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[54] **COMPOSITIONS CONTAINING TAXANE DERIVATIVES**

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Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 930,392, filed as PCT/FR92/00624, Jul. 3, 1992, Pat. No. 5,403,858.

[30] **Foreign Application Priority Data**

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[51] **Int. Cl.**[6] **A61K 31/335**; A61K 31/34; A61K 9/50

[52] **U.S. Cl.** **514/449**; 514/471; 514/408; 424/502

[58] **Field of Search** 514/471, 408, 514/449; 424/502

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[57] **ABSTRACT**

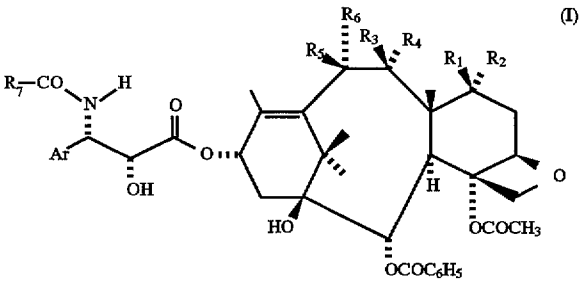
This invention relates to compositions containing taxane derivatives, consisting of a solution of such derivatives in a surfactant. These compositions can be used to prepare perfusion solutions.

53 Claims, No Drawings

COMPOSITIONS CONTAINING TAXANE DERIVATIVES

This is a continuation-in-part of Ser. No. 07/930,392, filed Aug. 23, 1993, now U.S. Pat. No. 5,403,858 a national phase application of PCT/FR92/00624, filed Jul. 3, 1992, hereby incorporated by reference.

The present invention relates to compositions and especially pharmaceutical dosage forms containing therapeutic agents having antitumor and antileukemic activity. It relates more especially to compositions suitable for injection containing taxane derivatives, such as, in particular, taxol or one of its analogues or derivatives of the formula (I)



in which R_1 and R_2 each represent a hydrogen atom or one of R_1 and R_2 represents a hydrogen atom and the other represents a hydroxy, acyloxy, or acylcarbonyloxy radical, or R_2 represents a hydrogen atom and R_1 forms a single bond together with the methyl carbon atom situated in the α position, so they can form together a cyclopropane ring, one of R_3 and R_4 represents a hydrogen atom and the other represents a hydroxy radical, or R_3 and R_4 taken together form a oxo radical, R_5 and R_6 each represent each a hydrogen atom or one of R_5 and R_6 represents a hydrogen atom and the other represents a hydroxy, acyloxy, acylcarbonyloxy or a alkoxymethylcarbonyloxy radical, or R_5 and R_6 taken together form a oxo radical, R_7 represents an alkoxy, alkenyloxy, cycloakyloxy or phenyl radical and Ar represents an aryl radical or preferably a phenyl radical optionally substituted by one or several atoms or radicals identical or different and selected from halogen, alkyl, alkoxy, dialkylamino, acylamino, alkylcarbonylamino or trifluoromethyl, or a 5 membered heterocyclic radical with one or more identical or different heteroatoms chosen from nitrogen, oxygen or sulfur, it being understood that alkyl radicals are straight chain or branched chain and contain 1 to 8 carbon atoms and the alkenyl radicals contain 2 to 8 carbon atoms and provided that when R_2 is a hydrogen atom and R_1 is a hydroxy radical, R_3 and R_4 cannot be simultaneously an oxo radical when R_6 is a hydrogen atom, R_5 is a hydroxy, acetyloxyradical, R_7 is a t.butoxy or a phenyl radical and Ar is a phenyl radical.

Among the taxane derivatives of the formula (I) the most preferred ones are the following where R_2 represents a hydrogen atom and R_1 represents a hydrogen atom or a hydroxy radical, or R_1 forms a single bond together with the methyl carbon atom situated in the α position, so they can form together a cyclopropane cycle, R_3 and R_4 taken together form an oxo radical, R_6 represents a hydrogen atom and R_5 represents a hydrogen atom or a hydroxy, acetyloxy or methoxyacetyloxy radical, or R_5 and R_6 taken together form an oxo radical, R_7 represents a t.butoxy or a phenyl radical and Ar is a phenyl radical, provided that when R_2 is a hydrogen atom and R_1 is a hydroxy radical, R_3 and R_4 cannot be simultaneously an oxo radical when R_5 is a hydrogen atom, R_6 is a hydroxy, acetyloxy radical R_7 is a t.butoxy or a phenyl radical and Ar is a phenyl radical.

Known taxane derivatives encompassed by the general formula (I) include two compounds which are known by the name of TAXOL and the name TAXOTERE.

These products exhibit in vivo substantial activity against malignant tumors, which has enabled them to be studied in the treatment of diseases resistant to other anticancer therapies.

Unfortunately, these products possess such low solubility in water that it has been necessary to prepare formulations for injection containing surfactant and ethanol. Ethanol is the best solvent for dissolving compounds of formula (I).

For example, according to the publication by Rowinsky, Lorraine, Cazenave and Donebower which appeared in the Journal of the National Cancer Institute, vol. 82, No. 15, pages 1247–1259 on 1st Aug. 1990, a first solution, termed "stock solution", containing approximately 6 mg/ml of taxol in a solvent mixture composed of:

50% by volume of ethanol

50% by volume of Cremophor EL,;

is prepared. On injection, this solution is mixed with a perfusion fluid containing sodium chloride or dextrose (glucose). To obtain a mixture which is stable from both a physical standpoint and a chemical standpoint, the authors of this paper state that it is necessary to limit the concentration of active principle in the perfusion solution to concentrations of approximately 0.03 to 0.6 mg/ml (see above publication, page 1251, column 1, third paragraph).

Now, it is desirable to be able to inject sufficient doses of active principle; to this end, clinicians would like to inject concentrations of active principle of between approximately 0.3 and 1 mg/ml in the perfusion fluid; above these doses, anaphylactic shock phenomena which are difficult to control, due in the main to the Cremophor, are seen (see the publication by Rowinsky, page 1250, second column, last paragraph).

Still according to this publication, to obtain such concentrations (between 0.3 and 1 mg/ml), it is necessary to inject solutions containing, at the same time as the active principle, concentrations of each of the following compounds, ethanol and most especially Cremophor, of approximately 8 g per 100 ml of solution. Since the treatment often requires the administration of high doses of active principle, and since the concentration of the active principle, and since the concentration of the active principle in the solution is relatively low, the injection of a large volume has the effect of causing, in addition to anaphylactic manifestations, manifestations of alcohol poisoning during the treatment.

The present invention provides compositions that make it possible either to reduce the ethanol concentrations greatly, or to eliminate Cremophor and ethanol completely from the perfusions.

For this purpose, according to a first implementation of the present invention, a composition suitable for use as a stock solution is prepared, containing a compound of formula I as defined above dissolved in a surfactant which may be a polysorbate, e.g. as marketed under the name "Tween", a polyoxyethylated vegetable oil as marketed, e.g., under the name "Emulphor", polyethoxylated castor oil, also known as glycerol polyethyleneglycol ricinoleate, as marketed, e.g., under the name Cremophor, preferably CREMOPHOR ® EL, and virtually free from ethanol. CREMOPHOR ® EL is a non-ionic solubilizer and emulsifier that can be obtained by reacting ethylene oxide with castor oil in a molar ratio of 35–40 mol ethylene oxide to 1 mol glyceride and is commercially available from BASF and has been assigned CAS Registry Number 61791-12-6. The main component of CREMOPHOR ® EL is glycerolpolyethyleneglycol

ricinoleate, which together with fatty acid esters of polyethylene glycol, represents the hydrophobic part of the product. The smaller, hydrophilic part consists of polyethylene glycols and ethoxylated glycerol.

The stock solution may be prepared by dissolving the active principle in ethanol, which is the best biocompatible solvent for the taxane derivatives, and then gradually adding the surfactant. Solutions containing 10 to 100 mg/ml of active principle in a mixture containing approximately 50% of surfactant can be prepared in this manner. The ethanol is then completely, or almost completely, eliminated.

To prepare, according to the present invention, the solution having a low ethanol content, the taxane derivative is dissolved in ethanol, and the surfactant, which enables micelles to be formed in containing the taxane derivative encapsulated in the surfactant after dilution in an aqueous medium, is then added. The ethanol contained in this solution is then removed at least partially by evaporation under vacuum or by any other suitable means.

According to a second method of preparing the stock solution, the taxane derivative is dissolved directly in the surfactant. According to a preferred method, a solution of surfactant containing, in particular, 1 to 2% of ethanol is prepared, and the taxane derivative is added continuously to this solution with stirring, e.g. using a helical grinder or a centrifugal disintegrator. The presence of a small amount of ethanol provides several advantages: the medium possesses a lower viscosity, and the wetting of the powder and the final filtration of the solution are improved.

The stock solution, having a low ethanol content, preferably contains less than 5% of ethanol; still more preferably, it contains less than 2% of ethanol. This solution is stable and can contain up to 200 mg/ml, preferably up to 80 mg/ml, of active principle in the surfactant.

A stock solution of taxol possesses still more preferably a concentration of between 6 and 20 mg/ml of active principle in the surfactant. This solution can be mixed, in particular to provide a final concentration of between 0.1 and 1 mg per milliliter, with the perfusion fluid, which can be physiological saline or a glucose solution. Perfusion prepared from the above stock solutions having a low ethanol content contain still more preferably between 0.3 and 0.5 mg/ml of taxol and less than 1 ml/l of ethanol.

The taxol perfusion containing the active principle without ethanol possesses a physical stability of between 8 and about one hundred hours. Physical stability is understood to mean that the solution does not exhibit any visible precipitation after 8 to 10 hours of storage at room temperature.

A stock solution of Taxotere preferably possesses a concentration of between 20 and 80 mg/ml of active principle in the surfactant. This solution can be mixed, in particular to provide a final concentration of between 0.1 and 0.5 mg per milliliter, with the perfusion fluid, which can be a physiological saline or a glucose solution. Perfusion prepared from the above stock solutions having a low ethanol content contain still more preferably between 0.1 and 0.3 mg/ml of Taxotere; they preferably contain less than 15 ml/l of surfactant and less than 1 ml/l of ethanol.

The Taxotere perfusion containing the active principle without ethanol possesses a physical stability which can reach several months.

The taxol or Taxotere perfusions may be injected into humans at a predetermined flow rate depending on the amount of active principle it is desired to inject. The anaphylactic shock phenomena which were observed with the solutions of the prior can be avoided with these solutions.

Thus, these perfusion have made it possible to reduce, relative to the prior art, the amount of surfactant injected into humans by approximately 80% and the amount of ethanol by almost 100%.

The invention is illustrated by the following Examples.

COMPARATIVE EXAMPLE ACCORDING TO THE PRIOR ART

Taxol (0.180 g) is dissolved in ethanol (15 ml). The mixture is made to volume with Cremophor to obtain a solution (30 ml) which contains taxol (6 mg/ml).

This solution is diluted in a 5% glucose perfusion solution in a proportion of 1 mg/ml; the perfusion solution in a proportion of 1 mg/ml; the perfusion solution contains 87.7 ml/l of Cremophor and 87.7 ml/l of ethanol. The perfusion solution is stable for more than 21 hours.

EXAMPLES 1–7

Taxotere (32 g) is dissolved in absolute ethanol (340 ml) and Polysorbate 80 (830 g) is then added. The ethanol is evaporated off in a rotary evaporator at 30° C. at a pressure of 15 mmHg for 2 hours. The solution obtained is stable; it contains Taxotere (40 mg/ml).

After dilution is a 5% glucose perfusion solution at concentrations of 0.1, 0.3 and 0.5 mg/ml, the stability of the solutions obtained is observed.

The same method is reproduced using a solution containing Taxotere (60 mg/ml).

The same test is reproduced using taxol solutions containing taxol (12 and 20 mg/ml).

The results are shown in Table 1.

Product	Solvent	Stock solution concentration	Active principle in the perfusion	Surfactant in the perfusion	Ethanol in the perfusion	Stability
taxol	Polysorbate	20 mg/ml	1 mg/ml	50 ml/l	<0.3 ml/l	>8 H
taxol	Polysorbate	20 mg/ml	0.3 mg/ml	15 ml/l	<0.09 ml/l	>24 H
taxol	Polysorbate	12 mg/ml	1 mg/ml	83.3 ml/l	<0.5 ml/l	>48 H
Taxotere	Polysorbate	40 mg/ml	0.5 mg/ml	11.6 ml/l	0.09 ml/l	8H–23H
Taxotere	Polysorbate	40 mg/ml	0.3 mg/ml	6.0 ml/l	0.05 ml/l	8H–23H
Taxotere	Polysorbate	40 mg/ml	0.1 mg/ml	2.3 ml/l	0.02 ml/l	29H–45H
Taxotere	Polysorbate	60 mg/ml	1.1 mg/ml	1.5 ml/l	<0.01 ml/l	8H–23H

EXAMPLE 8

Into a stainless steel reactor, Taxotere (258 g) is introduced and dissolved in ethanol (2425 g) with mechanical stirring for 45 minutes. Polysorbate 80 (6156 g) is added and the mixture is homogenized with mechanical stirring for 15

minutes. The solution is transferred to a reactor and the alcohol is distilled off under a reduced pressure of 10 to 50 millibars (1000 to 5000 Pa), the temperature being maintained at between 18° and 28° C. The alcohol is stilled off until its content is less than 2%.

The solution obtained is filtered through a filter having a pore size of 0.2 μm. It contains:

ethanol (1.3%)

Taxotere (39.6 mg/ml).

After dilution to mg/ml in a perfusion bag containing 5% glucose, the solution is stable without apparent precipitation for a period of more than two months.

EXAMPLE 9

Taxotere (160 mg) or taxol (160 mg) is dissolved in a mixture (10 ml) of absolute ethanol (2 ml) and Cremophor EL (218) (8 ml), and the ethanol is evaporated off in a rotary evaporator at 30° C. at a pressure of 25 mmHg for three hours. The solutions obtained are stable. They contain 20 mg/ml of Taxotere or taxol. After dilution in a 5% glucose perfusion solution at concentrations of 0.1 and 0.5 mg/ml, precipitation is observed at between 30 and 95 hours.

EXAMPLE 10

Polysorbate 80 (275.5 g) and absolute ethanol (5.4 g) are placed in a 500-ml Erlenmeyer flask, and the mixture is then stirred with a bar magnet until completely homogenized.

The solution prepared above (26.13 g) in a 50 ml flask, placed in a water bath heated beforehand and maintained throughout the test period at 30° C., is stirred at approximately 600 rpm with a bar magnet. With a spatula, Taxotere (1.076 g) is added in several portions so that the clumps disappear between two additions (the duration of the operation is approximately one hour). After incorporation of the last fraction of Taxotere, stirring is maintained until the solution becomes clear (approximately two hours).

EXAMPLE 11

4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl 3-t-butoxycarbonylamino-3-(2-fluorophenyl)-2-hydroxy-(2R, 3S)-propionate (20 mg) is placed in round bottom flask and dissolved in absolute ethanol (0.4 ml). After dissolution, polysorbate 80 (0.5 ml) is added and the mixture is homogenized with the aid of a magnetic stirrer. The flask is placed in a vacuum using a rotary evaporator and the alcohol is distilled off under reduced pressure (10 mmHg) for one hour. The solution obtained is perfectly clear and contains 40 mg/ml of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl 3-t-butoxycarbonylamino-3-(2-fluorophenyl)-2-hydroxy-(2R, 3S)-propionate. After dilution in a 0.9% aqueous sodium chloride perfusion solution to a concentration of 1 mg/ml, the solution obtained is stable for more than 24 hours.

EXAMPLE 12

4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl 3-t-butoxycarbonylamino-3-(4-chlorophenyl)-2-hydroxy-(2R, 3S)-propionate (20 mg) was placed in a round bottomed flask and dissolved in absolute ethanol (0.4 ml). After dissolution, polysorbate 80 (0.5 ml) was added and the mixture was homogenized with the aid of magnetic stirrer. The flask was placed in a vacuum using a rotary evaporator and the alcohol was distilled off under reduced pressure (10 mmHg) for one hour. The solution obtained is perfectly clear and contains 40 mg/ml of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl 3-t-butoxycarbonylamino-3-(4-chlorophenyl)-2-hydroxy-(2R, 3S)-propionate. After dilution in a 0.9% aqueous sodium chloride perfusion solution to a concentration of 1 mg/ml, the solution obtained was stable for more than 24 hours.

EXAMPLE 13

4α,10β-diacetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,8β-methylene-9-oxo-19-nor-11-taxen-13α-yl 3-t-butoxycarbonylamino-2-hydroxy-3-phenyl-2-(2R,3S)-propionate (20 mg) was placed in a round bottomed flask and dissolved in absolute ethanol (0.4 ml). After dissolution, polysorbate 80 (0.5 ml) was added and the mixture was homogenized with the aid of a magnetic stirrer. The flask was placed in a vacuum using a rotary evaporator and the alcohol was distilled off under reduced pressure (10 mmHg) for one hour. The solution obtained is perfectly clear and contains 40 mg/ml of 4α,10β-diacetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,8β-methylene-9-oxo-19-nor-11-taxen-13α-yl 3-t-butoxycarbonylamino-2-hydroxy-3-phenyl-(2R,3S)-propionate. After dilution in a 0.9% aqueous sodium chloride perfusion solution to a concentration of 1 mg/ml, the solution obtained was stable for more than 24 hours.

Although the invention has been described in conjunction with specific embodiments, it is evident that many alternatives and variations will be apparent to those skilled in the art in light of the foregoing description. Accordingly, the invention is intended to embrace all of the alternatives and variations that fall within the spirit and scope of the appended claims.

We claim:

1. A composition comprising a taxane derivative dissolved in a surfactant selected from polysorbate or polyethoxylated castor oil, and essentially free or free of ethanol.

2. The composition of claim **1**, wherein said polyethoxylated castor oil is a non-ionic solubilizer and emulsifier containing glycerol-polyethylene glycol ricinoleate, fatty acid esters of polyethylene glycol, polyethylene glycols, and ethoxylated glycerol.

3. The composition of claim **1**, said composition being a stock solution and containing less than 5% by volume ethanol.

4. The composition of claim **3**, said composition containing less than 2% by volume ethanol.

5. The composition of claim **1**, said composition being a perfusion containing less than 0.5 mg/ml of said taxane derivative of claim **1**, less than 1 ml/l of said ethanol, and less than 15 ml/l of said surfactant.

6. The composition of claim **1**, said composition being a perfusion containing less than or equal to 1 mg/ml of said taxane derivative of claim **1**, and less than 1 ml/l of said ethanol.

7. A stock solution comprising a taxane derivative dissolved in a surfactant selected from polysorbate or polyethoxylated castor oil, wherein said stock solution contains from 10 to 200 mg/ml of said taxane derivative, and wherein said stock solution is essentially free or free of ethanol.

8. The stock solution of claim **7**, wherein said stock solution contains from 10 to 80 mg/ml of said taxane derivative.

9. The stock solution of claim **8**, wherein said stock solution contains from 12 to 80 mg/ml of said taxane derivative.

10. The stock solution of claim **9**, wherein said stock solution contains from 20 to 80 mg/ml of said taxane derivative.

11. The stock solution of claim 7, wherein said surfactant is polysorbate.

12. The stock solution of claim 7, wherein said surfactant is polyethoxylated castor oil.

13. The stock solution of claim 12, wherein said polyethoxylated castor oil is a non-ionic solubilizer and emulsifier containing glycerol-polyethylene glycol ricinoleate, fatty acid esters of polyethylene glycol, polyethylene glycols, and ethoxylated glycerol.

14. A composition comprising the compound 4α,10β-diacetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,8β-methylene-9-oxo-19-nor-11-taxen-13α-yl 3-t-butoxycarbonylamino-2-hydroxy-3-phenyl-(2R,3S)-propionate dissolved in a surfactant selected from polysorbate or polyethoxylated castor oil, wherein said composition is essentially free or free of ethanol.

15. The composition of claim 14, wherein said polyethoxylated castor oil is a non-ionic solubilizer and emulsifier containing glycerol-polyethylene glycol ricinoleate, fatty acid esters of polyethylene glycol, polyethylene glycols, and ethoxylated glycerol.

16. The composition of claim 14, said composition being a stock solution containing less than 5% by volume ethanol.

17. The composition of claim 16, said composition containing less than 2% by volume ethanol.

18. The composition according to claim 16, said composition containing from 1 to about 2.5% by volume ethanol.

19. The composition of claim 14, said composition being a stock solution and containing from 10 to 80 mg/ml of said compound of claim 14.

20. The composition of claim 19, said composition containing from 20 to 80 mg/ml of said compound.

21. The composition of claim 14, said composition being a stock solution and containing from 6 to 20 mg/ml of said compound of claim 14.

22. The composition of claim 14, said composition being a perfusion containing less than 0.5 mg/ml of said taxane derivative of claim 14, less than 1 ml/l of said ethanol, and less than 15 ml/l of said surfactant.

23. The composition of claim 14, said composition being a perfusion containing less than or equal to 1 mg/ml of said taxane derivative of claim 14, and less than 1 ml/l of said ethanol.

24. The composition of claim 14, wherein said surfactant is polysorbate.

25. The composition of claim 14, wherein said surfactant is polyethoxylated castor oil.

26. The composition of claim 25, wherein said polyethoxylated castor oil is a non-ionic solubilizer and emulsifier containing glycerol-polyethylene glycol ricinoleate, fatty acid esters of polyethylene glycol, polyethylene glycols, and ethoxylated glycerol.

27. A composition comprising the compound 4α,10β-diacetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,8β-methylene-9-oxo-19-nor-11-taxen-13α-yl 3-t-butoxycarbonylamino-2-hydroxy-3-phenyl-(2R,3S)-propionate dissolved in a surfactant selected from polysorbate or polyethoxylated castor oil, wherein said composition is a stock solution containing from 6 to 200 mg/ml of said compound, and wherein said composition is essentially free or free of ethanol.

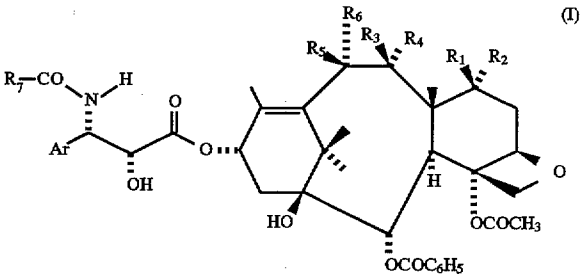
28. The composition of claim 27, wherein said composition contains from 10 to 200 mg/ml of said compound.

29. The composition of claim 28, wherein said surfactant is polysorbate.

30. The composition of claim 28, wherein said surfactant is polyethoxylated castor oil.

31. The composition of claim 30, wherein said polyethoxylated castor oil is a non-ionic solubilizer and emulsifier containing glycerol-polyethylene glycol ricinoleate, fatty acid esters of polyethylene glycol, polyethylene glycols, and ethoxylated glycerol.

32. A composition comprising a compound of formula (I):



(I)

in which R_2 represents a hydrogen atom and R_1 forms a single bond together with the methyl carbon atom situated in the α position, so they together form a cyclopropane ring,

one of R_3 and R_4 represents a hydrogen atom and the other represents a hydroxy radical, or

R_3 and R_4 taken together form an oxo radical,

R_5 and R_6 each represents a hydrogen atom or one of R_5 and R_6 represents a hydrogen atom and the other represents a hydroxy, acyloxy or an alkoxymethylcarbonyloxy radical, or

R_5 and R_6 taken together form an oxo radical,

R_7 represents an alkoxy, alkenyloxy, cycloalkoxy or phenyl radical and

Ar represents

a phenyl radical optionally substituted by one or several atoms or radicals which are identical or different and are selected from halogen, alkyl, alkoxy, dialkylamino, acylamino, and trifluoromethyl, or

a 5-membered heterocyclic radical with one or more identical or different heteroatoms selected from nitrogen, oxygen and sulfur

wherein said compound of formula (I) is dissolved in a surfactant selected from polysorbate or polyethoxylated castor oil, and further wherein said composition is essentially free or free of alcohol.

33. The composition of claim 32, wherein the alkyl radical and the alkyl portion of the radicals selected from alkoxymethylcarbonyloxy, alkoxy, and dialkylamino are independently straight or branched and contain 1 to 8 carbon atoms and the alkenyloxy radical contains 2 to 8 carbon atoms.

34. A perfusion comprising less than or equal to 1 mg/ml of said compound of formula (I) of claim 32, and less than 1 ml/l of said ethanol and less than 15 ml/l of surfactant.

35. The composition of claim 32, wherein R_3 and R_4 taken together form an oxo radical; either (i) R_6 represents a hydrogen atom and R_5 represents a hydrogen atom or a hydroxy, acetyloxy or methoxyacetyloxy radical, or (ii) R_5 and R_6 taken together form an oxo radical;

R_7 represents a t.butoxy or a phenyl radical; and

Ar is a phenyl radical.

36. The composition of claim 32, said composition being a stock solution containing less than 5% by volume ethanol.

37. The composition of claim 36, said composition containing less than 2% by volume ethanol.

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