(19) DANMARK

(10) DK/EP 2854765 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *A 61 K 9/08 (2006.01)* *A 61 K 9/00 (2006.01)* *A 61 K 31/519 (2006.01)* *A 61 K 47/20 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2019-07-01**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2019-03-27**

(86) Europæisk ansøgning nr.: **13737527.5**

(86) Europæisk indleveringsdag: **2013-05-29**

(87) Den europæiske ansøgnings publiceringsdag: **2015-04-08**

(86) International ansøgning nr.: **DE2013000292**

(87) Internationalt publikationsnr.: **WO2013178214**

(30) Prioritet: **2012-05-31 DE 102012010774**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

(73) Patenthaver: **STADA ARZNEIMITTEL AG, Stadastrasse 2-18, 61118 Bad Vilbel, Tyskland**

(72) Opfinder: **SCHRIDDE, Edgar, Eibenstrasse 7c, 30855 Langenhagen, Tyskland**

(74) Fuldmægtig i Danmark: **NORDIC PATENT SERVICE A/S, Bredgade 30, 1260 København K, Danmark**

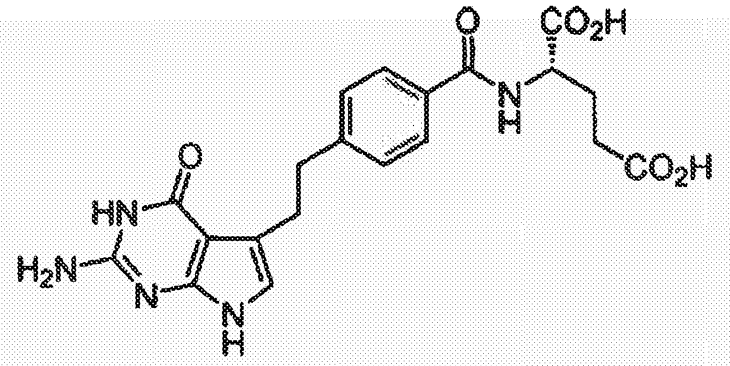
(54) Benævnelse: **FARMACEUTISK PEMETREXED-OPLØSNING**

(56) Fremdragne publikationer:
EP-B1- 1 265 612
KR-B1- 101 260 636

The present invention relates to a liquid pharmaceutical solution according to Claim 1, comprising

- a solvent;
- pemetrexed or a pharmaceutically acceptable salt thereof; and
- an antioxidant.

Pemetrexed is the INN (International Nonproprietary Name) for N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid. The structural formula of pemetrexed is as follows:



Pemetrexed is a medicament from the group of folic acid antagonists and is employed in the treatment of two types of lung cancer:

a) malignant pleural mesothelioma (a type of cancer of the visceral pleura, caused in general by exposure to asbestos), where it is employed together with cisplatin for patients having not previously received chemotherapy and for whom the cancer cannot be removed by surgery.

b) advanced "non-small-cell" lung cancer of the "non-squamous" type, where it is employed either together with cisplatin in previously untreated patients or on its own in patients having previously received medicinal

anti-cancer products. It can also be employed as a maintenance therapy in patients who have received platinum-based chemotherapy.

The activity of pemetrexed is based on the blocking of thymidylate synthase and of dihydrofolate reductase and of glycinamide ribonucleotide formyltransferase, thereby inhibiting the folate-dependent biosynthesis of thymidine and purine nucleotides (cf. Mutschler Arzneimittelwirkungen, Lehrbuch der Pharmakologie und Toxikologie, 9th edition, Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 2008, pp. 919-920; ISBN 978-3-8047-1952-1).

Pemetrexed is sold under the brand name Alimta® in the presentation form of a lyophilizate, in strengths of 100 mg and 500 mg. For administration, the sterile lyophilizate is first reconstituted with a 0.9% saline solution, to give a solution containing 25 mg/ml pemetrexed; this solution, with the recommended dose of 500 mg/m^2 body area, and after further dilution, diluted with 0.9% saline solution to 100 ml, is administered intravenously over the course of 10 minutes. The chemical and physical stability of the pemetrexed solution obtained by reconstitution of the lyophilizate, and that of the infusion solution prepared from it, is specified as being only 24 hours.

With regard to the safer handling of the cytostatic drug pemetrexed, it would be desirable to be able to give pemetrexed in the form of a solution. EP 1 265 612 B1 for that purpose proposes a pharmaceutical solution comprising a liquid solvent, pemetrexed or a pharmaceutically acceptable salt thereof, and an antioxidant selected from the group consisting of monothioglycerol, L-cysteine and thioglycolic acid. While the active ingredient in these solutions is stable towards oxidative breakdown, monothioglycerol and thioglycolic acid are highly objectionable toxicologically and accordingly are not monographed in the European Pharmacopoeia, while for cysteine it has been found that the solutions unfortunately only can be stored for a relatively short time. Indeed, owing to formation of particles, the solutions become cloudy relatively quickly and the deposition of a precipitate may be observed. The solutions are then unsuitable for intravenous injection.

It is an object of the present invention, therefore, to provide a pharmaceutical solution of the generic kind which is toxicologically unobjectionable, which exhibits relatively high stability and which can be stored for a relatively long time without clouding and certainly without depositing a precipitate.

This object is achieved, starting from a liquid pharmaceutical solution of the type specified at the outset, in that the antioxidant is selected from the group consisting of acetylcysteine and sodium 2-mercaptoethanesulfonate.

Surprisingly it has been found that a liquid pharmaceutical solution comprising a solvent containing, in solution, pemetrexed or a pharmaceutically acceptable salt thereof and also an antioxidant selected from the group consisting of acetylcysteine and sodium 2-mercaptoethanesulfonate is toxicologically unobjectionable, exhibits relatively high stability and can be stored for a relatively long time without clouding and certainly without depositing a precipitate.

The concept of "stability" understood in this context is that of the definition devised by the Arbeitsgemeinschaft für pharmazeutische Verfahrenstechnik [Consortium for pharmaceutical process technology] (APV), according to whose definition "stability" means the specification-compliant quality of the medicinal product up to the end of the term stipulated by the manufacturer. The quality of the medicinal product here is determined by the active ingredient content and purity, the sensorially perceptible, physicochemical and microbiological properties, where the active ingredient content is not to fall below 90% of the declared value up to the end of the term.

It has further been found that the solution according to the invention is distinguished by a relatively high sterilization stability. This ensures that the solution according to the invention can be made available in sterile form in accordance with the statutory provisions. Typical sterilization may be carried out, for example, at a temperature of 121°C over a period of 15 minutes in an

autoclave. Furthermore, the solution according to the invention is notable for relatively good patient compatibility.

The solution according to the invention is suitable for parenteral administration, as for example for intravenous administration. For parenteral administration, the solution according to the invention may be administered either immediately or else after further preparation. For immediate administration, the solution according to the invention may be injected intravenously, for example. Further preparation of the solution according to the invention may envisage, for example, the solution being adjusted to a desired active ingredient concentration, to a desired pH, etc., prior to parenteral administration, by means of a vehicle solution, such as a saline solution, for example.

In one preferred embodiment of the solution according to the invention, the solvent is selected from the group consisting of water, polyethylene glycol and ethanol, and from mixtures of two or more of the solvents mentioned. It has been possible to ascertain that the stated solvents or solvent mixtures have good dissolution properties for active ingredient and antioxidant, do not adversely affect the stability of the active ingredient, and do not promote the formation of particles in the solution.

It is particularly preferred in accordance with the invention for the solvent to be water.

According to a further preferred embodiment of the solution according to the invention, the pemetrexed is present in the solution dissolved in the form of its disodium salt. The pemetrexed disodium salt has relatively good solubility properties. Thus, for example, by means of the pemetrexed disodium salt, it is possible to provide solutions according to the invention which have a relatively high pemetrexed concentration, which exhibit high stability of the active ingredient and which have no tendency towards clouding or formation of precipitate. Such concentrates possess high patient acceptance and can be easily and safely handled by medical staff. For the administration of such concentrates,

they are simply diluted to the desired active ingredient concentration by means of a vehicle solution.

According to a further preferred embodiment of the solution according to the invention, the content of pemetrexed or of pharmaceutically acceptable salt thereof (based on the free pemetrexed) in the solution is 0.1 mg/ml to 100 mg/ml, more preferably 5 mg/ml to 80 mg/ml, even more preferably 10 mg/ml to 50 mg/ml and further preferably 20 mg/ml to 40 mg/ml. In the stated concentration ranges, the solution according to the invention exhibits only relatively low tendency to form particles and any associated clouding of the solution or formation of precipitate.

In a further preferred embodiment of the solution according to the invention, the content of pemetrexed or of pharmaceutically acceptable salt thereof (based on the free pemetrexed) in the solution is 10 mg/ml, 20 mg/ml, 25 mg/ml, 40 mg/ml or 50 mg/ml.

According to a further preferred embodiment of the solution according to the invention, the antioxidant is acetylcysteine. It has been possible to determine that acetylcysteine (or else N-acetyl-L-cysteine) in the solution according to the invention brings about relatively high stability on the part of the pemetrexed, and that a corresponding solution can be stored for a relatively long time without clouding and certainly without depositing a precipitate.

According to another preferred embodiment of the solution according to the invention, if acetylcysteine is present as antioxidant, the solution has a pH within a range from 7.5 to 11.5, more preferably a pH within a range from 8.0 to 10.5 and even more preferably a pH in a range from 8.5 to 10.5. It has been determined that the active ingredient in the solution according to the invention within the stated pH ranges is characterized by relatively high stability particularly with respect to oxidative degradation.

According to another preferred embodiment of the solution according to the invention, the antioxidant is sodium 2-mercaptoethanesulfonate. It has been possible to ascertain that sodium 2-mercaptoethanesulfonate in the solution according to the invention produces relatively high stability on the part of the pemetrexed and that a corresponding solution can be stored for a relatively long time without clouding and certainly without depositing a precipitate.

In another preferred embodiment of the solution according to the invention, if sodium 2-mercaptoethanesulfonate is present as antioxidant, the solution has a pH within a range from 7.5 to 11.5, more preferably a pH within a range from 8.0 to 10.5, even more preferably a pH in a range from 8.0 to 10.0 and further preferably a pH within a range from 8.3 to 9.3. It has been determined that the active ingredient in the solution according to the invention within the stated pH ranges is characterized by relatively high stability particularly with respect to oxidative degradation.

According to a further preferred embodiment of the solution according to the invention, the content of antioxidant in the solution is 0.1 mg/ml to 100 mg/ml, more preferably 0.5 mg/ml to 20 mg/ml, even more preferably 1.0 mg/ml to 5 mg/ml and further preferably 1 mg/ml to 3 mg/ml. It has been possible to determine that the active ingredient in the solution according to the invention within the stated concentration ranges is characterized by relatively high stability particularly with respect to oxidative degradation.

In accordance with a further preferred embodiment of the solution according to the invention, the solution further comprises one or more pharmaceutical excipients, selected from the group consisting of salts, carbohydrates for tonicity, chelating agents for complexation of heavy metals, acids for pH adjustment, bases for pH adjustment, buffer substances, preservatives for microbial preservation of the solution. The stated substances are well known to the competent skilled person from the prior art.

The present invention further relates to a pharmaceutical composition for preparation of the solution according to the invention, comprising pemetrexed or a pharmaceutically acceptable salt thereof and an antioxidant selected from the group consisting of acetylcysteine and sodium 2-mercaptoethanesulfonate. By means of the composition according to the invention, the solution according to the invention can easily be produced by the taking-up of the composition in a vehicle fluid.

In one preferred embodiment of the composition according to the invention, the composition is in solid form. It has been possible to determine that the active ingredient in the composition according to the invention in solid form is characterized by very high stability.

According to a further preferred embodiment of the composition according to the invention, the composition is a lyophilizate. This provides the facility for easy and complete reconstitution of the composition according to the invention to give the solution according to the invention.

According to a further preferred embodiment of the composition according to the invention, the composition further comprises a bulking agent. This provides the facility for being able to reconstitute the composition according to the invention easily and completely, over a relatively long period of time, to give the solution according to the invention. An example of a bulking agent preferred in accordance with the invention is mannitol.

The present invention further relates to an airtight-sealed container containing a pharmaceutical solution according to the invention or a pharmaceutical composition according to the invention. The solution or composition contained in the container of the invention is characterized by very high stability in relation to the active ingredient.

In one preferred embodiment of the airtight-sealed container of the invention, the container is formed of a material which is impermeable to oxygen.

According to a further preferred embodiment of the airtight-sealed container of the invention, the container is formed of glass.

According to a further preferred embodiment of the airtight-sealed container of the invention, the airtight-sealed container is a vial. Vials are known in the prior art. They are so-called injection vials, frequently in the form of puncture vials with plastic stoppers and a crimped aluminium cap, with the plastic stopper having its least thickness in the middle, for greater ease of puncturing.

A typical liquid pharmaceutical solution provided by the present invention is a solution comprising water as solvent, 10 mg/ml to 50 mg/ml pemetrexed disodium salt (based on the free pemetrexed) and 0.5 mg/ml to 20 mg/ml and preferably 1.0 mg/ml to 5 mg/ml acetylcysteine as antioxidant, the solution having a pH of 8.0 to 10.5 and preferably a pH of 8.5 to 10.5.

A further typical liquid pharmaceutical solution provided by the present invention is a solution comprising water as solvent, 10 mg/ml to 50 mg/ml pemetrexed disodium salt (based on the free pemetrexed) and 0.5 mg/ml to 20 mg/ml and preferably 1.0 mg/ml to 5 mg/ml sodium 2-mercaptoethanesulfonate as antioxidant, the solution having a pH of 8.0 to 10.0 and preferably a pH of 8.3 to 9.3.

The comparative and working examples below serve to elucidate the invention.

Comparative example:

Antioxidant in the form of 5.0 g of L-cysteine (Ph. Eur.) was added under aseptic conditions to 350 ml of injection-grade water as solvent and was dissolved therein to give a clear, first solution. Then 20.0 g of mannitol (Ph. Eur.) were added to the resulting first solution and dissolved therein to give a clear, second solution. The pH of the second solution was adjusted to a value of 8.5, using 1-molar sodium hydroxide solution and 1-molar hydrochloric acid.

The second solution with a pH of 8.5 was then admixed with 22.06 g of pemetrexed disodium salt (calculated as anhydrous substance; corresponding to 20.0 g of pemetrexed) and dissolved therein to give a clear, third solution. The pH of the third solution was adjusted to a value of 8.5, using 1-molar sodium hydroxide solution and 1-molar hydrochloric acid.

The resulting third solution with a pH of 8.5 was then made up to the final volume of 500 ml with injection-grade water as solvent, to give a fourth solution, and the pH of this solution was again adjusted, if necessary, to a value of 8.5 using 1-molar sodium hydroxide solution and 1-molar hydrochloric acid.

2.75 ml of the resulting fourth solution, after sterile filtration, were dispensed into an injection vial under aseptic conditions and provided with airtight sealing in the form of a stopper and crimped cap.

Table 1 below describes parameters of the pharmaceutical solution of the comparative example in the sealed injection vial:

Table 1:

Pemetrexed	40.00 mg/ml
Mannitol	40.00 mg/ml
L-cysteine	10.00 mg/ml
Sodium hydroxide	q.s.
Hydrogen chloride	q.s.
Injection-grade water	q.s. ad 1 ml
Injection vial	Type: 6R-DIN
Nominal volume	6.00 ml
Brim-full volume	10.00 ml
Dispensed volume	2.75 ml
Head space volume	7.25 ml
Oxygen content in the injection vial	21 vol%

Total amount of oxygen in the injection vial	67.93 µmol
Total amount of pemetrexed in the injection vial	110.00 mg
Total amount of L-cysteine in the injection vial	27.50 mg

The filled injection vial was stored at a temperature of 4°C over a period of two weeks and thereafter at a temperature of 40°C over a period of twelve weeks. After the storage, the contents of the injection vial were inspected. Significant precipitation could be ascertained.

Working example 1:

Antioxidant in the form of 5.0 g of acetylcysteine (Ph. Eur.) was added under aseptic conditions to 350 ml of injection-grade water as solvent and was dissolved therein to give a clear, first solution. Then 20.0 g of mannitol (Ph. Eur.) were added to the resulting first solution and dissolved therein to give a clear, second solution. The pH of the second solution was adjusted to a value of 8.5, using 1-molar sodium hydroxide solution and 1-molar hydrochloric acid.

The second solution with a pH of 8.5 was then admixed with 22.06 g of pemetrexed disodium salt (calculated as anhydrous substance; corresponding to 20.0 g of pemetrexed) and dissolved therein to give a clear, inventive solution. The pH of the inventive solution was adjusted to a value of 8.5, using 1-molar sodium hydroxide solution and 1-molar hydrochloric acid.

The resulting inventive solution with a pH of 8.5 was then made up to the final volume of 500 ml with injection-grade water as solvent, to give a further inventive solution, and the pH of this solution was again adjusted, if necessary, to a value of 8.5 using 1-molar sodium hydroxide solution and 1-molar hydrochloric acid.

2.75 ml of the resulting further inventive solution, after sterile filtration, were dispensed into an injection vial under aseptic conditions and provided with

airtight sealing in the form of a stopper and crimped cap, to give an airtight-sealed container of the invention.

Table 2 below describes parameters of the inventive pharmaceutical solution of working example 1 in the airtight-sealed container of the invention:

Table 2:

Pemetrexed	40.00 mg/ml
Mannitol	40.00 mg/ml
Acetylcysteine	10.00 mg/ml
Sodium hydroxide	q.s.
Hydrogen chloride	q.s.
Injection-grade water	q.s. ad 1 ml
Injection vial	Type: 6R-DIN
Nominal volume	6.00 ml
Brim-full volume	10.00 ml
Dispensed volume	2.75 ml
Head space volume	7.25 ml
Oxygen content in the injection vial	21 vol%
Total amount of oxygen in the injection vial	67.93 µmol
Total amount of pemetrexed in the injection vial	110.00 mg
Total amount of acetylcysteine in the injection vial	27.50 mg

The filled injection vial was stored at a temperature of 4°C over a period of two weeks and thereafter at a temperature of 40°C over a period of twelve weeks. After the storage, the contents of the injection vial were inspected. It was not possible to ascertain any clouding of the inventive solution or a precipitate therein.

Working example 2:

Antioxidant in the form of 5.0 g of sodium 2-mercaptoethanesulfonate (Ph. Eur.) was added under aseptic conditions to 350 ml of injection-grade water as solvent and was dissolved therein to give a clear, first solution. Then 20.0 g of mannitol (Ph. Eur.) were added to the resulting first solution and dissolved therein to give a clear, second solution. The pH of the second solution was adjusted to a value of 8.5, using 1-molar sodium hydroxide solution and 1-molar hydrochloric acid.

The second solution with a pH of 8.5 was then admixed with 22.06 g of pemetrexed disodium salt (calculated as anhydrous substance; corresponding to 20.0 g of pemetrexed) and dissolved therein to give a clear, inventive solution. The pH of the inventive solution was adjusted to a value of 8.5, using 1-molar sodium hydroxide solution and 1-molar hydrochloric acid.

The resulting inventive solution with a pH of 8.5 was then made up to the final volume of 500 ml with injection-grade water as solvent, to give a further inventive solution, and the pH of this solution was again adjusted, if necessary, to a value of 8.5 using 1-molar sodium hydroxide solution and 1-molar hydrochloric acid.

2.75 ml of the resulting further inventive solution, after sterile filtration, were dispensed into an injection vial under aseptic conditions and provided with airtight sealing in the form of a stopper and crimped cap, to give an airtight-sealed container of the invention.

Table 3 below describes parameters of the inventive pharmaceutical solution of working example 2 in the airtight-sealed container of the invention:

Table 3:

Pemetrexed	40.00 mg/ml
Mannitol	40.00 mg/ml
Sodium 2-mercaptoethanesulfonate	10.00 mg/ml
Sodium hydroxide	q.s.

Hydrogen chloride	q.s.
Injection-grade water	q.s. ad 1 ml
Injection vial	Type: 6R-DIN
Nominal volume	6.00 ml
Brim-full volume	10.00 ml
Dispensed volume	2.75 ml
Head space volume	7.25 ml
Oxygen content in the injection vial	21 vol%
Total amount of oxygen in the injection vial	67.93 µmol
Total amount of pemetrexed in the injection vial	110.00 mg
Total amount of sodium 2-mercaptoethanesulfonate in the injection vial	27.50 mg

The filled injection vial was stored at a temperature of 4°C over a period of two weeks and thereafter at a temperature of 40°C over a period of twelve weeks. After the storage, the contents of the injection vial were inspected. It was not possible to ascertain any clouding of the inventive solution or a precipitate therein.

Working examples 3 and 4:

Pemetrexed concentrates (25 mg/ml) for 100 mg and 500 mg infusion solutions

Working example 3: for aseptic preparation; 1 ml contains:

Pemetrexed disodium	27.57 mg (based on the anhydrous substance)
Mannitol	25.00 mg
Acetylcysteine	2.50 mg
Sodium hydroxide	0.682 mg-0.712 mg
Hydrogen chloride	0 mg-0.027 mg
Injection-grade water	962.22 mg
Nitrogen	

Solution density	1.018 g/ml

Working example 4: for standard operation (terminal sterilization in the final container); 1 ml contains:

Pemetrexed disodium	27.57 mg (based on the anhydrous substance)
Mannitol	25.00 mg
Acetylcysteine	3.00 mg
Sodium hydroxide	0.818 mg-0.854 mg
Hydrogen chloride	0 mg-0.032 mg
Injection-grade water	963.58 mg
Nitrogen	
Solution density	1.020 g/ml

For preparing the composition in accordance with working examples 3 and 4 in a 30-litre amount, 90% of the required amount of injection-grade water was charged (20°C to 25°C) to the mixing vessel and then purged with nitrogen gas for at least 10 minutes until the oxygen content was ≤ 0.5 mg/l.

The entire amount of acetylcysteine was introduced with stirring to the initial charge and stirred until fully dissolved. Thereafter the entire amount of mannitol was introduced with stirring into the initial charge and stirred until fully dissolved. The pH was adjusted using 10% (w/w) sodium hydroxide solution and, where necessary, using 10% (w/w) hydrochloric acid to a pH of 9.0 +/- 0.1.

Thereafter the entire amount of pemetrexed disodium was introduced with stirring into the resulting solution and stirred until fully dissolved. The pH was then adjusted using 10% (w/w) sodium hydroxide solution and, where necessary, using 10% (w/w) hydrochloric acid to a pH of 9.0 +/- 0.1.

The resulting mixture was made up to the desired final weight/volume with injection-grade water and stirred until fully dissolved. Thereafter the pH was

adjusted using 10% (w/w) sodium hydroxide solution and, where necessary, using 10% (w/w) hydrochloric acid to a pH of 9.0 +/- 0.1.

The resulting mixture was then purged with nitrogen gas for at least 10 minutes until the oxygen content was < 0.5 mg/l.

The mixture solution thus obtained was blanketed with nitrogen in the mixing vessel and tightly sealed. After in-process checking specimens had been taken, the solution was subjected to sterile filtration (20°C to 25°C) via sterilized filter membrane capsules with 0.2 µm pore size under aseptic conditions in a sterile storage tank which had been flushed with sterile nitrogen beforehand. The solution was dispensed (20°C to 25°C) under aseptic conditions at 4.35 ml in each case into heat-sterilized 3 ml special-shaped vials (Fiolax glass; 100 mg) or at 20.50 ml in each case into heat-sterilized 20R DIN vials (Fiolax glass; 500 mg).

During dispensing, preliminary gassing, filling gassing and after-gassing of the vials was carried out using sterile nitrogen. After mounting of the hollow stoppers and crimping of the vials, and after exterior washing, drying and leak testing (inverted storage; 12 hours), the vials were stored at 2°C to 8°C (working example 3) or subjected to terminal sterilization in the final container (121°C, 20 min) prior to storage at 2°C to 8°C (working example 4).

The storage of the vials for stability testing took place in the absence of light and at a controlled temperature of 5°C ± 3°C (long-term storage, at least 24 months), at 15°C ± 3°C (storage over a medium period, up to 12 months) and at 25°C ± 2°C/40% RH ± 5% RH (storage under accelerated conditions, up to 6 months).

Krav

1. Flydende farmaceutisk opløsning til parenteral administration, omfattende

- et opløsningsmiddel;
- pemetrexed eller et farmaceutisk acceptabelt salt heraf; og
- et antioxidationsmiddel,

kendetegnet ved, at antioxidationsmidlet er valgt fra gruppen af acetylcystein og 2-mercaptoethansulfonat-natrium.

2. Opløsning ifølge krav 1, **kendetegnet ved, at** opløsningsmidlet er valgt fra gruppen bestående af vand, polyethylenglycol og ethanol samt af blandinger af to eller flere af de nævnte opløsningsmidler.

3. Opløsning ifølge et af de foregående krav, **kendetegnet ved, at** pemetrexed i opløsningen er indeholdt opløst i form af sit dinatriumsalt.

4. Opløsning ifølge et af de foregående krav, **kendetegnet ved, at**opløsningens indhold af hhv. pemetrexed eller farmaceutisk acceptabelt salt heraf udgør 0,1 mg/ml til 100 mg/ml, foretrukket 5 mg/ml til 80 mg/ml, mere foretrukket 10 mg/ml til 50 mg/ml og endnu mere foretrukket 20 mg/ml til 40 mg/ml.

5. Opløsning ifølge et af de foregående krav, **kendetegnet ved, at** opløsningens indhold af hhv. pemetrexed eller farmaceutisk acceptabelt salt heraf udgør 10 mg/ml, 20 mg/ml, 25 mg/ml, 40 mg/ml eller 50 mg/ml.

6. Opløsning ifølge et af de foregående krav, **kendetegnet ved, at** antioxidationsmidlet er acetylcystein.

7. Opløsning ifølge krav 6, **kendetegnet ved, at** opløsningen har en pH-værdi i et område fra 7,5 til 11,5, foretrukket en pH-værdi i et område fra 8,0 til 10,5 og mere foretrukket en pH-værdi i et område fra 8,5 til 10,5.

8. Opløsning ifølge et af kravene 1 til 5, **kendetegnet ved, at** antioxidationsmidlet er 2-mercaptoethansulfonat-natrium.

9. Opløsning ifølge krav 8, **kendetegnet ved, at** opløsningen har en pH-værdi i et område fra 7,5 til 11,5, foretrukket en pH-værdi i et område fra 8,0 til 10,5, mere foretrukket en pH-værdi i et område fra 8,0 til 10,0 og endnu mere foretrukket en pH-værdi i et område fra 8,3 til 9,3.

10. Opløsning ifølge et af de foregående krav, **kendetegnet ved, at**opløsningens indhold af antioxidationsmiddel udgør 0,1 mg/ml til 100 mg/ml, foretrukket 0,5 mg/ml til 20 mg/ml, mere foretrukket 1,0 mg/ml til 5 mg/ml og endnu mere foretrukket 1 mg/ml til 3 mg/ml.

11. Opløsning ifølge et af de foregående krav, **kendetegnet ved, at** opløsningen desuden omfatter et eller flere farmaceutiske hjælpestoffer, valgt fra gruppen bestående af salte, kulhydrater til tonisering, chelatdannere til kompleksering af tungmetaller, syrer til indstilling af pH-værdi, baser til indstilling af pH-værdi, buffermidler, konserveringsmidler til mikrobiel konservering af opløsningen.

12. Farmaceutisk sammensætning til fremstilling af en opløsning ifølge et af de foregående krav, omfattende pemetrexed eller et farmaceutisk acceptabelt salt heraf samt et antioxidationsmiddel valgt fra gruppen bestående af acetylcystein og 2-mercaptoethansulfonat-natrium.

13. Sammensætning ifølge krav 12, **kendetegnet ved, at** sammensætningen foreligger i fast form.

14. Sammensætning ifølge et af de foregående krav, **kendetegnet ved, at** sammensætningen er et lyophilisat.

15. Hermetisk lukket beholder, indeholdende en farmaceutisk opløsning eller en farmaceutisk sammensætning ifølge et af de foregående krav.