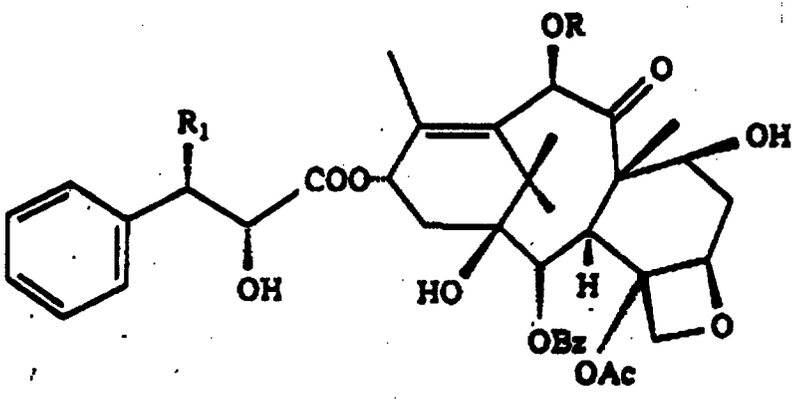
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NEW COMPOSITIONS BASED ON DERIVATIVES OF THE TAXANE CLASS

The present invention relates to a new pharmaceutical dosage form based on a therapeutic agent having antitumour and antileukaemic activity. It relates more especially to a new injectable dosage form containing products of the taxane family, such as, in particular, taxol or one of its analogues or derivatives of the following general formula:

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(I)

In the formula (I), R represents a hydrogen atom or an acetyl radical and the symbol R_1 represents a tert-butoxycarbonylamino or benzoyloxyamino radical. From this set of derivatives, the two derivatives for which R represents an acetyl group and R_1 a benzoyloxyamino group or that for which R represents a hydrogen atom and R_1 a tert-butoxycarbonylamino radical are preferred.

The first of these two compounds is better known by the name of taxol, and the second is known by the name of Taxotere.

These products exhibit in vivo substantial

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M0022 P.6/24

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activity against malignant tumours, which has enabled them to be studied in the treatment of diseases resistant to all other anticancer therapies.

Unfortunately, these products possess such low solubility in water that it has been necessary to prepare a formulation for an injectable preparation based on surfactant and ethanol. Ethanol is the best solvent which enables the molecules corresponding to the formula (I) to be solubilized.

As an example, according to the publication by Rowinsky, Lorraine, Cazenave and Donehower which appeared in the Journal of the National Cancer Institute, vol. 82, No. 15, pages 1247-1259 on 1st August 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.

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On injection, this solution is mixed with a perfusion fluid containing sodium chloride or dextrose. 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).

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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 in the solution is relatively low, the injection of a large volume has the effect of causing, in addition to anaphylactic manifestations, manifestations of alcoholism during the treatment.

It was discovered, by the use of the pharmaceutical dosage forms of the present invention, that it was possible either to decrease the ethanol concentrations greatly, or to eliminate Cremophor and ethanol completely in the perfusions.

For this purpose, according to a first method

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M0022 P.8/24

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for implementation of the invention, a stock solution is prepared, containing the active principle in a solvent mixture composed of ethanol, which is the best biocompatible solvent for active principles of the taxane class, and a surfactant chosen from polysorbates marketed, in particular, under the name Tween, polyoxyethylene glycol esters marketed, e.g., under the name Emulphor, or esters of polyethylene glycol and of castor oils marketed, e.g., under the name Cremophor.

The stock solution is prepared by dissolving the active principle in ethanol 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 subject of the present invention is as follows: ethanol, the best solvent for the active principle, may be almost completely eliminated.

To prepare, according to the first method for implementation of the invention, solutions having a low ethanol content, the active principle is dissolved in ethanol as described above, and any surfactant, chosen from those mentioned or others, enabling micelles to be formed containing the active principle 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.

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M0022 P.9/24

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According to a second method for preparing the stock solution, the active principle is dissolved directly in the surfactant. According to a better way of implementing the invention, a solution of surfactant containing, in particular, 1 to 2 % of ethanol is prepared, and the active principle is added in continuous fashion 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 is improved, as is the final filtration of the solution.

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 thus contain up to 200 mg/ml, and preferably up to 80 mg/ml, of active principle in the surfactant.

The 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, on the basis of a concentration of between 0.1 and 1 mg per millilitre with the perfusion fluid, which can be physiological solution or a glucose solution. Perfusions 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 contain less than 1 ml/l of

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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 the fact that the solution does not exhibit any visible criterion of precipitation after 8 to 10 hours of storage at room temperature.

The 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, on the basis of a concentration of between 0.1 and 0.5 mg per millilitre with the perfusion fluid, which can be a physiological solution or a glucose solution. Perfusions 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 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 are then 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 art are not observed with these solutions.

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Thus, these latter perfusions have made it possible to decrease, relative to the prior art, the amounts of surfactant injected into humans by approximately 80 % and the amounts of ethanol by almost 100 %.

The invention will be described more completely by means of the examples which follow, which are not to be considered as limiting the invention.

COMPARATIVE EXAMPLE ACCORDING TO THE PRIOR ART

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

This solution is diluted in a 5 % glucose 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 ACCORDING TO THE INVENTION

32 g of Taxotere are dissolved in 340 ml of absolute ethanol and 830 g of Polysorbate 80 are then added. The ethanol is evaporated off in a rotary evaporator at 30°C at a pressure of 15 mm of mercury for 2 hours.

The solution obtained is stable; it contains 40 mg/ml of Taxotere.

After dilution in a 5 % glucose perfusion solution at concentrations of 0.1, 0.3 and 0.5 mg/ml,

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the stability of the solutions obtained is observed.

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

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

The results are shown in Table 1.

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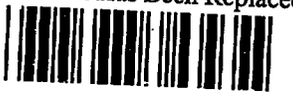


TABLE 1 ACCORDING TO THE INVENTION

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	> 8H
taxol	Polysorbate	20 mg/ml	0.3 mg/ml	15 ml/l	<0.09 ml/l	>24H
taxol	Polysorbate	12 mg/ml	1 mg/ml	83.3 ml/l	<0.5 ml/l	>48H
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	6.9 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	0.1 mg/ml	1.5 ml/l	<0.01 ml/l	8H-23H

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EXAMPLE 8

Into a stainless steel reactor, 258 g of Taxotere are introduced and dissolved with 2425 g of ethanol with mechanical stirring for 45 minutes.

6156 g of polysorbate 80 are 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 distilled 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:

- 1.3 % of ethanol
- 39.6 mg/ml of Taxotere.

After dilution to 1 mg/ml in a perfusion bag containing 5 % glucose, the solution is stable without apparent precipitation for a period of more than 2 months.

EXAMPLE 9

160 g of Taxotere or 160 mg of taxol are dissolved in 10 ml of a mixture of absolute ethanol and Chremophor EL(218), and the ethanol is evaporated off in a rotary evaporator at 30°C at a pressure of 25 mn of mercury for 3 hours.

The solutions obtained are stable. They

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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, a precipitation is observed at between 30 and 95 hours.

EXAMPLE 10

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

A 50-ml flask is charged with 26.13 g of the solution prepared above. The flask is placed in a water bath heated beforehand and maintained throughout the test period at 30°C. The solution is stirred at approximately 600 rpm with a bar magnet.

With a spatula, 1.076 g of Taxotere is added in several portions so as to cause the clumps to disappear between two additions (duration of the operation: approximately one hour). After incorporation of the last fraction of Taxotere, stirring is maintained until the solution becomes clear (duration of the operation: approximately two hours).

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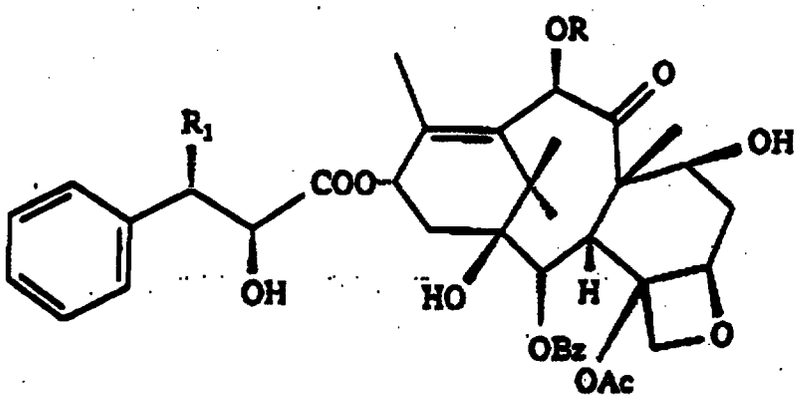


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CLAIMS

1. New compositions based on a derivative of formula (I)



(I)

in which R represents a hydrogen atom or an acetyl radical and the symbol R_1 represents a tert-butoxycarbonylamino or benzoyloxyamino radical, dissolved in a surfactant chosen from polysorbates, polyoxyethylene glycol esters and esters of polyethylene glycol and of hydrogenated castor oils, virtually free from ethanol.

2. Compositions according to claim 1, characterized in that they contain less than 5 % of ethanol, and preferably less than 2 % of ethanol.

3. Compositions according to either of claims 1 and 2, characterized in that, in the compound of formula (I), R represents hydrogen and R_1 a tert-butoxycarbonylamino radical.

4. Compositions according to either of claims 1 and 2, characterized in that, in the compound of formula (I), R represents an acetyl group and R_1 represents a benzoyloxyamino radical.

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5. Compositions according to any one of claims 1 to 4, characterized in that they contain up to 200 mg/ml, and preferably up to 80 mg/ml, of compounds of formula (I).

6. Compositions according to claims 3 and 5, characterized in that they contain 20 to 80 mg/ml of compounds of formula (I).

7. Compositions according to claims 4 and 5, characterized in that they contain 6 to 20 mg/ml of compounds of formula (I).

8. Method for preparing the compositions according to any one of the preceding claims, characterized in that the active principle is solubilized in ethanol, the surfactant is added and the ethanol is then evaporated off.

9. Method for preparing the compositions according to any one of claims 1 to 7, characterized in that the composition is prepared by slow addition of the active principle to a solution of the surfactant containing 1 to 2 % of ethanol.

10. Perfusion, characterized in that it contains less than 0.5 mg/ml, and preferably 0.1 to 0.3 mg/ml, of compound according to claim 3, and in that it contains less than 1 ml/l of ethanol and less than 15 ml/l of surfactant.

11. Perfusion, characterized in that it contains 1 mg/ml or less of compound according to claim 4 and in that it contains less than 1 ml/l of ethanol.

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