperature or under refrigeration.
- D. Rapamycin IV Diluent at 2 mg/ml Procedure:
1. Weigh the Polysorbate 80 into a suitable container.
 2. Add the appropriate weight of the Polyethylene Glycol 300 to the container
- 10
- in Step #1.
 3. Add Water for Injection to achieve the appropriate volume or weight.
 4. Mix until a solution results.
 5. Filter the solution from Step #4 through a 0.2 micron filter.
 6. Fill 12.0 mL \pm 0.1 mL (13.0 g \pm 0.1 g) of the solution from Step #5 into each
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- 20 mL flint vial, seal with a barrier faced stopper and crimp with an aluminum seal.
 7. Sterilize by steam autoclave.
 8. Store at room temperature or under refrigeration.
- E. Rapamycin IV Diluent at 4 mg/ml Procedure:
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 1. Weigh the Polysorbate 80 into a suitable container.
 2. Add the appropriate weight of the Polyethylene Glycol 300 to the container
- in Step #1.
 3. Add Water for Injection to achieve the appropriate volume or weight.
 4. Mix until a solution results.
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5. Filter the solution from Step #4 through a 0.2 micron filter.
 6. Fill 5.75 mL \pm 0.1 mL (6.2 g \pm 0.1 g) of the solution from Step #5 into each 10 mL flint vial, seal with a barrier faced stopper and crimp with an aluminum seal.
7. Sterilize by steam autoclave.
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8. Store at room temperature or under refrigeration.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises", is not intended to exclude other additives, components, integers or steps.

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The claims defining the invention are as follows:

1. An aqueous, injectable rapamycin solution obtainable by a process comprising mixing.
 - 5 (a) 0.1 to 10 weight percent of a concentrate solution of rapamycin in N,N-dimethylacetamide, the concentration of rapamycin in the concentrated solution ranging from 0.5mg/ml to 100mg/ml;

with

 - 10 (b) a diluent solution 0.1 to 10 weight percent of one or more polyoxyethylene sorbitan esters, 10 to 60 weight percent of either polyethylene glycol 200 or 300 or both and 36 to 90 volume percent water; wherein the concentration of rapamycin in the combined solution ranges from 0.05mg/ml to 5.0mg/ml.
- 15 2. A product containing a concentrate solution of rapamycin in a suitable container together with a diluent in the suitable container for mixing prior to IV injection to give a solution having a concentration of rapamycin in the range 0.05mg/ml to 5.0mg/ml; said concentrate solution comprising
 - 20 rapamycin N,N-dimethylacetamide in the range 0.5mg/ml to 100mg/ml, the diluent solution comprising 0.1 to 10 weight percent of one or more polyoxyethylene sorbitan esters, 10 to 60 weight percent of either polyethylene glycol 200 or 300 or both, 36 to 90 volume percent water.
- 25 3. A product or solution according to claim 1 or claim 2 wherein one polyoxyethylene sorbitan ester is present and the polyethylene glycol present is polyethylene glycol 300.
- 30 4. A product or solution according to any one of claims 1 to 3 wherein the concentration of rapamycin in the N,N-dimethylacetamide concentrate ranges from 0.5mg/ml to 50mg/ml.

5. A product or solution according to any one of claims 1 to 3 wherein the concentration of rapamycin in the N,N-dimethylacetamide concentrate ranges from 5.0mg/ml to 50mg/ml.
- 5 6. A product or solution according to any one of claims 1 to 5 for bolus injection wherein the concentration of rapamycin in the combination solution ranges from 0.1mg/ml to 4mg/ml.
7. A product or solution according to any one claims 1 and 3 to 6 wherein
10 N,N-dimethylacetamide concentrate of rapamycin comprises 0.2 to 8 weight percent of the total solution.
8. A product or solution according to claim 3 wherein the diluent comprises
15 1.0 to 8 weight percent polyoxyethylene sorbitan ester, 10 to 50 weight percent polyethylene glycol 300 and 40 to 90 volume percent of water.
9. A product or solution according to claim 3 wherein 30 to 90 percent by volume of the total solution is water.
- 20 10. A solution according to claim 1 for bolus injection, wherein the N,N-dimethylacetamide concentrate is 0.2 to 8 weight percent of the combined solution, the concentration of rapamycin in the concentrate ranging from 5mg/ml to 50mg/ml, and wherein the diluent solution comprises 1.0 to 8 weight percent of a polyoxyethylene sorbitan ester, 10 to 50 weight percent polyethylene glycol 300 and 40 to 90 volume percent water, and the concentration of rapamycin in the combined solution ranges from 0.1mg/ml to 4.0mg/ml.
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- 30 11. An aqueous, injectable rapamycin solution, said injectable solution comprising rapamycin in 0.1 to 10 weight percent N,N-dimethylacetamide, 0.09 to 7.5 weight percent of one or more polyoxyethylene sorbitan esters, 9 to 60 weight percent of either polyethylene glycol 200 or 300 or both and

30 to 90 volume percent of water, wherein the concentration of rapamycin in the solution ranges from 0.05mg/ml to 5.0mg/ml.

- 5
12. An aqueous, injectable rapamycin solution according to claim 11 wherein one polyoxyethylene sorbitan ester is present and the polyethylene glycol present is polyethylene glycol 300.
- 10
13. An aqueous, injectable rapamycin solution according to claim 11 or claim 12, particularly for bolus injection, wherein the concentration of rapamycin in the solution ranges from 0.1mg/ml to 4mg/ml
- 15
14. An aqueous, injectable rapamycin solution according to any one of claims 11 to 13 wherein the N,N-dimethylacetamide comprises 0.2 to 8 weight percent of the solution.
- 15
15. An aqueous, injectable rapamycin solution according to any one of claims 11 to 14 wherein the polyoxyethylene sorbitan ester comprises 2 to 7.5 weight percent of solution.
- 20
16. An aqueous, injectable rapamycin solution according to any one of claims 11 to 15 wherein the polyethylene glycol 300 comprises 10 to 50 weight percent of solution.
- 25
17. An aqueous, injectable rapamycin solution according to any one of claims 11 to 16 wherein water comprises 36 to 86 percent by volume of the total solution.
- 30
18. An aqueous, injectable rapamycin solution according to claim 12, for bolus injection, comprising rapamycin in 2 to 8 weight percent N,N-dimethylacetamide, 2 to 7.5 weight percent of a polyoxyethylene sorbitan ester, 10 to 50 weight percent polyethylene glycol 300 and 36 to 86 volume

percent of water, wherein the concentration of rapamycin in the solution ranges from 0.1mg/ml to 4.0mg/ml.

- 5 19. A process for preparing an aqueous, injectable rapamycin solution which comprises mixing;
- (a) 0.1 to 10 percent by weight of a concentrate solution of rapamycin in N,N-dimethylacetamide, the concentration of rapamycin in the concentrated solution ranging from 0.5mg/ml to 100mg/ml; with
- 10 (b) a diluent solution comprising 0.1 to 10 weight percent of one or more polyoxyethylene sorbitan esters, 10 to 60 weight percent of either polyethylene glycol 200 or 300 or both and 36 to 90 volume percent water; wherein the concentration of rapamycin in the combined solution ranges from 0.05mg/ml to 5.0mg/ml.
- 15 20. An aqueous, injectable rapamycin solution according to claim 1 substantially as hereinbefore described with reference to Example 3.
- 20 21. A product according to claim 2 substantially as hereinbefore described with reference to any one of Examples 1, 2 and 4.
22. A process according to claim 19 substantially as hereinbefore described with reference to Example 3.

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INTERNATIONAL SEARCH REPORT

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International Application No

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 A61K31/71; A61K47/16; A61K9/00		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to C ¹³ No. ¹³
A	US,A,3 929 992 (S. SEHGAL) 30 December 1975 cited in the application see column 6, line 46; claim 1 -----	1-19
A	EP,A,0 202 837 (SMITHKLINE BECKMANN CORPORATION) 26 November 1986 see page 4, line 14-1; example 2 -----	1-19
A	EP,A,0 041 795 (AYERST, MCKENNA AND HARRISON INC.) 16 December 1981 cited in the application see claims 1-10 -----	1-19
<p>¹⁰ Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
27 MAY 1993	23. 06. 93	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	FOERSTER W.K.	

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 27/05/93

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