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(54) Title: STABLE INJECTABLE SOLUTION OF PEMETREXED

(57) Abstract: The present invention relates to a stable, injectable solution of pemetrexed comprising pemetrexed or its pharmaceutically acceptable salt, water for injection, dissolved oxygen content in the range of 0 ppm to 0.2 ppm, wherein the solution is free of stabilizers or solubilizers and is contained in container sealed with a stopper, wherein the total impurities in the solution do not increase to more than 2.0 % by weight of pemetrexed when stored at room temperature for 1 year. The present invention further provides a process of preparing the stable, injectable solution of pemetrexed or its pharmaceutically acceptable salt having dissolved oxygen content in the range of 0 ppm to 0.2 ppm.



TITLE: STABLE INJECTABLE SOLUTION OF PEMETREXED**FIELD OF THE INVENTION**

The present invention relates to a stable, injectable solution of pemetrexed or its pharmaceutically acceptable salt having dissolved oxygen content in the range of 0 ppm to 0.2 ppm and process for preparation thereof.

BACKGROUND OF THE INVENTION

Pemetrexed, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-Glutamic acid (also known as pemetrexed diacid), is a potent inhibitor of several folate-requiring enzymes and is useful for the treatment of non-small cell lung cancer and mesothelioma. The currently marketed product of pemetrexed (Alimta[®]) is available in the form of lyophilized powder. This form of pharmaceutical product carries certain disadvantages such as the process of preparing these lyophilisates is complex and costly and powder reconstitution requires additional working steps which pose undesirable risks to personnel involved as well as risk of dilution errors. It is known that when pemetrexed is formulated as a concentrated solution which requires dilution before injection, pemetrexed has been stabilized by use of antioxidants. Examples of such products are pemetrexed 25 mg/ml concentrate for solution for infusion by Caduceus Pharma Ltd/Actavis UK Ltd. Another concentrated solution product by Eagle Pharmaceuticals which is awaiting USFDA approval, also takes help of cysteine hydrochloride, as an antioxidant. Although antioxidants are used to stabilize aqueous solution of pemetrexed which is highly susceptible to oxidation, these excipients such as anti-oxidants and other excipients like amines, amino acids, solubilizers, complexing agents etc. qualify as extraneous agents and must be avoided if possible. The health authorities all over the world are very concerned about the level of such extraneous agents in the pharmaceutical compositions, particularly those meant for injectable/parenteral use. It is all the more desirable to avoid these agents for compositions comprising anti-neoplastic drugs like pemetrexed, since patients undergoing chemotherapy, who are already facing severe side effects of the anti-neoplastic drug, cannot tolerate even a slight increase in the side effect which these extraneous agents may cause. Avoiding these excipients and still achieving an injectable aqueous solution of pemetrexed that have long term stability is a challenge and an unmet need. Few attempts have been made to avoid

the presence of an antioxidant while formulating pemetrexed concentrated sterile solutions, but with little success.

One such attempt is made and is described in PCT patent publication number WO2012-121523 (hereinafter referred to as the '523 application). It provides a method for preparing a pharmaceutical formulation in the form of an antioxidant-free solution for injection, the method of which comprises: (a) controlling a dissolved oxygen concentration in a solution for injection comprising pemetrexed or its salt by various degassing methods such as purging of the aqueous vehicle or solution and (b) filling a container for injection with the solution obtained from the step (a), in a glove box. WO'523 discusses conventional closed systems such as glove bag to control oxygen during filling operation. However, such processes which makes use of closed systems like globe box during filling involve manual handling operation and is not feasible for large-scale commercial manufacturing of a parenteral product under GMP environment in a pharmaceutical plant. Moreover, the compositions specified have dissolved oxygen levels upto 1 ppm and do not provide pemetrexed injectable solutions having dissolved oxygen levels of 0 to 0.2 ppm.

Thus, there is a need to develop a stable, injectable solution of pemetrexed or its pharmaceutically acceptable salts with the following characteristics:

- dissolved oxygen content from 0 to 0.2 ppm,
- free of extraneous agents like stabilizers (antioxidants) and solubilizers,
- extended storage stability,
- high assurance of sterility,
- amenable to manufacture commercially at large scale.

The present invention fulfills these needs and provides a stable, injectable, aqueous solution of pemetrexed or its pharmaceutically acceptable salts having the aforesaid desired characteristics. The present inventors have developed a commercially feasible process of preparing a stable, injectable solution of pemetrexed or its pharmaceutically acceptable salt, to provide sterile solution having dissolved oxygen levels of 0 to 0.2 ppm, the solution being free of extraneous agents like stabilizers (antioxidants) and solubilizers. The solution is stable and upon storage the total impurities are less than 2.0 % by weight upon long term storage.

SUMMARY OF THE INVENTION

The present invention provides a stable, injectable solution comprising pemetrexed or its pharmaceutically acceptable salt, water for injection, dissolved oxygen content in the range of 0 ppm to 0.2 ppm wherein the solution is free of stabilizers or solubilizers and is contained in container sealed with a stopper; wherein the total impurities in the solution do not increase to more than 2.0 % by weight of pemetrexed when stored at room temperature for 1 year.

The present invention further provides a process of preparing the stable, injectable solution of pemetrexed or its pharmaceutically acceptable salt having dissolved oxygen content in the range of 0 ppm to 0.2 ppm, the solution being free of stabilizers or solubilizers and is contained in container sealed with stopper.

BRIEF DESCRIPTION OF FIGURES

Figure 1 is a diagrammatic representation of a one leg stopper (Igloo stopper), having a flange portion '1', and a plug portion '2'. The plug portion has one radially disposed slot '3', and vent position nibs '4'.

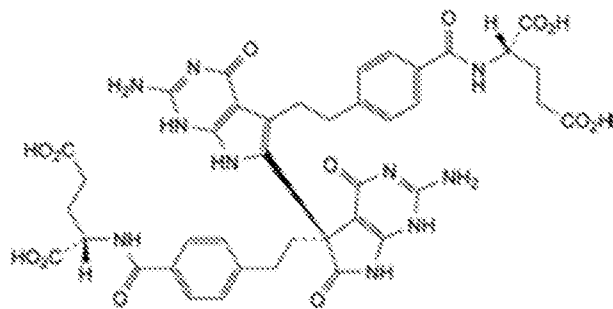
Figure 2 is a diagrammatic representation of a two leg stopper having a flange portion '1', and a plug portion '2'. The plug portion has diametrically disposed slot '3' and vent position nibs '4'.

Figure 3 is a diagrammatic representation of a three leg stopper having a flange portion '1', and a plug portion '2'. The plug portion has slots '3' and vent position nibs '4'.

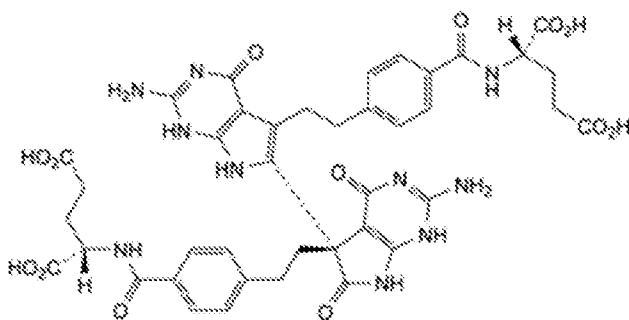
Figure 4 (A) and (B) are diagrammatic representation of non-slotted, conventional stopper as per prior art, having a flange portion '1', and a plug portion '2', wherein the plug portion is solid and does not have any slot.

DETAILED DESCRIPTION OF THE INVENTION

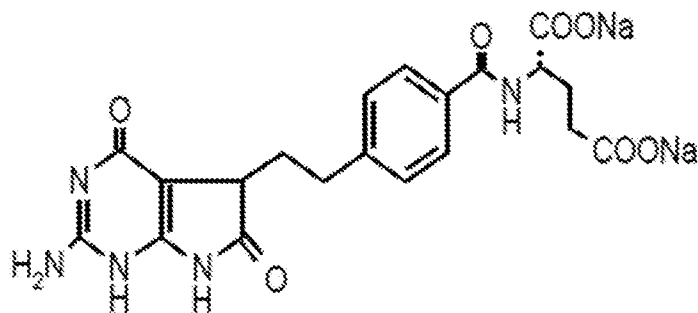
The known impurities include Impurity B, Impurity C and Impurity F. The Impurity B, as used herein in the specification is a degradation impurity of pemetrexed and is chemically named as (2S,2'S)-2,2'-[[(5R)-2,2'-diamino-4,4',6-trioxo-1,4,4',6,7,7'-hexahydro-1'H,5H-5,6'-bipyrrolo 2,3-d] pyrimidine-5,5'-diyl]bis(ethylene benzene-4,1-diylcarbonylimino)] dipentanedioic acid. The chemical structure of impurity B is as follows:



Impurity C, as used herein in the specification is another degradative impurity of pemetrexed and is chemically named as (2S,2'S)-2,2'-[[[(5S)-2,2'-diamino-4,4', 6-trioxo-1,4,4',6,7,7'-hexahydro-1'H,5H-5,6'-bipyrrolo[2,3-d]pyrimidine-5,5'-diyl]bis(ethylenebenzene-4,1-diylcarbonylimino)] dipentanedioic acid. The chemical structure of impurity C is as follows:



The Impurity F, as used herein is an oxidation impurity of pemetrexed and is chemically named as 4-{2-[(RS)-2-Amino-4,6 -dioxo-4, 5, 6, 7-tetrahydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl]ethyl}benzoyl)-L-glutamic acid disodium. It is generally known as ketopemetrexed and has the following chemical structure:



The total impurities, assay of drug, known impurities including Impurity B, Impurity C, Impurity F and any individual unknown impurity are analyzed by suitable techniques such as high performance liquid chromatography (HPLC). In one embodiment, HPLC technique is employed using mobile phase comprising a mixture of acetonitrile and ammonium formate buffer (having pH of about 3.5); the chromatographic column is C-8 ((150 x 4.6) mm, 3.5 μ) column and the chromatograms are recorded using UV spectroscopy.

The term 'stable' as used herein is intended to mean that the injectable solution comprising pemetrexed or its pharmaceutically acceptable salt according to the present invention when kept under storage at room temperature for at least one year, have total impurities of not more than 2.0 % by weight of pemetrexed. The total impurities do not increase to more than 2.0 % by weight of pemetrexed, preferably not more than 1.3 % by weight of pemetrexed, more preferably not more than 1.0 % by weight of pemetrexed, when the solution of the present invention is stored at room temperature (15°C-30°C) for at least one year.

The term 'total impurities' as used herein refers to summation of all known and unknown impurities of pemetrexed present in the injectable solution of the present invention, arising due to degradation of pemetrexed upon formulation or upon storage of the finished product. The total impurities are expressed as % by weight of pemetrexed i.e. % by weight of the labeled pemetrexed content.

The term 'stable' may also mean that the content of the individual known impurities as well as the highest unknown impurity in the solution upon storage are within the limits set by standard regulatory authorities like United States Pharmacopoeias or guidelines set by INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH).

For example, the content of individual impurity B and C is not more than 0.24 %, the limit for individual impurity F is not more than 0.6 % and highest unknown impurity is not more than 0.24 % upon storage of the solution at room temperature for at least one year.

Additionally, the injectable solution of the present invention may be said to be stable when the change in assay of pemetrexed during the manufacture of the finished dosage form prepared as

per the process described in the present invention, is within $\pm 2\%$ i.e. the assay does not vary beyond 98 % to 102 %. And also, the injectable solution is said to be stable when it is stored in the containers with stoppers for long term at room temperature, the pemetrexed assay remains within 90- 110 % of the labeled amount.

- 5 The phrase “injectable” or “injectable solution” as used herein implies that the solution meets the criteria’s of a parenteral product, particularly it is “sterile” which means that the solution has been brought to a state of sterility and the solution complies with the sterility requirements of the standard Pharmacopoeias like United States Pharmacopoeias (USP) until the end of the shelf life.

The phrase “free of stabilizers or solubilizers” as used herein means that the injectable solution
10 of the present invention is free of additional excipients such as antioxidants, amino acids, amines, complexing agents like cyclodextrins, co-solvents such as propylene glycol, polyethylene glycol, trimethylene glycol, butylene glycol and the like, oily excipients such as mineral oil. The injectable solution of the present invention is free of antioxidants including sulphite antioxidants such as sodium metabisulfite, sodium sulphite, sodium bisulphite or other
15 generally used antioxidants such as thioglycerol, ascorbic acid, lipoic acid, propyl gallate, etc. Suitably, the injectable solution of the present invention is free of amino acids or amines such as cysteine, lysine, methionine, diethanolamine, tromethamine, meglumine etc. Suitably, the injectable solution of pemetrexed is free of chelating agents such as disodium edetate, ethylenediamine tertaacetic acid, diethylenetriamine pentaacetic acid etc.

- 20 The term ‘approximately’ or ‘about’ as employed herein means $\pm 10\%$ of the stated value. Preferably the term ‘about’ when prefixed to pressure values for example ‘about X Torr’ implies a pressure of $X \pm 5\%$ Torr.

According to the present invention, the pharmaceutically acceptable salts of pemetrexed that may be used include, but are not limited to, sodium, disodium, potassium, lithium, calcium,
25 magnesium, aluminum, zinc, ammonium, trimethylammonium, triethylammonium, monoethanolammonium, triethanolammonium, tromethamine, pyridinium, substituted pyridinium, and the like. Although, any suitable pharmaceutically acceptable salts of pemetrexed may be used, preferably, the pharmaceutically acceptable salt is pemetrexed disodium heptahydrate.

The amount or concentration of pemetrexed or its pharmaceutically acceptable salts referred to in the present disclosure is expressed as amounts equivalent to pemetrexed free acid form. Pemetrexed or its pharmaceutically acceptable salt may be present in the solution of the present invention in an amount ranging from about 2.0 mg/ml to about 100.0 mg/ml, preferably 20.0 mg/ml to about 50.0 mg/ml, such as for example 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50 mg/ml, more preferably in an amount ranging from about 20 mg/ml to about 30 mg/ml. In one embodiment, pemetrexed disodium heptahydrate salt is used and it is present in an amount ranging from 20 mg/ml to 30 mg/ml, for example 25 mg/ml (expressed as amount equivalent to pemetrexed free acid form).

The dissolved oxygen content in the injectable solution according to the present invention is 0.2 parts per million (ppm) or less i.e. 0 to 0.2 parts per million, such as 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18 or 0.19 ppm. The dissolved oxygen content in the solution contained in the container may be determined by using dissolved oxygen meters such as marketed under the brand name Seven GOTM, Seven Duo Go ProTM (registered trademark -METTLER TOLEDO), or by using other methods known in the art such as Winkler-Azide titration method, method using diaphragm electrode (instrumental analysis) etc.

In one preferred embodiment, the dissolved oxygen concentration is measured using a dissolved oxygen meter (DO meter). Suitably, the container containing the solution of the present invention whose dissolved oxygen concentration is to be determined is opened in a closed chamber having nitrogen atmosphere (i.e. having oxygen concentration of less than 1 ppm) and the sensor of the DO meter is placed immediately in the sample (aqueous solution), followed by pressing of READ button to start a measurement. The display shows the reading of the sample in either the single channel or dual channel mode. The endpoint format blinks, indicating a measurement is in progress. As soon as the measurement is stable, the stability icon appears, and the result, i.e. value of dissolved oxygen concentration is recorded.

The head space oxygen present in the head space of the container after filling of the injectable solution of pemetrexed is 1.0 % v/v or less, preferably 0.5 % v/v or less, such as 0.4, 0.3, 0.2, 0.1 or 0% v/v, preferably 0.3 % v/v or less, more preferably 0.2 % v/v or less. The head space oxygen levels may be determined by methods known in the art such as measurement by Oxygen

Analyser /Electric sensor (Oxygen Analyzer, MODEL 905V, Quantek Instruments), Headspace Gas Chromatography, Electrochemical Analysers, Frequency Modulation Spectroscopic techniques, Fluorescence Quenching methods, Quadrupole MS analyzers and the like.

5 In one embodiment, the head space oxygen levels is determined by sensor based oxygen analyser, MODEL 905V, by Quantek Instruments. The Model 905V is a low volume sensor design. The oxygen sensor internal chamber through which sample gas flows has a very small volume of about 0.1 cc. The sensor is located inside the instrument case close to the front panel to minimize tubing length, and connects to the front panel fitting vial 1/32 ID (0.3 in.) inert tubing. The vent port of the sensor connects to a short piece of narrow-bore tubing for sample
10 exhaust and introduction of zero or calibration gases. The head space oxygen can be determined conveniently in short span of time following this method. Suitably, a needle is inserted onto the male luer fitting of the sample probe, which is used to puncture through the container/vial septum into the headspace of the vial. 1 to 2 cc of gas is pulled out from the vial head space using a plastic syringe connected through sensor and needle punctured in vial septum. This
15 allows for headspace gas to pass through the needle, tubing and into the sensor. A stable reading is obtained in about 15 seconds. The analysis time per sample is about 30 seconds.

The injectable solution according to the present invention may also comprise parenterally acceptable excipients such as, but not limited to, osmotic agents or tonicity adjusting agents, pH adjusting agents, buffers.

20 In one embodiment, the osmotic agent is used to adjust the tonicity of the solution and make the solution iso-osmolar to the parenteral/plasma fluids. The osmotic agent that may be used is selected from, but is not limited to sodium chloride, potassium chloride, mannitol, sorbitol, dextrose, sucrose and the like or mixtures thereof.

The injectable solution has a pH in the range of 6 to 11, preferably about 7.0 to 8.0, such as for
25 example 7.05, 7.10, 7.15, 7.20, 7.25, 7.30, 7.35, 7.40, 7.45, 7.50, 7.55, 7.60, 7.65, 7.70, 7.75, 7.80, 7.85, 7.90 or 7.95.

The pH of the solution may be adjusted in the desired range by use of a pH adjusting agent and if needed a buffer may be used to maintain the pH in the said range.

The pH adjusting and/or buffering agent that may be used include, but are not limited to sodium hydroxide, potassium hydroxide, hydrochloric acid, sulfuric acid, acetic acid, sodium acetate, tartaric acid, and the like and mixtures thereof. In one preferred embodiment, the pH adjusting agent is sodium hydroxide and hydrochloric acid. In one embodiment, the pH may be auto-
5 adjusted in the desired range by the ingredients present in the solution of the present invention.

The injectable solution of the present invention is contained in a container such as a vial, a bottle, a barrel of a pre-filled syringe and the like. In one embodiment the container may be made up of a rigid material such as glass, particularly, type I glass, that is borosilicate glass as defined in US Pharmacopeia chapter <660>. Non limiting examples of the container include a glass vial, a
10 glass bottle, or a glass barrel of a pre-filled syringe. The solution is filled into the container in different fill volumes ranging from 1 ml to 100 ml, such as approximately 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90 or 95 ml, preferably 1 ml to 50 ml.

In preferred embodiment, the container is a vial made up of type I glass.

15 In one preferred specific embodiment, the container is a glass vial having a “blowback” feature, which is a diametric indentation on the inside of the vial’s lip in the neck region, to mate with an indentation or protrusion on the stopper.

In one preferred embodiment, the fill volume is 4 ml and the vial capacity is 5 ml. In another preferred embodiment, the fill volume is 20 ml and the vial capacity is 20 ml. In another
20 preferred embodiment, the fill volume is 40 ml and the vial capacity is 50 ml.

There may be different styles of blowback features in vial neck. In one embodiment, the blowback feature is a US blowback style, which is a ring indentation in the plug-sealing surface of the vials.

In another embodiment, the blowback feature is a European style blowback, in which the vial
25 neck is widened below the sealing surface.

The blowback feature of the vial assists in holding the stopper over the neck of the container when in a partially or half stoppered position, i.e. it allows for the stopper to be securely and evenly seated in the mouth of the vial and help maintain the position of the partially seated

stopper by engaging with nibs or rings present on the stopper, thus preventing the stopper from “pop out” or drop-in” during the process. The blowback feature also assists in securing an air-tight fit with the stopper when fully stoppered and it prevents “pop-out” of the stopper before sealing.

- 5 In one embodiment, the container is stoppered with the help of a resilient closure or stopper.

Preferably, the resilient closure or stopper is a slotted stopper that has at least one partial or complete slot.

- 10 Particularly, the design of the stopper is such that it has a stopper plug portion that has at least one slot (plug portion is represented by marking ‘2’ in Figures 1, 2 and 3) and a flange portion (see marking ‘1’ in Figures 1, 2 and 3). The flange portion has greater diameter than the said plug portion.

In one embodiment, the stopper has one sided slot or radially disposed slot and is referred to as an Igloo stopper (Figure 1). The slotted stopper having one sided slot in the plug portion is represented by marking ‘3’ in Figure 1.

- 15 In another embodiment, the stopper has two sided slot or diametrically disposed slot and is referred to as two leg stopper (Figure 2). The two sided slot in the plug portion of the stopper is represented by marking ‘3’ in Figure 2.

- In another embodiment the stopper has three sided slot and is referred to as three leg stopper (Figure 3). The three sided slot in the plug portion of the stopper is represented by marking ‘3’ in
20 Figure 3.

In one or more embodiments, the slotted stopper may have plurality of slots in the stopper plug portion.

- 25 The slot/s present in the body portion allows for exchange of gases through them and permits communication of the outer environment with the interior of the container, when the stopper plug is partially inserted in the mouth of the container, i.e. when the stopper is in partially or half stoppered position. The rate of exchange of gases between the container headspace and outer environment through the slotted stoppers in partially or half stoppered position is optimum as

desired. The rate is slower as compared to the exchange rate when no slotted stopper is placed over the vial.

The flange portion of stopper is adapted to overlie the mouth of the container and assist in sealing said container when said plug portion of the slotted stopper is completely inserted in the mouth of the container.

In one embodiment when the stopper is in partially or half stoppered position, i.e. in the 'up' position, it allows a path for the exchange of gases through the container. When the stopper is completely pushed inside the mouth/neck of the container, i.e. in down or lowered position, the gap between the slotted stopper and container is closed i.e. container is fully stoppered. In this position no further exchange of gases or liquid can take place i.e. a fluid tight fit is produced at the interface of the stopper and the neck of the vial. In one embodiment, the stopper plug region may have protrusions also called as vent position nibs, projecting outwards (see marking '4' in figures 1, 2 & 3). These nibs assist in holding the stopper over the neck of the container when the said stopper is partially inserted in the mouth of the container. The blowback feature of the vial may further assist in holding the stopper over the neck of the container, i.e. it allows for the 2 or 3 legged stopper with vent position nibs to be securely and evenly seated in the mouth of the vial when in half stoppered position and prevent the stopper from "pop out" or drop-in" during the process.

Suitably, the stopper is made up of an elastomeric material. Such elastomeric material includes, but is not limited to, rubber or other polymeric or plastic material. In one embodiment, the stopper may be made up of bromobutyl or chlorobutyl based elastomeric rubber formulation.

In one preferred embodiment, the stopper is made up of rubber material that has an oxygen transmission rate of $100 \text{ cc/m}^2 \cdot 24 \text{ hour}$ or less.

In one or more embodiments, the fully stoppered container is further sealed. In one embodiment, a cap may be used to permanently seal the container/vial. The cap may be a flip-off metal crimp like cap, like an aluminum cap which can be crimped over the flange portion of the slotted stopper and vial neck, thus locking the stopper in place and permanently sealing the vial.

In one or more preferred embodiments, the container may be surrounded or packaged by a secondary container or packaging. The secondary container or packaging may suitably be a pouch or bag or film or overwrap or carton and the like that surrounds the container.

5 In one embodiment, the second container is a sealed film. In one embodiment, the second container provides protection to the solution of pemetrexed from light and it may be made up of a material having oxygen, light and moisture barrier properties. The material constituting secondary containers include, but are not limited to aluminum or various polymers and copolymers like polyamide, ethylene vinyl alcohol copolymer.

10 In one embodiment, the second packaging further comprises an oxygen scavenger. The oxygen scavenger may be placed in the space between the main container and the second container. In another preferred embodiment, the second container is a multilayered overwrap pouch, having one layer made up of oxygen scavenging material.

The stable, injectable solution of pemetrexed or its pharmaceutically acceptable salt can be obtained by certain processes that allow large-scale commercial manufacturing of the product
15 under Good Manufacturing Processes. Particularly, these processes allow manufacture of large batch size of the order of 100 litres to 2000 litres or more, at a fast rate. For instance, the stable injectable solution of pemetrexed contained in the containers having sizes varying from 1 ml to 100 ml may be manufactured by the process of the invention in large scale, at a fast rate of the order of 1000 to 10000 containers or more per hour. In one embodiment, containers having 5 ml
20 fill volume may be manufactured on a large scale of the order of 1,00,000 to 2,50,000 containers, at a rate of about 4000 to 10000 containers per hour. In another embodiment, containers having 5 ml fill volume may be manufactured at a large scale in the order of 50,000 to 1,50,000 containers, at a rate of about 2500 to 5000 containers per hour.

On the other hand, processes described in the prior art use machinery that operates manually for
25 eg. glove box to fill one container/vial at a time by manual operation. Such processes that involve manual unit operations can work only for small scale and is not suitable for large scale manufacturing. Further, it is important to note that the processes according to the present invention can be carried out at room temperature and therefore no additional equipment's are required to control temperatures for eg. freezing or high temperatures above room temperature.

The stable, injectable solution of the present invention can be obtained by processes in which the container are filled with the solution of pemetrexed and partially stoppered, and are placed into a closed chamber. The closed chamber is subjected to cycle of reducing air pressure by applying vacuum followed by release of the pressure by supply of inert gas. The air pressure is reduced to a pressure in the range of about 100 Torr to 560 Torr, preferably from about 100 Torr to 525 Torr.

The process by which the injectable solution of the present invention is obtained, does not include extreme reduction in pressure i.e. below 100 Torr for example 30 Torr or 50 Torr. When there is a drastic reduction in pressure, the inventors faced an undesirable problem of loss of volume of injectable solution. Without wishing to be bound by any theory, there occurs water loss due to reduction in pressure below 80-100 Torr. The loss or reduction in volume leads to increase in assay of pemetrexed in solution. The assay increases to more than 2.0 % and in some cases to more than 4.0 % which is beyond the desirable limit of not more than 2.0 %.

The step of reduction of pressure in optimum range followed by release of pressure by supply of inert gas is generally carried out at least two times after which the half stoppered filled containers are fully stoppered and then the sealed filled containers are subjected to sterilization by known techniques, preferably by autoclaving.

In one or more preferred embodiments, the process involves an additional step of holding the injectable solution filled in the container inside the closed chamber for a period of at least 1 hour. The step of holding is preferably carried out after the cycles of reducing air pressure and release of the pressure by supply of inert gas are over. Subsequent to step of holding the injectable solution filled in the container inside the closed chamber, the process may further involve step of reducing air pressure (to a particular pressure) and release of the pressure by supply of inert gas. The processing conditions and intermediate processing steps can vary. For instance, the process can be varied by varying the target reduced air pressure, the cycles or repetitions of the step of 'reducing air pressure followed by release of the pressure' or varying the time of holding the container in the chamber.

Suitably, the chamber in which the partially stoppered, filled container is placed is a closed chamber which has provisions to adjust the air pressure. It further has provision for inert gas supply. In one embodiment, such chamber is a lyophilizer wherein there are provisions of

reducing the air pressure to the magnitude of about 80 Torr to 560 Torr. It further has provisions to supply inert gas and achieve atmospheric pressure of about 760 Torr within the chamber using the inert gas. Suitably, the inert gas that may be used includes nitrogen, argon, neon, helium or mixtures thereof. Such treated filled containers are then subjected to sterilization by moist heat sterilization. This is carried out in an autoclave at a temperature of about 100⁰C to 125⁰C, for a period of time of 5 minute to 60 minutes.

In one embodiment, the closed chamber is connected to a vacuum pump, which may be used to reduce the air pressure inside the chamber to a desired value. In one embodiment, the closed chamber is connected to an inert gas supply, which can supply inert gas to the closed chamber and help increase the pressure of gas inside the closed chamber.

In one embodiment, there is a pressure sensor (pressure transmitter/Pirani gauge) which measures the pressure inside the chamber and help in monitoring and maintenance of specified pressure while performing various operations.

Various specific embodiments of the processes followed to obtain the stable injectable solution of pemetrexed of the present invention are described herein below:

In one embodiment, the present invention provides a stable, injectable solution comprising pemetrexed or its pharmaceutically acceptable salt, water for injection, dissolved oxygen content in the range of 0 ppm to 0.2 ppm, the solution being free of stabilizers or solubilizers and is contained in container sealed with stopper, obtained by a process comprising steps of:

- i. preparing a solution of pemetrexed or its pharmaceutically acceptable salt in water for injection and filling the solution in containers;
- ii. partially stoppering the containers of step (i) with slotted stoppers having at least one slot and placing them in a closed chamber;
- iii. applying reduced air pressure of about 100 Torr to 525 Torr to the closed chamber followed by release of the pressure to achieve atmospheric pressure of about 760 Torr by supplying an inert gas;
- iv. repeating step iii) at least two times;
- v. full stoppering and sealing the containers and subjecting them to moist heat sterilization.

In particular embodiments, the step of applying reduced pressure (iii) is repeated at least 2 times or more such that dissolved oxygen content of the solution is in the range of 0 to 0.2 ppm. The reduction in air pressure may be carried out by application of vacuum. Preferably, the step of reducing the pressure and supplying inert gas to the chamber to release the pressure (step iii) may be repeated 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 times.

The air pressure is reduced to a pressure in the range of about 100 Torr to 560 Torr, preferably from about 100 to 525 Torr, such as for example, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 276, 280, 285, 290, 300, 305, 310, 315, 320, 325, 330, 335, 340, 345, 350, 355, 360, 365, 370, 375, 380, 385, 390, 391, 395, 400, 405, 410, 415, 420, 425, 430, 435, 440, 445, 450, 455, 460, 465, 470, 475, 480, 485, 490, 495, 500, 505, 510, 515, 520 or 525 Torr. This is followed by release of the pressure by supplying an inert gas to achieve the normal/ initial atmospheric pressure in the chamber, which is about 760 Torr. The pressure achieved after release of the vacuum is generally about 760 Torr, but it may vary. For example the pressure may vary from 561 Torr to 860 Torr or more. The stoppers having at least one slot allows for exchange of gases when in half stoppered position and is an important feature to carry out the instant process.

In one embodiment step iii) is carried out 2 to 10 times, such as 2, 3, 4, 5, 6, 7, 8, 9 or 10 times. Preferably, the step iii) is carried out 2 to 8 times, more preferably 3 to 6 times.

In another embodiment, the step iii) is carried out at reduced air pressure of about 80 to 560 Torr, preferably at 100 to 525 Torr, more preferably at 100 to 275 Torr.

In one or more embodiments, the step iii) is repeated 2 to 10 times, at a reduced air pressure of 100 to 525 Torr.

In one or more embodiments, the step iii) is repeated 2 to 10 times, at a reduced air pressure of 100 to 275 Torr.

In one or more embodiments, the step iii) is repeated 4 to 10 times at a reduced air pressure of 275 to 390 Torr.

In one or more embodiments, the step iii) is repeated 8 to 12 times at a reduced pressure of 391 to 525 Torr.

In preferred embodiments, the present invention provides a stable, injectable solution comprising pemetrexed or its pharmaceutically acceptable salt, water for injection, dissolved oxygen content in the range of 0 ppm to 0.2 ppm and is contained in containers sealed with stopper, wherein the total impurities in the solution do not increase to more than 1.0 % by weight of pemetrexed when stored at room temperature for 1 year, wherein the injectable solution is prepared by a process which comprises the following steps:

- i. preparing a solution of pemetrexed or its pharmaceutically acceptable salt in water for injection and filling the solution in containers;
- ii. partially stoppering the containers of step (i) with slotted stoppers having at least one slot and placing them in a closed chamber;
- iii. applying a reduced air pressure of about 100 to 275 Torr to the closed chamber followed by release of the pressure to achieve atmospheric pressure of about 760 Torr by supplying an inert gas;
- iv. repeating step iii) at least two times;
- v. full stoppering and sealing the containers and subjecting them to moist heat sterilization.

In some preferred embodiments, the present invention provides a stable, injectable solution comprising pemetrexed or its pharmaceutically acceptable salt, water for injection, dissolved oxygen content in the range of 0 ppm to 0.2 ppm and is contained in containers sealed with stopper, wherein the total impurities in the solution do not increase to more than 2.0 % by weight of pemetrexed when stored at room temperature for 1 year, wherein the injectable solution is prepared by a process which comprises the following steps:

- i. preparing a solution of pemetrexed or its pharmaceutically acceptable salt in water for injection and filling the solution in containers;
- ii. partially stoppering the containers of step (i) with slotted stoppers having at least one slot and placing them in a closed chamber;
- iii. applying a reduced air pressure of about 276 to 390 Torr to the closed chamber followed by release of the pressure to achieve atmospheric pressure of about 760 Torr by supplying an inert gas;
- iv. repeating step iii) at least four times;
- v. full stoppering and sealing the containers and subjecting them to moist heat sterilization.

In some preferred embodiments, the present invention provides a stable, injectable solution comprising pemetrexed or its pharmaceutically acceptable salt, water for injection, dissolved oxygen content in the range of 0 ppm to 0.2 ppm and is contained in containers sealed with stopper, wherein the total impurities in the solution do not increase to more than 2.0 % by weight of pemetrexed when stored at room temperature for 1 year, wherein the injectable solution is prepared by a process which comprises the following steps:

- i. preparing a solution of pemetrexed or its pharmaceutically acceptable salt in water for injection and filling the solution in containers;
- ii. partially stoppering the containers of step (i) with slotted stoppers having at least one slot and placing them in a closed chamber;
- iii. applying a reduced air pressure of about 391 to 525 Torr to the closed chamber followed by release of the pressure to achieve atmospheric pressure of about 760 Torr by supplying an inert gas;
- iv. repeating step iii) at least eight times;
- v. full stoppering and sealing the containers and subjecting them to moist heat sterilization.

In one embodiment, there is provided a process for preparing a stable injectable solution of pemetrexed or its pharmaceutically acceptable salt, the process comprising the steps of:

- i. preparing a solution of pemetrexed or its pharmaceutically acceptable salt in water for injection and filling the solution in containers;
- ii. partially stoppering the containers of step (i) with slotted stoppers having at least one slot and placing them in a closed chamber;
- iii. applying reduced air pressure of about 100 Torr to 525 Torr to the closed chamber followed by release of the pressure to achieve atmospheric pressure of about 760 Torr by supplying an inert gas;
- iv. repeating step iii) at least two times;
- v. full stoppering and sealing the containers and subjecting them to moist heat sterilization.

In one particular embodiment, the step iii) is repeated two times at a reduced air pressure of 100 Torr. In one particular embodiment, the step iii) is repeated six times at a reduced air pressure of 100 Torr.

In one particular embodiment, the step iii) is repeated three times at a reduced air pressure of 225 Torr. In one particular embodiment, the step iii) is repeated four to five times at a reduced air pressure of 225 Torr.

5 In one particular embodiment, the step iii) is repeated nine times at a reduced air pressure of 525 Torr. In one particular embodiment, the step iii) is repeated ten times at a reduced air pressure of 525 Torr.

Preferably, in one or more embodiments, the process according to the present invention may further comprise a step of holding the container in the closed chamber after step (iii), for a period of at least 1 hour or more, and optionally repeating step (iii).

10 Preferably, in one or more embodiment, the process comprises a step of holding the container in the closed chamber after step (iv), for a period of at least 1 hour or more, followed by repeating step (iii) at least once.

Surprisingly, it was observed that when the process involves the step of holding the container in the closed chamber after step (iv), for a period of at least 1 hour or more, the dissolved oxygen
15 content of the solution in the range of 0 to 0.2 ppm is achieved by comparatively lesser repetitions of step (iii).

In one or more embodiments, the content of dissolved oxygen is relatively lower when the process involves the step of holding the container in the closed chamber as compared to when process does not involve the said step, although in both cases the dissolved oxygen content being
20 in the range of 0 to 0.2 ppm.

According to one embodiment, the stable injectable solution comprising pemetrexed or its pharmaceutically acceptable salt, water for injection, dissolved oxygen content in the range of 0 ppm to 0.2 ppm, solution being free of stabilizers or solubilizers and contained in container sealed with stopper, is obtained by a process which comprises the following steps:

- 25
- i. preparing a solution of pemetrexed or its pharmaceutically acceptable salt in water for injection and filling the solution in containers;
 - ii. partially stoppering the containers of step i) with slotted stopper having at least one slot and placing them in a closed chamber;

- iii. applying reduced air pressure of about 100 Torr to 560 Torr to the closed chamber followed by release of the pressure to achieve atmospheric pressure of about 760 Torr by supplying an inert gas;
- iv. repeating step iii) at least two times;
- 5 v. holding the container in the closed chamber after step iv), for a period of at least 1 hour and optionally repeating step iii);
- vi. full stoppering and sealing the containers and subjecting them to moist heat sterilization.

In one embodiment, there is provided a process for preparing a stable injectable solution of pemetrexed or its pharmaceutically acceptable salt, the process comprising the steps of:

- 10 i. preparing a solution of pemetrexed or its pharmaceutically acceptable salt in water for injection and filling the solution in containers;
- ii. partially stoppering the containers of step i) with slotted stoppers having at least one slot and placing them in a closed chamber;
- iii. applying reduced air pressure of about 100 Torr to 560 Torr to the closed chamber
- 15 followed by release of the pressure to achieve atmospheric pressure of about 760 Torr by supplying an inert gas;
- iv. repeating step iii) at least two times;
- v. holding the container in the closed chamber after step iv), for a period of at least 1 hour and optionally repeating step (iii).
- 20 vi. full stoppering the containers and subjecting them to moist heat sterilization.

The process may comprises steps which have varying combinations of - repetition of step (iii) at reduced air pressure of 100 to 560 Torr at least two times, holding the container in the closed chamber for a period of 1 hour or more, preferably about 2 - 20 hours and optionally repeating either of step (iii) or step (iii) to (v) for desired number of times. The step (iii) is repeated at least

25 2 times, preferably at least 3 times or more. In one embodiment step (iii) is carried out 2 to 10 times, such as 2, 3, 4, 5, 6, 7, 8 or 9 times.

Preferably, the step (iii) is carried out 2 to 8 times, more preferably 2 to 6 times.

In yet another embodiment, the step (iii) is carried out at reduced air pressure of about 100 to 560 Torr, preferably at 100 to 525 Torr, more preferably at 100 to 390 Torr.

In one or more embodiment, the step (v) is carried out by holding the container in the closed chamber having the inert gas for a period of at least 1 hour, preferably about 2 - 20 hours such as 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 hours.

In preferred embodiments, the process according to the present invention comprises steps of repetition of step iii) at reduced air pressure of 100 to 560 Torr for at least two times, holding the container in the closed chamber for a period of 1 hour or more, preferably about 2 - 20 hours and repeating step iii) at least once, at reduced air pressure of 100 to 560 Torr, wherein the air pressure in step iii) carried out after the holding step is same or different from the air pressure in step iii) carried out before the holding step.

In another preferred embodiments, the present invention provides a stable, injectable solution comprising pemetrexed or its pharmaceutically acceptable salt, water for injection, dissolved oxygen content in the range of 0 ppm to 0.2 ppm, the solution is free of stabilizers or solubilizers and is contained in container sealed with stopper, wherein the injectable solution is prepared by a process which comprises the following steps:

- i. preparing a solution of pemetrexed or its pharmaceutically acceptable salt in water for injection and filling the solution in containers;
- ii. partially stoppering the containers of step (i) with slotted stopper having at least one slot and placing them in a closed chamber;
- iii. applying reduced air pressure of about 100 Torr to 390 Torr to the closed chamber followed by release of the pressure to achieve atmospheric pressure of about 760 Torr by supplying an inert gas;
- iv. repeating step iii at least two times;
- v. holding the container in the closed chamber after step (iv), for a period of at least 1 hour
- vi. repeating step (iii) at least once;
- vii. full stoppering and sealing the containers and subjecting them to moist heat sterilization.

In some preferred embodiments, present invention provides a stable, injectable solution comprising pemetrexed or its pharmaceutically acceptable salt, water for injection, dissolved oxygen content in the range of 0 ppm to 0.2 ppm, the solution is free of stabilizers or solubilizers

and is contained in container sealed with stopper, wherein the injectable solution is prepared by a process which comprises the following steps:

- i. preparing a solution of pemetrexed or its pharmaceutically acceptable salt in water for injection and filling the solution in containers;
- 5 ii. partially stoppering the containers of step (i) with slotted stopper having at least one slot and placing them in a closed chamber;
- iii. applying reduced air pressure of about 390 Torr to 560 Torr to the closed chamber followed by release of the pressure to achieve atmospheric pressure of about 760 Torr by supplying an inert gas;
- 10 iv. repeating step iii) at least six times;
- v. holding the container in the closed chamber after step (iv), for a period of at least 1 hour
- vi. repeating step iii) at least once;
- vii. full stoppering and sealing the containers and subjecting them to moist heat sterilization.

In one or more specific embodiments, the process comprises repeating step iii) two times or more
15 at reduced air pressure of 100 Torr followed by holding the container in the closed chamber having the inert gas for a period of one hour or more and again repeating step iii) one time or more at reduced air pressure of 100 - 525 Torr.

In one or more specific embodiments, the process comprises repeating step iii) two times or more
20 at reduced air pressure of 100 Torr followed by step v) involving holding the container in the closed chamber having the inert gas for a period of 2 – 10 hours and again repeating step iii) at least once at reduced air pressure of 100 Torr.

In another specific embodiment, the process comprises repeating step iii) three times at reduced
air pressure of 100 Torr followed by holding the container in the closed chamber having the inert
gas for a period of seven hours and again repeating step iii) three times at reduced air pressure of
25 100 Torr.

In yet another one specific embodiment, the process comprises repeating step iii) two times or
more at reduced air pressure of 225 Torr followed by step v) involving holding the container in
the closed chamber having the inert gas for a period of 2-20 hours and repeating step iii) at least
once at a reduced air pressure of 100 to 525 Torr.

Further, in other embodiment, the process comprises repeating step iii) four times at reduced air pressure of 225 Torr followed by holding the container in the closed chamber having the inert gas for a period of about 2-20 hours.

5 In one specific embodiment, the process comprises repeating step iii) four times at reduced air pressure of 225 Torr followed by holding the container in the closed chamber having the inert gas for a period of about 6 - 20 hours and repeating step iii) three times at reduced air pressure of 225 Torr.

10 In one specific embodiment, the process comprises repeating step iii) three times at reduced air pressure of 225 Torr followed by holding the container in the closed chamber having the inert gas for a period of about 2-10 hours and repeating step iii) two times at reduced air pressure of 100 Torr.

15 In one specific embodiment, the process comprises repeating step iii) six times at reduced air pressure of 525 Torr followed by holding the container in the closed chamber having the inert gas for a period of about 2-20 hours and repeating step iii) at least once at reduced air pressure of 525 Torr.

In one specific embodiment, the process comprises repeating step iii) six times at reduced air pressure of 525 Torr followed by holding the container in the closed chamber having the inert gas for a period of about 3 hours and repeating step iii) three times at reduced air pressure of 525 Torr.

20 In one specific embodiment, the process comprises repeating step iii) three times at reduced air pressure of 225 Torr followed by holding the container in the closed chamber having the inert gas for a period of about 3 hours and repeating step iii) two times at reduced air pressure of 100 Torr.

25 In one specific embodiment, the process comprises repeating step iii) three times at reduced air pressure of 100 Torr followed by holding the container in the closed chamber having the inert gas for a period of three hours and repeating step iii) three times at reduced air pressure of 100 Torr, followed by holding the container for a period of three hours and again repeating step iii) three times at reduced air pressure of 100 Torr.

In one specific embodiment, the process comprises repeating step iii) three times at reduced air pressure of 225 Torr followed by holding the container in the closed chamber having the inert gas for a period of three hours and repeating step iii) three times at reduced air pressure of 225 Torr, followed by holding the container for a period of three hours and repeating step iii) three times at reduced air pressure of 225 Torr.

In some embodiments, the process comprises repetition of step iii) at reduced air pressure of 80 to 560 Torr two or more times, followed by cycles involving one hour hold in the closed chamber and repetition of step iii).

The injectable solution of pemetrexed of the present invention is found to be stable in that the total impurities in the solution do not increase to more than 2.0 % by weight of pemetrexed when stored at room temperature (15°C-30°C) for 1 year.

In preferred embodiments, the total impurities remains not more than 2.0 % by weight of pemetrexed when the aqueous solution (contained in the container) is stored at room temperature for a period of upto 2 years or longer.

In some preferred embodiments, the total impurities remains not more than 1.3 % by weight of pemetrexed when the aqueous solution (contained in the container) is stored at room temperature (15°C-30°C) for a period of 1 year or longer.

In more preferred embodiments, the total impurities remains not more than 1.0 % by weight of pemetrexed when the aqueous solution (contained in the container) is stored at room temperature (15°C-30°C) for a period of 1 year or longer.

Also, the content of the individual known impurities as well as highest unknown impurity in the injectable solution are within the limits set by standard regulatory authorities like United States Pharmacopoeias or guidelines set by INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH). For example, the injectable solution comprising pemetrexed according to the present invention is stable and have individual impurity B and C not more than 0.24 %, the individual impurity F not more than 0.6 % and highest unknown impurity not more than 0.24 %, when the solution of the present invention is stored at room temperature (15°C-30°C) for a period of at least 1 year.

Further, the change in assay of pemetrexed during the manufacture of the finished dosage form prepared as per the process described in the present invention is within $\pm 2\%$ i.e. the assay does not vary beyond 98 % to 102 %.

Further, the assay of pemetrexed remains well within the acceptance criteria of 90.0% -110.0%, preferably within the range of 95.0 % to 105.0 % of the label claim, upon storage of the solution at room temperature (15°C-30°C) for at least 1 year, preferably 1.5 years, more preferably 2 years. The injectable solution thus has long term storage stability, particularly at room temperature. On the contrary, the injectable solution of pemetrexed with dissolved oxygen content higher than 0.2 ppm, for eg. 0.32 ppm, when stored at room temperature for long term were found to be unstable. This is illustrated in the comparative examples described below. Thus, the present invention provided an injectable solution of pemetrexed having dissolved oxygen content in the range of 0 to 0.2 ppm, which is robust and stable. Not only the injectable solution is chemically stable, but can be obtained by processes that are feasible at a large scale and not limited to small scale using manual operations. Further advantageously, the process according to the present invention does not necessitate use of degassing methods such as purging of vehicle or pemetrexed solution with inert gas while preparing the solution.

In the context of this specification "comprising" is to be interpreted as "including".

Aspects of the invention comprising certain elements are also intended to extend to alternative embodiments "consisting" or "consisting essentially" of the relevant elements.

Where technically appropriate, embodiments of the invention may be combined.

Embodiments are described herein as comprising certain features/elements. The disclosure also extends to separate embodiments consisting or consisting essentially of said features/elements.

Technical references such as patents and applications are incorporated herein by reference.

Any embodiments specifically and explicitly recited herein may form the basis of a disclaimer either alone or in combination with one or more further embodiments.

Hereinafter, the invention will be more specifically described by way of Examples. The examples are not intended to limit the scope of the invention and are merely used as illustrations.

EXAMPLE 1

According to preferred embodiment of the present invention, the example illustrates stable, injectable, aqueous solution of pemetrexed in a glass container (vial).

Table 1: Details of injectable solution of pemetrexed

Ingredients	Amount
Pemetrexed disodium heptahydrate eq. to pemetrexed base	25 mg/ml
Sodium Chloride	9 mg/ml
Water for Injection	q.s.
Dissolved oxygen content	0 ppm – 0.2 ppm
pH of the solution	6.0 – 8.0

- 5 The solution was prepared as per the following process. Pemetrexed disodium heptahydrate and sodium chloride were dissolved in water for injection. The pH of the resulting solution was measured and when the pH was found to be outside the range of 6.0 to 8.0, it was adjusted in this range using a pH adjusting agent, such as sodium hydroxide and/or hydrochloric acid. The solution of pemetrexed so formed was filled in a glass container. The process was carried out at
- 10 room temperature (25-30°C). The glass container having the aqueous solution of pemetrexed was half stoppered or partially stoppered using a slotted stopper. The partially stoppered, filled glass container was then placed in a closed chamber in which air pressure can be adjusted. In different batches, the pressure of air in the chamber was reduced to specific pressure values in the range of 100 Torr to 525 Torr by applying vacuum. The pressure was released by supplying an inert gas
- 15 into the closed chamber until the pressure within the chamber reaches to the atmospheric pressure of 760 Torr. The step of reduction in pressure (application of vacuum) and supply of inert gas to the chamber was repeated for at least 2 times and/or for sufficient times until dissolved oxygen level (in the solution) of less than 0.2 ppm and headspace oxygen content of less than 0.5% was obtained. The filled glass containers were then fully stoppered by securely
- 20 placing the stopper over the glass containers. The glass containers were removed from the chamber and sealed using a flip-off aluminium crimping cap. The sealed glass containers were subjected to moist heat sterilization in an autoclave at a temperature of about 121°C for 15 minutes.

EXAMPLE 2-9

The stable, injectable solution of pemetrexed were prepared similar to example 1 but by varying the process parameters as given below in Table 2 and characterized by determining dissolved oxygen content and loss of volume of injectable solution measured in term of change in assay of pemetrexed.

Table 2: Details of Examples 2-9:

EXAMPLES Example	Process Parameters		Characterization	
	Pressure reduced from 760 Torr to X Torr X Torr	Number of repetitions #	Dissolved Oxygen (ppm)	Loss of volume of injectable solution measured in term of change in assay of pemetrexed *
Example 2	100	2	0.10	1.69
Example 3	160	2	0.06	1.93
Example 4	225	4	0.11	ND
Example 5	225	2	0.11	ND
Example 6	280	4	0.16	1.31
Example 7	380	4	0.13	1.23
Example 8	420	8	0.14	1.20
Example 9	525	8	0.19	1.63

*Change in Assay of Pemetrexed= Assay of pemetrexed in autoclaved solution – Assay of pemetrexed in solution filled in vial before half stoppering; ND- not determined.

Number of times pressure reduced from 760 Torr to (X) Torr and (X) Torr to 760 Torr

10 Stability Testing: The pemetrexed solution of Example 4 and 5 contained in glass vials, and stoppered with Igloo slotted stopper, were placed in a secondary packaging carton and then charged for stability testing at room temperature (25°C, 60% relative humidity) and at accelerated stability testing condition (40°C/75% relative humidity). The content of total impurities and Impurity F are given below in Table 3:

15 Table 3: Stability data of Example 4 and 5:

Example	Pressure reduced from 760 to X Torr	Number of repetitions (#)	Dissolved Oxygen (ppm)	Time Points (Months)	25°C, 60% relative humidity		40°C ± 2°C/75% RH ± 5%	
					% Total Impurities	Impurity F	% Total Impurities	Impurity F
Example 4	225	4	0.11	0 (Initial)	0.147	0.01	0.147	0.01
				2 M	0.246	0.04	0.669	0.12
Example 5	225	2	0.11	0 (Initial)	0.157	0.01	0.157	0.01
				2 M	0.277	0.05	0.729	0.13

Number of times pressure reduced from 760 Torr to (X) Torr and (X) Torr to 760 Torr

EXAMPLE 10

Table 4: Details of injectable solution of pemetrexed

Ingredients	Amount
Pemetrexed disodium heptahydrate eq. to pemetrexed base	25 mg/ml
Sodium Chloride	9 mg/ml
Water for Injection	q.s. to 1 ml
Dissolved oxygen content	0 ppm – 0.2 ppm
pH of the solution	6.0 – 8.0

Process: Pemetrexed disodium heptahydrate and sodium chloride were dissolved in water for injection. The pH of the resulting solution was measured and if the pH was found to be outside the range of 6.0 to 8.0, it was adjusted in this range using a pH adjusting agent, such as sodium hydroxide and/or hydrochloric acid. The solution of pemetrexed so formed was filled in glass container(s), i.e. glass vials. The glass vials having the aqueous solution of pemetrexed were half stoppered or partially stoppered using slotted igloo stopper. The partially stoppered, filled glass vials were then placed in a closed chamber maintained at room temperature (25-30°C). The pressure of air in the chamber was reduced to a pressure of about 225 Torr by applying vacuum. The pressure was released by supplying an inert gas into the closed chamber until the pressure within the chamber reaches to the atmospheric pressure of 760 Torr. The step of reduction in pressure (application of vacuum) and supply of inert gas to the chamber is repeated 4 times. Subsequent to this the vials were kept in the closed chamber for a period of about 20 hours hold, followed by repetition of step of reduction in pressure (to a pressure of 225 Torr) and supply of inert gas 3 times. The filled glass vials were then fully stoppered by securely placing the stopper over the glass vial. The glass vials were removed from the chamber and sealed using a flip-off aluminium crimping cap. The sealed glass vials were subjected to moist heat sterilization in an autoclave at a temperature of about 121°C for 15 minutes. The filled, sealed and autoclaved vials were covered in a secondary packaging (carton).

EXAMPLE 11-15

Examples 11-15 illustrates stable, injectable solution of pemetrexed prepared by following a process similar to one described in Example 10, but varying the target reduced air pressure in the chamber; varying the number of repetition's of the step of reduction in pressure and supply of inert gas to the chamber and varying the time of hold for which the vials were kept in the closed

chamber. The dissolved oxygen level and the change in assay of pemetrexed from initial were determined. The details are given below in Table 5.

Table 5: Details of Example 11-15 with process parameters and solution characteristics:

EXAMPLES	Process Parameters				Characterization	
	Pressure reduced from 760 Torr to X Torr X Torr	Number of repetitions (n) #	Hold Time After (n) repetitions	Number of repetitions after Hold Time	Dissolved Oxygen (ppm)	Loss of volume of injectable solution measured in term of change in assay of pemetrexed *
Example 11	225	2	7	3	0.0	ND
Example 12	380	4	2	1	0.18	0.72
Example 13	380	2	6	1	0.18	-1.32
Example 14	460	6	2	1	0.16	-1.38
Example 15	525	8	2	1	0.16	0.90

*Change in Assay of Pemetrexed = Assay of pemetrexed in autoclaved solution – Assay of pemetrexed in solution filled in vials before half stoppering.; ND- not determined.

Number of times pressure reduced from 760 Torr to (X) Torr and (X) Torr to 760 Torr

Stability testing: The autoclaved vials obtained according to Example 10 (filled, sealed, autoclaved vials covered in a carton) were subjected to storage stability testing at varying storage conditions, namely at room temperature (25°C, 60 % relative humidity), at refrigerated condition (temperature 2-8°C) and at accelerated stability testing condition (40°C/75% relative humidity). The assay of drug as well as content of known and unknown impurities was analyzed at different time points upon storage. The content of total impurities and individual impurities like the impurity B, impurity C, impurity F and highest unknown impurity were analyzed by HPLC or high performance liquid chromatography method. The observation at different storage conditions are given below in Table 6:

Table 6: Stability data for solution of example 10:

Storage Condition	Time Points (Months)	DO (ppm)	Assay %	% Impurity F (Keto-pemetrexed)	% Highest Unknown Impurity	% Total Impurities
Initial	0	0.03	99.6	0.03	0.02	0.16
2-8°C; (5°C ± 3°C)	12	0.11	99.02	0.04	0.03	0.21
25°C ± 2°C/ 60% RH ± 5%	12	0.15	99.02	0.08	0.05	0.40
40°C ± 2°C/ 75% RH ± 5%	6	0.2	101.5	0.06	0.04	0.48

DO- Dissolved Oxygen; RH- Relative Humidity

The stability results (Table 6) show that the injectable aqueous solution of pemetrexed according to the present invention (example 10), remains stable upon storage at room temperature ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $60\% \text{ RH} \pm 5\%$) and at $2-8^{\circ}\text{C}$ for extended periods of at least 1 year, wherein the total impurities were less than 1.0 % by weight of pemetrexed upon storage. Even when stored at accelerated stability condition of 40°C / 75% relative humidity for six months, the total impurities remained less than 1.0 % by weight of pemetrexed. Each of the individual impurities like impurity B, impurity C, Impurity F, the highest unknown impurity and other known impurities remained below 0.2 % by weight. The assay value of pemetrexed remained almost unchanged upon storage and the values are maintained within the range of 95%-105%. Further, it was observed that the aqueous solution of pemetrexed remained physically stable, such that no precipitation or crystallization or color change took place upon storage and the value of percentage transmittance of the solution remained greater than 95% upon storage.

COMPARATIVE EXAMPLE 1

A comparative injectable solution of pemetrexed having a dissolved oxygen content of 0.32 ppm was prepared as follows. Solution of pemetrexed disodium heptahydrate and sodium chloride having pH 6.0 - 8.0 was prepared in water for injection and was filled in glass container(s) (i.e. glass vials). The glass vials having the aqueous solution of pemetrexed were half stoppered or partially stoppered using slotted stopper and were placed in a closed chamber maintained at room temperature ($25-30^{\circ}\text{C}$). The pressure of air in the chamber was reduced to 225 Torr by applying vacuum followed by release of the pressure to 760 Torr by supplying an inert gas into the closed chamber. This step of reduction in pressure and release of the pressure by supply of inert gas to the chamber was carried out only once and was not repeated. The filled glass vials were then fully stoppered by securely placing the stopper over the glass vial. The glass vials were removed from the chamber and sealed using a flip-off aluminium crimping cap. The sealed glass vials were subjected to moist heat sterilization in an autoclave at a temperature of about 121°C for 15 minutes. The dissolved oxygen content in pemetrexed solution filled in said vial was determined and it was found to be 0.32 ppm.

Stability testing: The autoclaved vials were kept in carton and were kept on storage stability testing at accelerated stability testing condition ($40^{\circ}\text{C}/75\%$ relative humidity). The content of

total impurities and Impurity F was evaluated initially and upon 2 month storage and the results are presented below in Table 7.

Table 7: Processing parameters of comparative example 1 and stability testing observations

Example	Pressure Reduction to (Torr)	Number of repetitions (n)	Dissolved Oxygen (ppm)	Time Points (Months)	% Total Impurities	Impurity F
					40°C ± 2°C/75% RH ± 5%	
Comparative Example 1	225	1	0.32	0	0.190	0.02
				2	1.197	0.22

It was observed that the total impurities increased significantly (to more than 1.0 %) in just 2 months. Also the content of Impurity F increased significantly to more than 0.2 % in 2 months. In contrast to this, the content of total impurities as well as known Impurity F observed in case of the formulations prepared according to the present invention, which have dissolved oxygen content in the range of 0 ppm to 0.2 ppm were very low. {see for instance stability observations of Examples 4, 5 (Table 3) and Example 10 (Table 6)}. As is evident from the stability data given in Table 6 for formulation example 10, the content of total impurities was merely 0.48 % (i.e. less than 1.0 %) and Impurity F was merely 0.12 (i.e. less than 0.2%) after 6 months of storage at 40°C/75% relative humidity. So also, for formulation example 4 according to the present invention, the content of total impurities was merely 0.669 (i.e. less than 1.0 %) and the content of known Impurity F was merely 0.12 (i.e. less than 0.2%) after 2 months of storage at 40°C/75% relative humidity.

COMPARATIVE EXAMPLE 2

A comparative injectable solution of pemetrexed having a dissolved oxygen content of 1.45 ppm is prepared following prior art known processes which does not involve use of slotted stoppers and does not involve cycles of reduction and release of pressure. A non-slotted rubber stopper illustrated in figure 4 is used. The composition and process details are given below.

Table 8: Comparative Example 2 composition details:

Ingredients	Amount
Pemetrexed disodium heptahydrate eq. to pemetrexed base	25 mg/ml
Isotonicity agent (mannitol)	25 mg/ml
Water for Injection	q.s.
Dissolved oxygen content	1.45 ppm
pH of the solution (adjusted using sodium hydroxide/ hydrochloric acid)	6.0 – 8.0

Pemetrexed disodium heptahydrate and isotonicity agent (mannitol) were dissolved in water for injection previously purged with argon gas. The pH of the resulting solution was adjusted to 7.2 using a pH adjusting agent such as sodium hydroxide and/or hydrochloric acid. The solution of pemetrexed so formed was aseptically filtered. The filtered bulk solution was purged with inert Argon gas to lower dissolved oxygen level to less than 1 ppm. The solution (20 ml) was filled in a 20 ml glass vial. The head space of the vial was flushed with argon gas followed by stoppering the vial using non-slotted rubber stopper (Figure 4). The stoppered vials were sealed with flip off aluminium crimping cap. The sealed glass vials were terminally sterilized by subjecting to moist heat sterilization at a temperature of 121°C for 15 minutes in an autoclave. The filled, sealed and autoclaved vials were placed in a secondary packaging (carton).

Stability testing: The sealed autoclaved vials according to the comparative example 2, were subjected to storage stability testing at varying storage conditions, namely at room temperature (25°C, 60% relative humidity), at refrigerated condition (temperature 2-8°C) and at accelerated stability testing condition (40°C/75% relative humidity). The assay of drug, the content of highest unknown impurity and total impurities were analyzed at different storage time points using HPLC or high performance liquid chromatography method. The observations are given below in Table 9.

Table 9: Stability testing observations for solution of comparative example 2:

Storage Condition	Time Points (Months)	Stability parameters			
		DO (ppm)	Assay %	% Highest Unknown Impurity	% Total Impurities
	0 Initial	1.45	98.1	0.188	0.53
25°C ± 2°C/ 60% RH ± 5%	1	-	97.6	0.415	2.15
	6	-	92.8	0.576	2.19
40°C ± 2°C/ 75% RH ± 5%	1		95.3	0.579	2.36
	6	-	95.1	0.809	2.55

DO- Dissolved Oxygen; RH- Relative Humidity

The stability results show that the injectable aqueous solution of pemetrexed according to comparative example 2, having a dissolved content of > 0.2 ppm, when stored at room temperature ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\%$), or at accelerated stability condition of $40^{\circ}\text{C} /75\%$ relative humidity, shows formation of substantially higher % of total impurities and highest
5 unknown impurity. The total impurities goes beyond the desired limit of 2.0 % by weight of pemetrexed and the highest unknown impurity goes beyond the desired limit of 'not more than' 0.24 % by weight, merely after 1 months of storage at room temperature (see Table 9).The assay values also drops.

It is evident from the stability data of comparative examples 1 and 2 and working examples that
10 the dissolved oxygen content of 0 ppm to 0.2 ppm is critical in stabilization of aqueous solution of pemetrexed and providing long term stability.

CLAIMS:

1. A stable, injectable solution comprising pemetrexed or its pharmaceutically acceptable salt, water for injection, dissolved oxygen content in the range of 0 ppm to 0.2 ppm, wherein the solution is free of stabilizers or solubilisers and is contained in container
5 sealed with a stopper, wherein the total impurities in the solution do not increase to more than 2 % by weight of pemetrexed when stored at room temperature for 1 year.
2. A stable, injectable solution as claimed in claim 1, wherein the container is made up of a rigid material and the stopper is a slotted stopper that has at least one partial or complete slot.
- 10 3. A stable, injectable solution as claimed in claim 2, wherein the container is a glass vial and its design includes a diametric indentation on the inside of the vial's lip in the neck region.
4. A stable, injectable solution as claimed in claim 1, wherein the container is packaged by a secondary container selected from a pouch, bag, film, overwrap or carton.
- 15 5. A stable, injectable solution as claimed in claim 1 wherein the solution in the container is subjected to repetitions of step of reducing air pressure followed by release of the pressure by supply of an inert gas and then to moist heat sterilization.
6. A stable, injectable solution as claimed in claim 1, wherein the injectable solution is prepared by a process which comprises the following steps:
20
 - i. preparing an solution of pemetrexed or its pharmaceutically acceptable salt in water for injection and filling the solution in containers;
 - ii. partially stoppering the containers of step (i) with slotted stoppers having at least one slot and placing them in a closed chamber;
 - iii. applying a reduced air pressure of about 100 Torr to about 275 Torr to the closed
25 chamber followed by release of the pressure to achieve atmospheric pressure of about 760 Torr by supplying an inert gas;
 - iv. repeating step (iii) at least two times;

- v. full stoppering and sealing the containers and subjecting them to moist heat sterilization.

7. A stable, injectable solution as claimed in claim 1, wherein the injectable solution is prepared by a process which comprises the following steps:

- 5 i. preparing a solution of pemetrexed or its pharmaceutically acceptable salt in water for injection and filling the solution in containers;
- ii. partially stoppering the containers of step (i) with slotted stoppers having at least one slot and placing them in a closed chamber;
- 10 iii. applying a reduced air pressure of about 276 Torr to about 390 Torr to the closed chamber followed by release of the pressure to achieve atmospheric pressure of about 760 Torr by supplying an inert gas;
- iv. repeating step (iii) at least four times;
- v. full stoppering and sealing the containers and subjecting them to moist heat sterilization.

15 8. A stable, injectable solution as claimed in claim 1, wherein the injectable solution is prepared by a process which comprises the following steps:

- i. preparing a solution of pemetrexed or its pharmaceutically acceptable salt in water for injection and filling the solution in containers;
- 20 ii. partially stoppering the containers of step (i) with slotted stoppers having at least one slot and placing them in a closed chamber;
- iii. applying a reduced air pressure of about 391 Torr to about 525 Torr to the closed chamber followed by release of the pressure to achieve atmospheric pressure of about 760 Torr by supplying an inert gas;
- iv. repeating step (iii) at least eight times;
- 25 v. full stoppering and sealing the containers and subjecting them to moist heat sterilization.

9. A stable, injectable solution as claimed in claim 1, wherein the injectable solution is prepared by a process which comprises the following steps:

- 30 i. preparing a solution of pemetrexed or its pharmaceutically acceptable salt in water for injection and filling the solution in containers;

- ii. partially stoppering the containers of step (i) with slotted stopper having at least one slot and placing them in a closed chamber;
 - iii. applying reduced air pressure of about 100 Torr to about 390 Torr to the closed chamber followed by release of the pressure to achieve atmospheric pressure of about 760 Torr by supplying an inert gas;
 - iv. repeating step (iii) at least two times;
 - v. holding the container in the closed chamber after step (iv), for a period of at least 1 hour;
 - vi. repeating step (iii) at least once;
 - vii. full stoppering and sealing the containers and subjecting them to moist heat sterilization.
10. A stable, injectable solution as claimed in claim 1, wherein the injectable solution is prepared by a process which comprises the following steps:
- i. preparing a solution of pemetrexed or its pharmaceutically acceptable salt in water for injection and filling the solution in containers;
 - ii. partially stoppering the containers of step (i) with slotted stopper having at least one slot and placing them in a closed chamber;
 - iii. applying reduced air pressure of about 391 Torr to about 560 Torr to the closed chamber followed by release of the pressure to achieve atmospheric pressure of about 760 Torr by supplying an inert gas;
 - iv. repeating step (iii) at least six times;
 - v. holding the container in the closed chamber after step (iv), for a period of at least 1 hour;
 - vi. repeating step (iii) at least once;
 - vii. full stoppering and sealing the containers and subjecting them to moist heat sterilization.

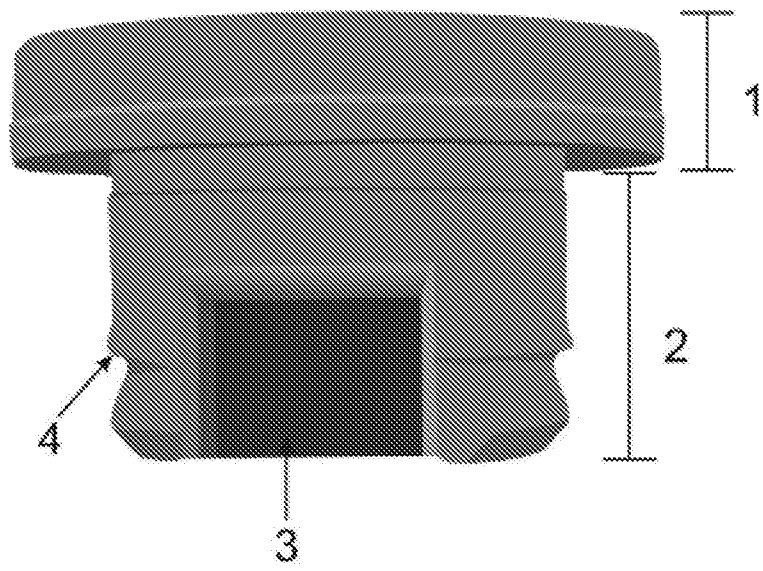


FIGURE 1

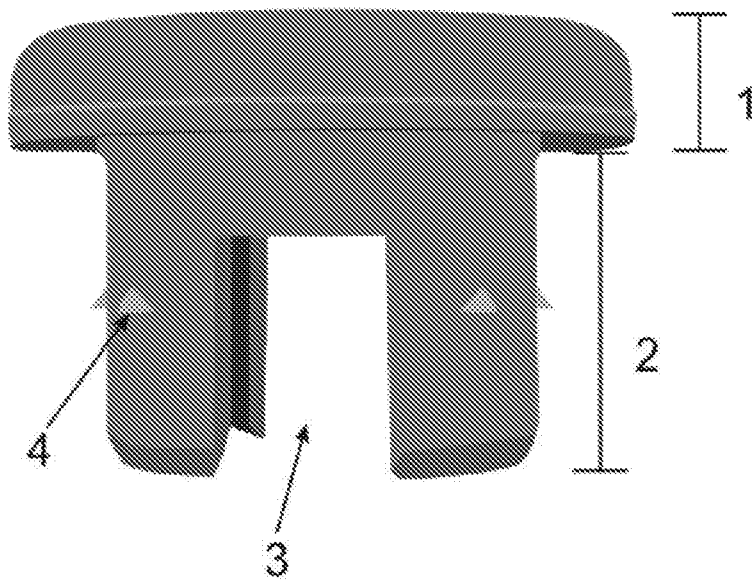


FIGURE 2

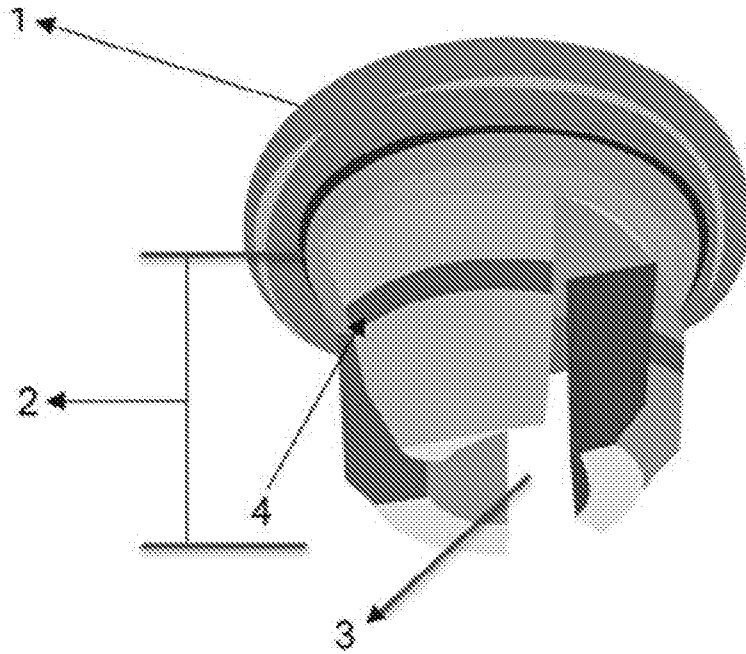


FIGURE 3

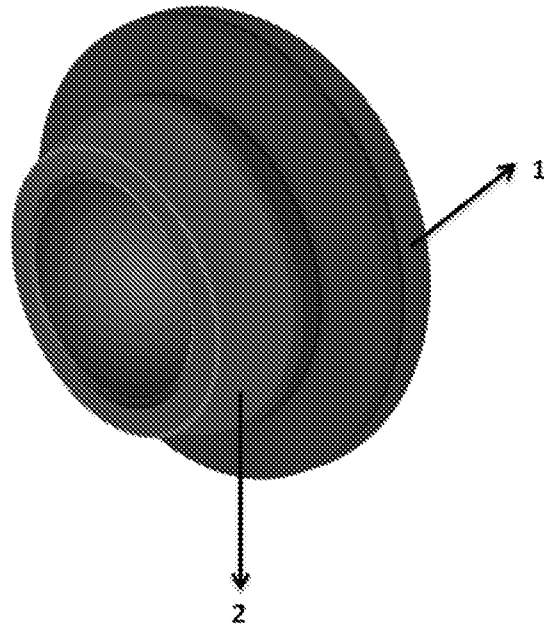


FIGURE 4(A)

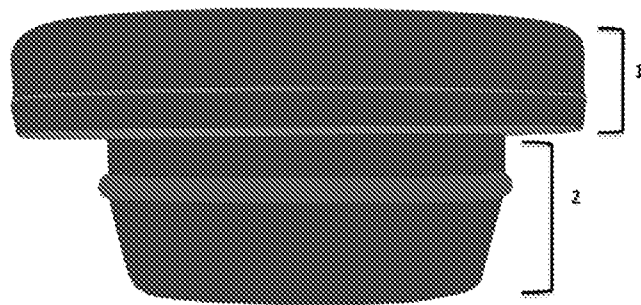


FIGURE 4 (B)

INTERNATIONAL SEARCH REPORT

International application No.

PCT / IN 2017/050264

A. CLASSIFICATION OF SUBJECT MATTER IPC: B65B 3/00 (2006.01); B65B 31/02 (2006.01); A61K 31/522 (2006.01) According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K, B65B 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) EPODOC, WPI		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012121523 A2 (KUHNIL PHARM. CO., LTD, SONG, TAE-HO, SEO, SUNG-KI, LEE, MASE) 13 September 2012 (13.09.2012) paragraphs [7], [8], [24]; claims	1-4
Y		6-10
X	WO 2013144814 A1 (FRESENIUS KABI ONCOLOGY LTD) 03 October 2013 (03.10.2013) page 6, lines 14-22; claims 1-5,14	1-4
Y		6-10
Y	WO 2012016301 A1 (HOSPIRA AUSTRALIA PTY LTD, WENSLEY, EMMA J, KNILL, ANDREW MALCOLM, SUENDERMANN, JOHN FREDRIC) 09 February 2012 (09.02.2012) claims 1-2,19,20,23,106-108; figure 2B	6-10
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "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) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "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 "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 "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 "&" document member of the same patent family		
Date of the actual completion of the international search 20 September 2017 (20.09.2017)		Date of mailing of the international search report 25 September 2017 (25.09.2017)
Name and mailing address of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. +43 / 1 / 534 24-535		Authorized officer KRENN M. Telephone No. +43 / 1 / 534 24-435

INTERNATIONAL SEARCH REPORT

International application No.

PCT / IN 2017/050264

Box No. II		Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)
<p>This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:</p> <p>1. ☐ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:</p> <p>2. ☒ Claims Nos.: 5 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:</p> <p>Claim 5 represents a conventional product claim which is however illicitly characterized by process features.</p> <p>3. ☐ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).</p>		
Box No. III		Observations where unity of invention is lacking (Continuation of item 3 of first sheet)
<p>This International Searching Authority found multiple inventions in this international application, as follows:</p> <p>1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.</p> <p>2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.</p> <p>3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:</p> <p>4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:</p> <p>Remark on Protest</p> <p>☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.</p> <p>☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.</p> <p>☐ No protest accompanied the payment of additional search fees.</p>		

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT / IN 2017/050264

Patent document cited in search report			Patent family member(s)			Publication date
WO	A2	2012121523	CN	A	103476397	2013-12-25
			WO	A2	2012121523	2012-09-13
			TW	A	201300139	2013-01-01
			KR	B1	101069128	2011-09-30
WO	A1	2013144814	US	A1	2015073000	2015-03-12
			IN	A	912DE2012	2015-09-11
			WO	A1	2013144814	2013-10-03
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			CN	A	106966036	2017-07-21
			NZ	A	606713	2015-04-24
			CN	A	103770967	2014-05-07
			SG	A1	187766	2013-03-28
			EP	A1	3208202	2017-08-23
			SG	A	10201506066X	2015-09-29
			MX	A	2013001454	2013-06-05
			KR	A	20130103489	2013-09-23
			EP	A1	2601105	2013-06-12
			WO	A1	2012016301	2012-02-09
			CA	A1	2807601	2012-02-09
			AU	A1	2016208368	2016-08-18
			AU	A1	2011286179	2013-02-28
			JP	A	2013532566	2013-08-19
			US	A1	2013205719	2013-08-15