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(54) Title: STABLE PHARMACEUTICAL COMPOSITIONS OF TEMSIROLIMUS

(57) Abstract: The present invention relates to pharmaceutical compositions containing temsirolimus, stabilized with lipoic, caprylic and linoleic acid.



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## STABLE PHARMACEUTICAL COMPOSITIONS OF TEMSIROLIMUS

### Field of the invention

The present invention relates to pharmaceutical compositions containing temsirolimus, which are stabilized with lipoic, caprylic and linoleic acid.

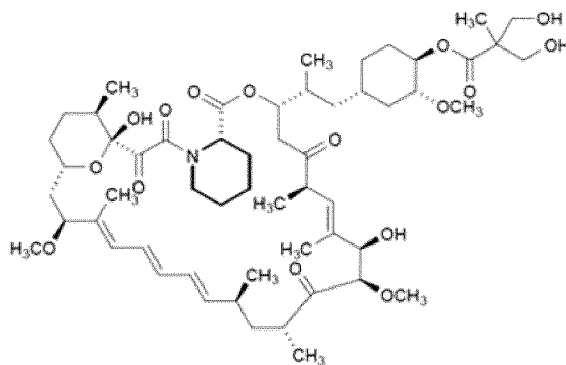
### Background of the invention

Temsirolimus (CCI-779), a 42-bis(hydroxymethyl) propionic acid ester derived from rapamycin, selectively inhibits the kinase mammalian target of rapamycin (mTOR) and consequently blocks the translation of cell cycle regulatory proteins and prevents overexpression of angiogenic growth factors.

Temsirolimus is approved for intravenous administration by the U.S. Food and Drug Administration (FDA) for treatment of advanced renal cell carcinoma (RCC) and by the European Medicines Agency (EMA) for treatment of advanced renal cell carcinoma and mantle cell lymphoma.

The chemical name of temsirolimus is 42-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]rapamycin and the chemical structure is represented by formula 1 shown below.

Regarding stereochemistry, three isomers A, B and C can exist and they interconvert in solution. Isomer B is the predominant isomer ( $\geq 97\%$ ) in both solution and solid states, whereas Isomer A is only observed in solution state.

Formula 1.

Currently, temsirolimus is marketed as an injectable formulation kit comprising two vials, wherein first concentrate vial contains temsirolimus (25 mg/ml), dehydrated alcohol (39.5% w/v), dl-alpha-tocopherol (0.075% w/v), propylene glycol (50.3% w/v) and anhydrous citric acid (0.0025% w/v); and second diluent vial contains: polysorbate 80 (40.0% w/v), polyethylene glycol 400 (42.8% w/v) and dehydrated alcohol (19.9% w/v).

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Temsirolimus concentrate vial must be diluted with the diluent provided in the second vial before addition in sodium chloride 9 mg/ml (0.9%) solution for injection and then administered to the patient in need thereof.

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According to the prior art, there are couple of problems to overcome in order to provide a stable temsirolimus composition for parenteral administration:

First, temsirolimus is poorly soluble in aqueous solvents and pH adjustment or salt formations are useless in improving aqueous solubility.

Second, although temsirolimus is soluble in certain organic solvents such as ethanol, propylene glycol, polyethylene glycol and dimethylacetamide, its chemical instability (associated with oxidative degradation or due to the breaking of the lactone bond resulting in the

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formation of the ring opened compounds) in these solvents and precipitation upon dilution with aqueous infusion solutions is inevitable.

5 The first aforementioned problem of low solubility in water, as well as precipitation upon dilution with aqueous infusion solution, is resolved by selection of compatible organic co-solvents and addition of a surfactant, while the low chemical stability is enhanced by addition of antioxidant and/or chelating agent in the solution of parenterally acceptable co-solvents as it can be seen from the state of the art:

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The marketed composition of temsirolimus includes temsirolimus as the active substance, dl-alpha tocopherol (Vitamin E) as an antioxidant, dehydrated alcohol, propylene glycol and polyethylene glycol 400 as solvents, polysorbate 80 as a surfactant, and anhydrous citric acid as a  
15 stabilizer.

**WO2004011000** provides parenteral formulations of rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) wherein acceptable antioxidants include citric acid, dl-alpha-tocopherol,  
20 BHA, BHT, monothioglycerol, ascorbic acid, propyl gallate, and mixtures thereof.

U.S. Application **US2012252835** describes a stable composition of temsirolimus for parenteral administration wherein the composition includes  
25 butylated hydroxyanisole (BHA) or butylated hydroxytoluene (BHT) as antioxidants and alcoholic solvent and the pH of the composition is below 5.0.

In **WO2014118696**, liquid and lyophilized pharmaceutical  
30 compositions comprising temsirolimus in combination with an organic acid, inorganic acid and amino acid are provided. Examples of organic acid include ascorbic acid, citric acid, tartaric acid, lactic acid, oxalic acid, formic acid,

benzene sulphonic acid, benzoic acid, maleic acid, malonic acid, glutamic acid, succinic acid, aspartic acid, diatrizoic acid, acetic acid and mixtures thereof. Examples of inorganic acid include hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid and mixtures thereof. Examples of amino acid  
5 include cysteine, glycine, alanine, lysine, arginine, glutathione, methionine, leucine, aspartic acid and mixtures thereof. Also, addition of antioxidants selected from citric acid, dl-alpha-tocopherol, BHA, BHT, monothioglycerol, ascorbic acid, propyl gallate and mixtures thereof is disclosed.

10 In **WO2011151704**, pharmaceutical antioxidant-free compositions of rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid are provided, in particular comprising parenterally acceptable solvent, lactic acid and a surfactant.

15 In **WO2005010010**, purified CCI-779 isomer C is provided, as are pharmaceutical compositions containing the same, wherein antioxidant is selected from citric acid, dl-alpha-tocopherol, BHA, BHT, monothioglycerol, ascorbic acid, propyl gallate, and mixtures thereof.

20 **WO2006089312** provides CCI-779 oral dosage form in which acceptable antioxidants include citric acid, dl-alpha-tocopherol, butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT), monothioglycerol, ascorbic acid, propyl gallate, and mixtures thereof.

25 **WO2007075621** provides a method of preparing a rapamycin composition having increased potency wherein the method involves selecting a rapamycin compound having less than 1.5% oxidative and hydrolytic rapamycin impurities and formulating the selected rapamycin with an antioxidant and optional excipients. Antioxidants that can be used include  
30 citric acid, alpha tocopherol, BHA, BHT (2,6-di-tert-butyl-4-methylphenol), monothioglycerol, vitamin C, and propyl gallate.

In Chinese publication **CN103099806**, temsirolimus for injection is described, wherein suitable antioxidants are alpha-tocopherol, ascorbic acid, sodium bisulfite and citric acid.

5 In **CN103989676**, a liquid composition of temsirolimus, ethyl alcohol, organic acid and propylene glycol is disclosed.

Various prior art documents aim at solving the problem with chemical instability of solid temsirolimus compositions in form of antioxidant addition:

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PCT publication **WO0033878** relates to the stabilization of a pharmaceutically active ingredient sensitive to oxidation, particularly rapamycins. Preferred antioxidants according to the description are 2,6-di-tert-butyl-4-methylphenol (BHT), vitamin E or C, wherein BHT being particularly preferred.

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**WO2005011688** discloses lyophilized CCI-779 formulations and solutions useful for preparing freeze-dried CCI-779 formulations wherein examples of suitable antioxidants include BHT, BHA, alpha-tocopherol, ascorbic acid, erythorbic acid, dithiothreitol, dithioerythreitol, glutathione, ascorbyl palmitate, monothioglycerol, propyl gallate, sodium bisulfite, sodium metabisulfite.

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**WO2004026280** provides solid oral formulations of rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779). Acceptable antioxidants include, but are not limited to, citric acid, dl-alpha-tocopherol, BHA, BHT, monothioglycerol, ascorbic acid, and propyl gallate.

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The invention described in **WO2005070393** provides pharmaceutical compositions containing a stable and bioavailable form of micronized CCI-779, and optionally, an antioxidant or a chelating agent, or mixtures thereof, in an immediate release dosage form for oral administration. Acceptable

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antioxidants include citric acid, dl-alpha-tocopherol, butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT), monothioglycerol, ascorbic acid, propyl gallate, and mixtures thereof.

5           According to the prior art described above, the challenge of the moment is how to provide temsirolimus compositions where oxidative/hydrolytic degradation and quality decline is prevented. As can be seen from the marketed formulation, as well as from prior art, it is crucial to have an antioxidant present in the formulation to prevent degradation of the  
10   drug.

          However, inventors of the present invention have surprisingly found that various lipophilic acids – with or without antioxidant properties stabilize rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic  
15   acid in organic solvents.

### **Summary of the invention**

          Oxidation is one of the major processes that have destructive effect  
20   on stability of a drug. In order to provide a stable pharmaceutical formulation, active pharmaceutical ingredients susceptible to chemical degradation by oxidation are often formulated with antioxidants whose main purpose is to retard or inhibit the oxidative breakdown of active ingredients upon exposure to atmospheric oxygen and to improve the shelf life of such  
25   products.

          Some of the most common antioxidants used in pharmaceutical industry are butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), sodium metabisulfite, propyl gallate, cysteine, tocopherols and  
30   ascorbic acid.

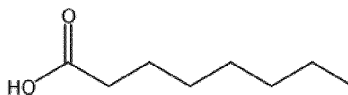
In recent studies, some of these excipients are reported to be associated with adverse reactions, therefore, the need to find less or non-toxic excipients as alternative ways of stabilization of pharmaceutical preparations is emerging.

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According to the present invention, lipophilic acids selected from the group consisting of caprylic (octanoic), lipoic and linoleic acid are used as stabilizing agents, and they show surprisingly good stabilizing effect on temsirolimus.

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Caprylic acid, also known by the systematic name octanoic acid, is a saturated fatty acid containing eight carbon atoms, making it one of the medium-chain fatty acids. Caprylic acid, a naturally occurring constituent of many foods, is absorbed and metabolized by man. Some studies have shown that caprylic acid has antibacterial, antiviral and antifungal properties. Caprylic acid is also taken as a dietary supplement.



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Formula 2. Caprylic acid

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Lipoic acid or 1,2-dithiolane-3-pentanoic acid, also known as thiocctic acid, is a naturally occurring dithiol compound synthesized enzymatically in the mitochondrion from octanoic acid. Lipoic acid has been described as a potent biological antioxidant, a detoxification agent, and a diabetes medicine; it has been used to improve age-associated cardiovascular, cognitive, and neuromuscular deficits, and has been implicated as a modulator of various inflammatory signaling pathways.



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Formula 3. Lipoic acid

Linoleic acid is a polyunsaturated omega-6 fatty acid.



Formula 4. Linoleic acid

5           The newly developed pharmaceutical compositions, according to the present invention, show chemical stability comparable to the marketed product and even better chemical stability than those formulations known from the prior art containing other commonly used antioxidants, when they are stored at 40°C, 25°C or 2-8°C for a period ranging from 1 week to 6  
10 (12) months.

This invention, in one embodiment, provides a parenteral formulation containing temsirolimus, an organic solvent selected from ethanol, propylene glycol, polyethylene glycol or combinations thereof; a surfactant selected from polysorbate 20 or polysorbate 80; citric acid as a chelating/stabilizing agent and lipophilic acid selected from caprylic, lipoic, and linoleic acid.

In a second embodiment, invention is provided in two vials kit, comprising a first vial comprising temsirolimus and a second vial comprising a diluent, wherein the first vial contains temsirolimus in concentration of 20 to 30 mg/mL, preferably 25 mg/mL, an organic solvent selected from ethanol, propylene glycol, polyethylene glycol or combinations thereof from about 10% to about 90% w/v of the formulation; citric acid in a concentration of 0.001 to 0.005% w/v and lipophilic acid selected from caprylic, lipoic, and linoleic acid in a concentration ranging from 0.001% to 1% w/v, or 0.01% to 0.5% w/v, although lower or higher concentrations may be desired. Particularly desirable concentration of lipophilic acid is from 0.01 to 0.1% w/v, with a most preferred concentration of 0.075% w/v.

According to the second embodiment, the second diluent vial contains an organic solvent selected from ethanol, propylene glycol, polyethylene glycol or combinations thereof, and a surfactant selected from polysorbate 20 or polysorbate 80 wherein the surfactant will comprise at least 5% w/v, or at least 10% w/v, of the diluent solution.

In a third embodiment, compositions according to the present invention are provided in two vials kit, comprising a first vial comprising temsirolimus and a second vial comprising a diluent, wherein the first vial contains temsirolimus in a concentration of 25 mg/mL, dehydrated ethanol in a concentration of 39.5% w/V, propylene glycol in a concentration of 50.3% w/V, citric acid in a concentration 0.0025% w/V and lipophilic acid selected from caprylic, lipoic, and linoleic acid in a concentration 0.075% w/V.

According to the third embodiment, the second diluent vial contains polysorbate 80 in a concentration of 40.0% w/v, polyethylene glycol 400 in a concentration of 42.8% w/v and dehydrated ethanol in a concentration of 19.9% w/v.

According to the present invention, when compositions are provided as two vials kit, prior to administration to a patient, content of the two vials are mixed together and added into the infusion fluid.

Temsirolimus compositions described herein are useful for the treatment of renal cell carcinoma and mantle cell lymphoma.

Other objects, features and advantages of the present invention will become apparent from the following detailed description and examples. It should be understood, however, that the detailed description and the examples, while indicating specific embodiments of the invention, are given by way of illustration only.

**Detailed description of the invention**

The term "pharmaceutical composition" as used herein, means a composition that is made under conditions such that it is suitable for administration to a patient and contains pharmaceutically acceptable excipients, e.g. without limitation to stabilizers, bulking agents, surfactants, buffers, carriers, diluents, vehicles, solubilizers and binders.

As used herein, the terms "pharmaceutical composition", "pharmaceutical formulation", "composition" and "formulation" are used interchangeably.

Term "stable" here refers to a pharmaceutical formulation containing temsirolimus having sufficient stability to have utility as a pharmaceutical product and meets defined shelf life specifications for this product as a marketed product.

Preferably, a stable pharmaceutical composition has sufficient stability to allow storage at a convenient temperature, wherein the storage temperature is preferably from 2°C to 30°C, more preferably from 2°C to 25°C, and even more preferably from 2°C to 8°C, for a reasonable period of time, e.g. the shelf-life of the product which can be as short as one month but is typically 12 months or longer.

Temsirolimus is known to degrade at a really fast rate and alternative methods for preparation of temsirolimus compositions that have good chemical stability and therefore less degradation impurities formation over time are needed.

In order to determine the degradation profile of temsirolimus in the presence of antioxidants, known antioxidants suggested from the prior art and general literature such as alpha-tocopheryl hydrogen succinate, monothioglycerol, sodium-lactate, N-acetylcysteine, ascorbic acid, gentisic acid and ascorbyl-palmitate were tested and data obtained are presented below.

As can be seen from the following results, most of the suggested antioxidants did not work toward stabilization of temsirolimus. To the

contrary, the suggested antioxidants promoted the decomposition of temsirolimus and formation of impurities.

Unexpectedly, acids selected from caprylic, lipoic and linoleic acid, showed good stabilization effect on temsirolimus and slower rate of impurities formation.

The following compositions were prepared and tested:

1. Composition similar to the marketed product with concentration of alpha-tocopherol of 0.075% w/V

| Ingredient         | Quantity    |
|--------------------|-------------|
| Temsirolimus       | 25 mg/mL    |
| Dehydrated Ethanol | 39.5% w/V   |
| Propylene glycol   | 50.3% w/V   |
| Citric acid        | 0.0025% w/V |
| Alpha-tocopherol   | 0.075% w/V  |

2. Composition wherein alpha-tocopherol was used in higher concentration of 0.45% w/V

| Ingredient         | Quantity    |
|--------------------|-------------|
| Temsirolimus       | 25 mg/mL    |
| Dehydrated Ethanol | 39.5% w/V   |
| Propylene glycol   | 49.9% w/V   |
| Citric acid        | 0.0025% w/V |
| Alpha-tocopherol   | 0.45% w/V   |

3. Compositions wherein alpha-tocopherol was replaced with antioxidants suggested in the prior art and selected from group consisting of alpha-tocopheryl hydrogen succinate, monothioglycerol, sodium-lactate, N-acetylcysteine, ascorbic acid, gentisic acid, and ascorbyl-palmitate in a concentration of 0.075% w/V

| Ingredient         | Quantity    |
|--------------------|-------------|
| Temsirolimus       | 25 mg/mL    |
| Dehydrated Ethanol | 39.5% w/V   |
| Propylene glycol   | 50.3% w/V   |
| Citric acid        | 0.0025% w/V |
| Antioxidant        | 0.075% w/V  |

4. Compositions of temsirolimus, which contain lipophilic acids according to this invention in concentration of 0.075% w/V

| Ingredient         | Quantity    |
|--------------------|-------------|
| Temsirolimus       | 25 mg/mL    |
| Dehydrated Ethanol | 39.5% w/V   |
| Propylene glycol   | 50.3% w/V   |
| Citric acid        | 0.0025% w/V |
| Lipophilic acid    | 0.075% w/V  |

5. Composition of temsirolimus without addition of antioxidants

| Ingredient         | Quantity    |
|--------------------|-------------|
| Temsirolimus       | 25 mg/mL    |
| Dehydrated Ethanol | 39.5% w/V   |
| Propylene glycol   | 50.8% w/V   |
| Citric acid        | 0.0025% w/V |

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The following examples were provided in two vial compositions of temsirolimus wherein the compositions of the vials were prepared as described below:

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Preparation of the content of the first vial – concentrate:

The temperature of the solution in the formulation vessel is maintained at 2-8°C and the solution is protected from light throughout the compounding process. Approximately 50% of the required quantity of propylene glycol is added into the formulation vessel. Then, required quantity of citric acid is added and solution is stirred until complete dissolution.

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Separately, stock solution of lipophilic acid or antioxidant is prepared in 20-30% of total quantity of dehydrated ethanol and added into formulation vessel under constant stirring. Alternatively, lipophilic acid or antioxidant is added directly into formulation vessel and stirred.

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The remainder of total required quantity of dehydrated ethanol is then added into formulation vessel. At this stage, temsirolimus is slowly added into formulation vessel under constant stirring. After complete dissolution is achieved, volume is made up to 100% with propylene glycol and then solution is purged with nitrogen to achieve dissolved oxygen content of not more than 2 ppm. This solution is filtered through a suitable 0.22 µm

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sterilizing grade filter, filled in Type I clear glass vials and overlaid with nitrogen, prior stoppering with suitable Type I rubber stoppers.

Preparation of the second diluent vial:

5           Solution is prepared in the formulation vessel at room temperature (18-25°C). Firstly, required amount of polyethylene glycol is added to the formulation vessel. Under constant stirring, required quantity of polysorbate 80 is added to the formulation vessel, with subsequent addition of approximately 40% of the required quantity of dehydrated ethanol. Solution  
10 is mixed until complete mixing of components is achieved. Volume is made up to 100% with dehydrated ethanol and then solution is purged with nitrogen to achieve dissolved oxygen content of not more than 2 ppm. This solution is filtered through a suitable 0.22 µm sterilizing grade filter, filled in Type I clear glass vial and overlaid with nitrogen, prior stoppering with  
15 suitable Type I rubber stoppers.

          Immediately after preparation of every individual composition, analysis for initial assay and related substances content followed, and afterwards compositions were loaded in stability chambers for stress testing at 40°C/75% RH; accelerated stability testing at 25°C/60% RH and long  
20 term stability testing at 2-8°C.

          Temsirolimus assay and related substances were determined using routine HPLC methods known to those skilled in the art, for example as described in U.S Application Publication No. 2007/0142422.

          Analysis of the formulations of the present invention can be  
25 performed using other techniques known in the art, including, for example, gas chromatography, and NMR.

          In the tables presented below, assay of active substance – temsirolimus, is expressed as a content of isomer B and isomer C. Isomer A is monitored as a separate value and it is not included in total impurities  
30 content.

It has been observed that compositions of temsirolimus when formulated with lipophilic acid selected from caprylic, lipoic, and linoleic acid show comparable or even better chemical stability in comparison to chemical stability obtained by addition of known antioxidants selected from alpha-  
5 tocopherol, alpha-tocopheryl hydrogen succinate, monothioglycerol, sodium-lactate, N-acetylcysteine, ascorbic acid, gentisic acid and ascorbyl-palmitate.

Table 1. Comparative stress test data of temsirolimus formulations containing known antioxidants vs. temsirolimus formulations containing lipophilic acids at 40°C/75% RH for a period of 7 days, 14 days and 1 month

| Formulation                                          | Initial                               |                           | 7 days                                |                                                   |                           |                                   | 14 days                                |                                                      |                            |                                      | 1 month                                |                                                      |                            |                                      |
|------------------------------------------------------|---------------------------------------|---------------------------|---------------------------------------|---------------------------------------------------|---------------------------|-----------------------------------|----------------------------------------|------------------------------------------------------|----------------------------|--------------------------------------|----------------------------------------|------------------------------------------------------|----------------------------|--------------------------------------|
|                                                      | Total impurities % (Ti <sub>0</sub> ) | Assay % (A <sub>0</sub> ) | Total impurities % (Ti <sub>7</sub> ) | $\left  \Delta \text{Ti}_7 - \text{Ti}_0 \right $ | Assay % (A <sub>7</sub> ) | $\left  \Delta A_0 - A_7 \right $ | Total impurities % (Ti <sub>14</sub> ) | $\left  \Delta \text{Ti}_{14} - \text{Ti}_0 \right $ | Assay % (A <sub>14</sub> ) | $\left  \Delta A_0 - A_{14} \right $ | Total impurities % (Ti <sub>1m</sub> ) | $\left  \Delta \text{Ti}_{1m} - \text{Ti}_0 \right $ | Assay % (A <sub>1m</sub> ) | $\left  \Delta A_0 - A_{1m} \right $ |
| Antioxidant free                                     | 0,00                                  | 102,7                     | 0,25                                  | 0,25                                              | 96,9                      | 5,8                               | 0,41                                   | 0,41                                                 | 95,1                       | 7,6                                  | 5,22                                   | 5,22                                                 | 63,1                       | 39,6                                 |
| $\alpha$ -tocopherol (0.075% w/V)                    | 0,07                                  | 102,9                     | 0,25                                  | 0,18                                              | 102,4                     | 0,5                               | NA                                     | NA                                                   | NA                         | NA                                   | NA                                     | NA                                                   | NA                         | NA                                   |
| $\alpha$ -tocopherol (0.45% w/V)                     | 0,12                                  | 101,5                     | 0,26                                  | 0,14                                              | 99,3                      | 2,2                               | 0,35                                   | 0,23                                                 | 100,5                      | 1,0                                  | 0,52                                   | 0,40                                                 | 99,9                       | 1,6                                  |
| $\alpha$ -tocopherol hydrogen succinate (0.075% w/V) | 0,10                                  | 100,0                     | 0,36                                  | 0,26                                              | 97,5                      | 2,5                               | 0,62                                   | 0,52                                                 | 97,1                       | 2,9                                  | 0,76                                   | 0,66                                                 | 94,7                       | 5,3                                  |
| Monothioisopropanol (0.075% w/V)                     | 0,08                                  | 100,6                     | 0,29                                  | 0,21                                              | 98,2                      | 2,4                               | 0,50                                   | 0,42                                                 | 98,9                       | 1,7                                  | 1,18                                   | 1,1                                                  | 85,1                       | 15,5                                 |
| Sodium lactate (0.075% w/V)                          | 0,19                                  | 102,0                     | 3,13                                  | 2,94                                              | 98,5                      | 3,5                               | 4,63                                   | 4,44                                                 | 95,2                       | 6,8                                  | 8,66                                   | 8,47                                                 | 88,7                       | 13,3                                 |
| N-acetylcysteine (0.075% w/V)                        | 0,08                                  | 100,1                     | 3,77                                  | 3,69                                              | 69,7                      | 30,4                              | 5,66                                   | 5,58                                                 | 63,8                       | 36,3                                 | 13,16                                  | 13,08                                                | 48,8                       | 51,3                                 |
| Ascorbic acid (0.075% w/V)                           | 0,08                                  | 100,7                     | 0,87                                  | 0,79                                              | 97,3                      | 3,4                               | 1,25                                   | 1,17                                                 | 99,8                       | 0,9                                  | 3,06                                   | 2,98                                                 | 90,7                       | 10,0                                 |
| Glutamic acid (0.075% w/V)                           | 0,12                                  | 101,2                     | 1,83                                  | 1,71                                              | 93,1                      | 8,1                               | 3,34                                   | 3,22                                                 | 92,0                       | 9,2                                  | 7,71                                   | 7,59                                                 | 76,0                       | 25,2                                 |
| Ascorbyl-palmitate (0.075% w/V)                      | 0,27                                  | 100,0                     | 0,84                                  | 0,57                                              | 98,4                      | 1,6                               | 2,00                                   | 1,73                                                 | 93,8                       | 6,2                                  | 2,48                                   | 2,21                                                 | 91,9                       | 8,1                                  |
| Lipoic acid (0.075% w/V)                             | 0,08                                  | 100,2                     | 0,50                                  | 0,42                                              | 97,0                      | 3,2                               | 0,68                                   | 0,60                                                 | 96,0                       | 4,2                                  | 1,20                                   | 1,12                                                 | 93,6                       | 6,6                                  |
| Caprylic acid (0.075% w/V)                           | 0,15                                  | 99,6                      | 0,38                                  | 0,23                                              | 99,8                      | 0,2                               | 0,63                                   | 0,48                                                 | 97,0                       | 2,6                                  | 1,10                                   | 0,95                                                 | 93,9                       | 5,7                                  |
| Linoleic acid (0.075% w/V)                           | 0,14                                  | 100,3                     | 0,37                                  | 0,23                                              | 97,1                      | 3,2                               | 0,45                                   | 0,31                                                 | 97,6                       | 2,7                                  | 1,05                                   | 0,91                                                 | 91,1                       | 9,2                                  |

\* NA – DATA NOT AVAILABLE

Table 2. Comparative accelerated stability data of temsirolimus formulations containing known antioxidants vs. temsirolimus formulations containing lipophilic acids at 25°C/60% RH for a period of 1 month, 3 and 6 months

| Formulation                                          | Initial                               |                           |                                        | 1 month                    |                            |                            | 3 months                               |                            |                            | 6 months                               |                            |                            |
|------------------------------------------------------|---------------------------------------|---------------------------|----------------------------------------|----------------------------|----------------------------|----------------------------|----------------------------------------|----------------------------|----------------------------|----------------------------------------|----------------------------|----------------------------|
|                                                      | Total impurities % (TI <sub>0</sub> ) | Assay % (A <sub>0</sub> ) | Total impurities % (TI <sub>1m</sub> ) | Assay % (A <sub>1m</sub> ) | Assay % (A <sub>1m</sub> ) | Assay % (A <sub>1m</sub> ) | Total impurities % (TI <sub>3m</sub> ) | Assay % (A <sub>3m</sub> ) | Assay % (A <sub>3m</sub> ) | Total impurities % (TI <sub>6m</sub> ) | Assay % (A <sub>6m</sub> ) | Assay % (A <sub>6m</sub> ) |
| Antioxidant free                                     | 0,00                                  | 102,7                     | 0,30                                   | 0,30                       | 99,6                       | 3,1                        | 0,41                                   | 94,6                       | 8,1                        | 1,77                                   | 88,0                       | 14,7                       |
| $\alpha$ -tocopherol (0.075% w/V)                    | 0,07                                  | 102,9                     | 0,27                                   | 0,20                       | 98,8                       | 4,1                        | 0,34                                   | 99,9                       | 3,0                        | 0,53                                   | 97,1                       | 5,8                        |
| $\alpha$ -tocopherol (0.45% w/V)                     | 0,12                                  | 101,5                     | 0,29                                   | 0,17                       | 99,2                       | 2,3                        | 0,33                                   | 97,1                       | 4,4                        | 0,44                                   | 98,9                       | 2,6                        |
| $\alpha$ -tocopheryl hydrogen succinate (0.075% w/V) | 0,10                                  | 100,0                     | 0,31                                   | 0,21                       | 98,4                       | 1,6                        | 0,48                                   | 97,6                       | 2,4                        | 0,75                                   | 98,5                       | 1,5                        |
| Monothioglycerol (0.075% w/V)                        | 0,08                                  | 100,6                     | 0,26                                   | 0,18                       | 99,2                       | 1,4                        | 0,41                                   | 94,7                       | 5,9                        | 0,84                                   | 89,6                       | 11,0                       |
| Sodium-lactate (0.075% w/V)                          | 0,19                                  | 102,0                     | 2,57                                   | 2,38                       | 96,7                       | 5,3                        | 5,47                                   | 93,2                       | 8,8                        | NA                                     | NA                         | NA                         |
| N-acetylcysteine (0.075% w/V)                        | 0,08                                  | 100,1                     | 12,03                                  | 11,95                      | 53,1                       | 47,0                       | 65,19                                  | 10,6                       | 89,5                       | NA                                     | NA                         | NA                         |
| Ascorbic acid (0.075% w/V)                           | 0,08                                  | 100,7                     | 0,80                                   | 0,72                       | 93,9                       | 6,8                        | 1,68                                   | 95,0                       | 5,7                        | NA                                     | NA                         | NA                         |
| Gentisic acid (0.075% w/V)                           | 0,12                                  | 101,2                     | 1,24                                   | 1,12                       | 91,1                       | 10,1                       | 2,72                                   | 89,9                       | 11,3                       | NA                                     | NA                         | NA                         |
| Ascorbyl-palmitate (0.075% w/V)                      | 0,27                                  | 100,0                     | 0,89                                   | 0,62                       | 97,8                       | 2,2                        | 1,55                                   | 95,4                       | 4,6                        | 3,38                                   | 92,1                       | 7,9                        |
| Lipoic acid (0.075% w/V)                             | 0,08                                  | 100,2                     | 0,38                                   | 0,30                       | 97,6                       | 2,6                        | 0,51                                   | 97,2                       | 3,0                        | 0,88                                   | 98,2                       | 2,0                        |
| Caprylic acid (0.075% w/V)                           | 0,15                                  | 99,6                      | 0,34                                   | 0,19                       | 97,1                       | 2,5                        | 0,73                                   | 97,1                       | 2,5                        | 1,07                                   | 94,4                       | 5,2                        |
| Linoleic acid (0.075% w/V)                           | 0,14                                  | 100,3                     | 0,25                                   | 0,11                       | 97,2                       | 3,1                        | 0,52                                   | 97,7                       | 2,6                        | 0,98                                   | 93,4                       | 6,9                        |

\*NA – DATA NOT AVAILABLE

Table 3. Comparative long term stability data of temsirolimus formulations containing known antioxidants vs. temsirolimus formulations containing lipophilic acids at 2-8°C for a period of 1 month, 3 and 6 months

| Formulation                                  | Initial                               |                           | 1 month                                |                            |                                      | 3 months                           |                                        |                            | 6 months                             |                                    |                                        |                            |                                      |                                    |
|----------------------------------------------|---------------------------------------|---------------------------|----------------------------------------|----------------------------|--------------------------------------|------------------------------------|----------------------------------------|----------------------------|--------------------------------------|------------------------------------|----------------------------------------|----------------------------|--------------------------------------|------------------------------------|
|                                              | Total impurities % (TI <sub>0</sub> ) | Assay % (A <sub>0</sub> ) | Total impurities % (TI <sub>1m</sub> ) | Assay % (A <sub>1m</sub> ) | Δ TI <sub>1m</sub> - TI <sub>0</sub> | Δ A <sub>0</sub> - A <sub>1m</sub> | Total impurities % (TI <sub>3m</sub> ) | Assay % (A <sub>3m</sub> ) | Δ TI <sub>3m</sub> - TI <sub>0</sub> | Δ A <sub>0</sub> - A <sub>3m</sub> | Total impurities % (TI <sub>6m</sub> ) | Assay % (A <sub>6m</sub> ) | Δ TI <sub>6m</sub> - TI <sub>0</sub> | Δ A <sub>0</sub> - A <sub>6m</sub> |
| Antioxidant free                             | 0,00                                  | 102,7                     | 0,25                                   | 100,7                      | 0,25                                 | 2,0                                | 0,31                                   | 98,8                       | 0,31                                 | 3,9                                | 0,23                                   | 97,4                       | 0,23                                 | 5,3                                |
| α-tocopherol (0.075% w/V)                    | 0,07                                  | 102,9                     | 0,22                                   | 99,8                       | 0,15                                 | 3,1                                | 0,20                                   | 99,7                       | 0,13                                 | 3,2                                | 0,26                                   | 98,3                       | 0,19                                 | 4,6                                |
| α-tocopherol (0.45% w/V)                     | 0,12                                  | 101,5                     | 0,22                                   | 100,4                      | 0,10                                 | 1,1                                | 0,27                                   | 99,0                       | 0,15                                 | 2,5                                | 0,26                                   | 99,8                       | 0,14                                 | 1,7                                |
| α-tocopheryl hydrogen succinate (0.075% w/V) | 0,10                                  | 100,0                     | 0,26                                   | 99,0                       | 0,16                                 | 1,0                                | 0,26                                   | 99,2                       | 0,16                                 | 0,8                                | 0,33                                   | 99,5                       | 0,23                                 | 0,5                                |
| Monothioglycerol (0.075% w/V)                | 0,08                                  | 100,6                     | 0,21                                   | 101,2                      | 0,13                                 | 0,6                                | 0,28                                   | 98,5                       | 0,20                                 | 2,1                                | 0,24                                   | 99,2                       | 0,16                                 | 1,4                                |
| Sodium-lactate (0.075% w/V)                  | 0,19                                  | 102,0                     | 0,51                                   | 99,5                       | 0,32                                 | 2,5                                | 0,88                                   | 99,4                       | 0,69                                 | 2,6                                | NA                                     | NA                         | NA                                   | NA                                 |
| N-acetylcysteine (0.075% w/V)                | 0,08                                  | 100,1                     | 0,85                                   | 79,3                       | 0,77                                 | 20,8                               | 0,97                                   | 79,2                       | 0,89                                 | 20,9                               | NA                                     | NA                         | NA                                   | NA                                 |
| Ascorbic acid (0.075% w/V)                   | 0,08                                  | 100,7                     | 0,29                                   | 99,1                       | 0,21                                 | 1,6                                | 0,53                                   | 96,6                       | 0,45                                 | 4,1                                | NA                                     | NA                         | NA                                   | NA                                 |
| Gentisic acid (0.075% w/V)                   | 0,12                                  | 101,2                     | 0,26                                   | 98,9                       | 0,14                                 | 2,3                                | 0,41                                   | 99,3                       | 0,29                                 | 1,9                                | NA                                     | NA                         | NA                                   | NA                                 |
| Ascorbyl-palmitate (0.075% w/V)              | 0,27                                  | 100,0                     | 0,64                                   | 98,2                       | 0,37                                 | 1,8                                | 0,64                                   | 98,9                       | 0,37                                 | 1,1                                | 0,72                                   | 98,7                       | 0,45                                 | 1,3                                |
| Lipoic acid (0.075% w/V)                     | 0,08                                  | 100,2                     | 0,26                                   | 98,0                       | 0,18                                 | 2,2                                | 0,27                                   | 98,8                       | 0,19                                 | 1,4                                | 0,27                                   | 101,4                      | 0,19                                 | 1,2                                |
| Caprylic acid (0.075% w/V)                   | 0,15                                  | 99,6                      | 0,22                                   | 98,3                       | 0,07                                 | 1,3                                | 0,27                                   | 99,4                       | 0,12                                 | 0,2                                | 0,28                                   | 98,5                       | 0,13                                 | 1,1                                |
| Linoleic acid (0.075% w/V)                   | 0,14                                  | 100,3                     | 0,23                                   | 98,1                       | 0,09                                 | 2,2                                | 0,32                                   | 99,3                       | 0,18                                 | 1,0                                | 0,28                                   | 99,4                       | 0,14                                 | 0,9                                |

\*NA – DATA NOT AVAILABLE

## CLAIMS

1. Pharmaceutical composition comprising temsirolimus and a lipophilic acid selected from the group consisting of caprylic, lipoic and linoleic acid.
2. Pharmaceutical composition according to claim 1, wherein concentration of lipophilic acid is from 0.001% to 1% w/v.
3. Pharmaceutical composition according to claim 1, wherein concentration of lipophilic acid is from 0.01% to 0.5% w/v.
4. Pharmaceutical composition according to claim 1, wherein concentration of lipophilic acid is from 0.01 to 0.1% w/v.
5. Pharmaceutical composition according to any one of claims 1 to 4, comprising an organic solvent selected from ethanol, propylene glycol, polyethylene glycol or combinations thereof; and citric acid as a chelating/stabilizing agent.
6. Pharmaceutical composition according to claim 5, further comprising a surfactant selected from polysorbate 20 or polysorbate 80.
7. Pharmaceutical composition according to any one of claims 1 to 5, wherein concentration of temsirolimus is from 20 to 30 mg/mL.
8. Pharmaceutical composition according to any one of claims 1 to 5, wherein concentration of temsirolimus is 25 mg/mL.
9. Pharmaceutical composition according to claim 1, comprising temsirolimus in a concentration of 25 mg/mL, dehydrated ethanol in a concentration of 39.5% w/V, propylene glycol in a concentration of 50.3% w/V, citric acid in a concentration 0.0025% w/V and a lipophilic acid selected from caprylic, lipoic, or linoleic acid in a concentration 0.075% w/V.
10. Pharmaceutical composition according to any of the preceding claims 1-9 for use in treatment of renal cell carcinoma and mantle cell lymphoma.
11. Two vials kit, comprising (i) a first vial comprising temsirolimus and a lipophilic acid selected from the group consisting of caprylic, lipoic and linoleic acid, and (ii) a second vial comprising a diluent.

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2017/051815

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|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>INV. A61K9/00      A61K47/12      A61K31/436      A61P35/00<br>ADD.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                            |                                                                                                                               |
| According to International Patent Classification (IPC) or to both national classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                            |                                                                                                                               |
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>A61K                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                            |                                                                                                                               |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                            |                                                                                                                               |
| Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)<br>EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, EMBASE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                            |                                                                                                                               |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                            |                                                                                                                               |
| Category*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Citation of document, with indication, where appropriate, of the relevant passages                                                                                         | Relevant to claim No.                                                                                                         |
| X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | US 2012/087959 A1 (KHOPADE AJAY JAYSINGH [IN] ET AL) 12 April 2012 (2012-04-12)                                                                                            | 1-11                                                                                                                          |
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| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | -----<br>US 2012/071349 A1 (QI HAIYAN [US])<br>22 March 2012 (2012-03-22)<br>the whole document<br>paragraphs [0134], [0155], [0156]<br>-----                              | 1                                                                                                                             |
| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | WO 2010/056754 A2 (OF THE UNIVERSITY OF TEXAS SYS [US]; SHARP ZELTON DAVE [US]; STRONG JO) 20 May 2010 (2010-05-20)<br>the whole document<br>claims 4,5,31<br>-----<br>-/- | 1                                                                                                                             |
| <div style="display: flex; justify-content: space-between;"> <span><input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.</span> <span><input checked="" type="checkbox"/> See patent family annex.</span> </div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                            |                                                                                                                               |
| <div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent 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> </div> <div style="flex: 1;"> <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 when the document is taken alone</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>"&amp;" document member of the same patent family</p> </div> </div> |                                                                                                                                                                            |                                                                                                                               |
| Date of the actual completion of the international search<br><br><div style="text-align: center; font-size: 1.2em;">21 March 2017</div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                            | Date of mailing of the international search report<br><br><div style="text-align: center; font-size: 1.2em;">27/03/2017</div> |
| Name and mailing address of the ISA/<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                            | Authorized officer<br><br><div style="text-align: center; font-size: 1.2em;">Hillers, Nathalie</div>                          |

## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2017/051815

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                        |                       |
|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category*                                            | Citation of document, with indication, where appropriate, of the relevant passages                                                                     | Relevant to claim No. |
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2017/051815

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