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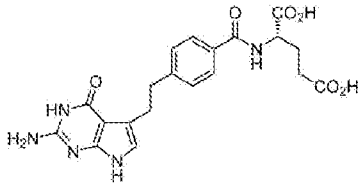
(54) Title: STABLE LIQUID FORMULATIONS OF PEMETREXED

(57) Abstract: The present invention provides a stable ready to use liquid parenteral formulations of Pemetrexed or a pharmaceutically acceptable salt thereof. Further this invention also describes process of preparing such formulations.

STABLE LIQUID FORMULATIONS OF PEMETREXED

Background of the Invention

Pemetrexed belongs to the class of chemotherapy drugs called folate antimetabolites and is used in the treatment of malignant pleural mesothelioma and non-small cell lung cancer. Pemetrexed has the chemical name N-{4-[2-(2-Amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamic acid. The chemical structure is represented below:



Pemetrexed was approved by the Food and Drug Administration (FDA) in February 2004 under the brand name Alimta® for the treatment of malignant pleural mesothelioma in combination with cisplatin. Alimta® is available as sterile lyophilized powder for intravenous infusion, in single-dose vials containing 100 mg or 500 mg equivalent Pemetrexed. In July 2004, the drug was approved by the FDA as a second line agent for the initial treatment of advanced or metastatic non-small cell lung cancer.

Pemetrexed was first disclosed in US patent No. 5,344,932. Crystalline forms of Pemetrexed disodium are described in WO/2001/014379.

US patent 7,138,521 to Chelius et al., describes a stable crystalline heptahydrate form of Pemetrexed having a characteristic X-ray diffraction pattern.

WO/2008/124485 to Raghavendracharyulu et al., discloses various crystalline forms of Pemetrexed diacid and amorphous Pemetrexed disodium.

EP 1943252 to Jonathan et al., discloses a process for the preparation of a lyophilized di-base-addition salt of Pemetrexed, in particular, a Pemetrexed disodium salt, directly from Pemetrexed diacid or an acid or base addition salt thereof.

Pemetrexed is available under the brand name Alimta® as sterile lyophilized powder for intravenous infusion, in single-dose vials. However, reconstitution of the lyophilized product is clinically inconvenient and also lyophilization process is time consuming and often incurs significant expense. Hence, there is a strong need to develop alternate formulations of Pemetrexed.

The inventors have developed ready to use liquid formulation of Pemetrexed which overcomes the disadvantages of the formulations reported in prior art.

Summary of the invention

One aspect of the invention provides stable ready to use liquid parenteral pharmaceutical formulation comprising of Pemetrexed diacid, amino acids and water.

Yet another aspect of the invention provides stable ready to use liquid parenteral pharmaceutical formulation comprising of Pemetrexed diacid, one or more aminoacids, water and optionally other pharmaceutically acceptable adjuvants.

Detailed description of the invention

This invention relates to ready to use liquid parenteral pharmaceutical formulations of Pemetrexed, wherein Pemetrexed diacid is used as the active agent.

As used herein, "ready to use Pemetrexed" formulations refers to formulations that contain Pemetrexed in dissolved or solubilized form and are to be intended to be used as such or upon further dilution in intravenous diluents.

The term "about", as used herein, refers to any value which lies within the range defined by a variation of up to ±15% of the value.

In one embodiment, ready to use liquid parenteral pharmaceutical formulations of Pemetrexed comprise:

i. Pemetrexed Diacid
ii. One or more amino acids selected from glycine, histidine, arginine, lysine or salts thereof.
iii. One or more solvents.
iv. Optionally other pharmaceutically acceptable adjuvants.

In yet another embodiment, ready to use liquid parenteral pharmaceutical formulations of Pemetrexed comprise:

i. Pemetrexed Diacid
ii. One or more amino acids selected from glycine, histidine, arginine, lysine or salts thereof.
iii. Water.
iv. Optionally, saccharides/sugars selected from sucrose, mannitol, glucose, fructose and chelating agents selected from DOTA, DTPA and EDTA.

In one of the preferred embodiment, ready to use liquid parenteral pharmaceutical formulations of Pemetrexed comprise:

i. Pemetrexed Diacid
ii. One or more amino acids selected from glycine, histidine, arginine, lysine or salts thereof.
iii. Water

wherein the percentage of amino acids in the formulation ranges from about 1% to 30% w/w, based on the total weight of the formulation.

Suitable amino acids according to the present invention include, but not limited to glycine, histidine, arginine, lysine, methionine, proline, glutamic acid or salts thereof. Percentage of amino acids in the formulation ranges from about 1% to 30% w/w, based on the total weight of the formulation. Preferably the percentage of amino acids in the formulation ranges from about 1% to 20% w/w, based on the total weight of the formulation.

The pharmaceutical compositions of the present invention may comprise one or more saccharides/sugars such as, but not limited to sucrose, glucose, xylose, galactose, fructose, lactose, maltose, mannitol, xylitol, raffinose, dextrose, trehalose and the like. Of these the preferred saccharides are sucrose and mannitol.

The pharmaceutical compositions of the present invention may comprise chelating agents such as, but not limited to DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DTPA (diethylenetriaminepentaacetic acid), EDTA (Ethylenediamine tetraacetic acid), DOTRP(tetraethyleneglycol-1,5,9-triazacyclododecane-N,N',N",-tris(methylenephosphonic acid), EGTA (ethylene glycol-bis(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid), HEDTA (N-(hydroxyethyl) ethylenediaminetriacetic acid) and the like.

The pharmaceutical compositions of the present invention may optionally contain one or more anti-oxidants, preservatives, buffers, pH adjusting agents, stabilizers and the like.

Pemetrexed diacid is practically insoluble in water. The inventors have surprisingly found that the presence of amino acids in the formulation yields a stable aqueous liquid formulation of Pemetrexed overcoming the disadvantages associated with prior art.

Solubility studies of Pemetrexed were performed with various amino acids alone and in combination with other excipients in water at 25°C to check the solubility. All the below combinations were found to be clear. The data is summarized in Table 1.

Table 1: Solubility study of Pemetrexed diacid in various amino acids

Quantities in mg						Qty in ml	Description
Pemetrexed diacid	**Histidine**	**Arginine**	**Glycine**	**Ammonium acetate**	**Sucrose**	**Water**	
100	100	-	100	100	-	2.5	Clear
100	100	-	200	100	-	2.5	Clear
100	100	-	100	100	50	2.5	Clear
100	100	-	200	100	50	2.5	Clear
100	100	-	100	-	-	2.5	Clear
100	100	-	100	-	50	2.5	Clear
100	100	-	50	100	-	2.5	Clear
100	100	-	50	100	50	2.5	Clear
50	-	116	-	-	-	1	Clear
50	-	133	-	-	-	1	Clear
50	-	166	-	-	-	1	Clear

Pemetrexed formulations prepared according to the invention were tested for stability under accelerated conditions. Surprisingly no significant increase in total impurities was observed even at the accelerated conditions.

Table 2: Stability data for the product obtained from Example 1

Condition	**2-8°C**			**25°C/60%RH**			**30°C/65%RH**			**40°C/75%RH**		
	2Wk	1M	2M	2Wk	1M	2M	2Wk	1M	2M	2Wk	1M	2M
Total Impurities	0.31	0.39	0.40	0.37	0.34	0.51	0.35	0.35	0.56	0.38	0.44	0.86
Assay (%)	99.6	99.2	99.4	100	99.3	99.7	101	100.3	99.2	101	99.1	99.0
pH	9.38	9.71	9.78	9.43	9.7	9.75	9.50	9.80	9.74	9.55	9.76	9.75

Table 3: Stability data for the product obtained from Example 4

Condition	Initial	1M	2M	1M	2M	1M	2M	1M	2M
		2-8°C		25°C/60%RH		30°C/65%RH		40°C/75%RH	
pH	6.10	6.15	6.01	6.13	6.03	6.12	6.02	6.09	6.04
Osmolality	454	449	439	450	443	445	443	451	442
Total Impurities	0.27	0.30	0.35	0.28	0.37	0.38	0.42	0.62	0.66

The invention further relates to a process of preparing ready to use liquid parenteral pharmaceutical formulation of Pemetrexed diacid comprising

(i) Addition of amino acid(s) and saccharide (if required), to the water.

(ii) Addition of the chelating agent (if required)

(iii) Addition of the Pemetrexed diacid to the above solution followed by stirring till a clear solution is obtained.

(iv) Addition of amino acid(s) (if required) to adjust the pH of the solution.

(v) Filtering and filling of the solution in suitable container or vials followed by stoppering and sealing of the vials.

The following examples further describe certain specific aspects and embodiments of the present invention and demonstrate the practice and advantages thereof. It is to be understood that the examples are given by way of illustration only and are not intended to limit the scope of the invention in any manner.

Example 1

S.No	**Ingredients**	**Qty/vial (mg)**
1	Pemetrexed diacid	100
2	Arginine	200-300
3	Sucrose	30-80
4	DOTA	0.5-5
5	Water for injection	1.6mL

Manufacturing process:

Water for injection was taken in a compounding vessel and arginine was added and stirred, followed by the addition of sucrose. DOTA was added to the above solution and stirred. Pemetrexed Diacid was added and stirred till a clear solution was obtained. The solution was filtered, followed by stoppering and sealing of the vials.

Pemetrexed formulation prepared according to the invention was tested for stability at various conditions. The stability data of the invention formulation is summarized in Table 2. The product is tested for stability by storing at various conditions like 2-8°C, 25°C±60%RH, 30°C±65%RH and 40°C±75%RH for a period of 2 months.

Example 2

S.No	Ingredients	Qty/Vial	%w/w	Qty/Vial	%w/w
1	Pemetrexed diacid	60.00mg	2.2	60.00mg	2.2
2	D-Histidine	50.00 mg	1.8	50.00 mg	1.8
3	Glycine	100.00mg	3.7	100.00mg	3.7
4	L-Arginine	5.00mg	0.2	10.00mg	0.4
5	L- Lysine Monohydrochloride	5.00mg	0.2	10.00mg	0.4
6	Water for Injection	2.5mL	91.9	2.5mL	91.6

Manufacturing process:

Water for injection was taken in a compounding vessel and glycine and histidine were added and stirred. Pemetrexed diacid was added and stirred. L-arginine and L-lysine were added to the above solution to adjust the pH around 5.8 to 6.0. The solution was filtered, followed by stoppering and sealing of the vials.

Example 3

S.No	Ingredients	Qty/vial	%w/w
1	Pemetrexed diacid	100mg	4.00
2	Arginine	333mg	13.3
3	Sucrose	63mg	2.5
4	DOTA	1mg	0.04
5	Water for injection	2.0mL	80.1

Manufacturing process: Water for injection was taken in a compounding vessel and arginine was added and stirred, followed by the addition of sucrose. DOTA was added to the above solution and stirred. Pemetrexed Diacid was added and stirred till a clear solution was obtained. The solution was filtered, followed by stoppering and sealing of the vials.

Example 4:

S.No	Ingredients	Qty/ml	%w/w
1	Pemetrexed diacid	15 mg	1.5
2	L-Histidine	12.5 mg	1.3
3	Glycine	25 mg	2.5
4	L-Arginine	2.5 mg	0.3
5	L- Lysine monohydrochloride	2.5 mg	0.3
6	Water for Injection	Q.S. to 1 mL	100

Manufacturing process:

Water for injection was taken in a compounding vessel and glycine and histidine were added and stirred. Pemetrexed diacid was added and stirred till a clear solution was obtained. L-arginine and L-lysine were added to the above solution to adjust the pH of the solution to around 6.1. The solution was filtered, followed by stoppering and sealing of the vials.

Pemetrexed formulation prepared according to the invention was tested for stability at 2-8°C, 25±2°C/60±5%RH, 30±2°C/65±5%RH and 40±2°C/75±5%RH for a period of 2 months. The data is summarized in Table 3.

We claim

Claim 1: A stable, ready to use liquid parenteral pharmaceutical formulation of Pemetrexed comprising

(i) Pemetrexed diacid
(ii) One or more amino acids
(iii) One or more solvents
(iv) Optionally other pharmaceutically acceptable adjuvants thereof.

Claim 2: The liquid parenteral pharmaceutical formulation according to claim 1, wherein the percentage of aminoacids ranges from about 1% to 30%, based on total weight of the formulation.

Claim 3: The stable, ready to use liquid parenteral pharmaceutical formulation of claim 1, wherein the amino acids are selected from the group comprising glycine, histidine, arginine, lysine, methionine, proline, glutamic acid or salts thereof.

Claim 4: The stable, ready to use liquid parenteral pharmaceutical formulation of claim 1, wherein pharmaceutically acceptable adjuvants can be selected from saccharides/sugars and /or chelating agents.

Claim 5: The stable, ready to use liquid parenteral pharmaceutical formulation of claim 4, wherein saccharides/sugars are selected from sucrose, glucose, xylose, galactose, fructose, lactose, maltose, mannitol, xylitol, raffinose, dextrose, trehalose and chelating agents are selected from DOTA, DTPA and EDTA.

Claim 6: A stable, ready to use liquid parenteral pharmaceutical formulation of Pemetrexed comprising

(i) Pemetrexed diacid

(ii) One or more amino acids selected from arginine, histidine, glycine, lysine or salts thereof.

(iii) Water and

(iv) Optionally other pharmaceutically acceptable adjuvants thereof.

Claim 7: A stable, ready to use liquid parenteral pharmaceutical formulation of Pemetrexed comprising

(i) Pemetrexed diacid

(ii) One or more amino acids selected from arginine, histidine, glycine, lysine or salts thereof.

(iii) Water

(iv) Saccharides/sugars and/or chelating agents.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/053391

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/00 Version=2016.01

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

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)

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2013179310A1 by MYLAN LAB LTD, 2013-12-05 (5th Dec 2013) page 8 & para 1-3	1-7

☐ 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	Date of mailing of the international search report
12-08-2016	12-08-2016

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/053391

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
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:

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).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

The present Pemetrexed formulations as claimed in claim 1-7 can be classified in the following groups:
Gr 1: A Pemetrexed formulations comprising the Active Pharmaceutical Index (API) amino acids and water.
Gr 2: A Pemetrexed formulations comprising the Active Pharmaceutical Index (API) amino acids, water and adjuvants.
The Group 1 & 2 are differs in the 'use of adjuvants' in the formulation preparation and as the said difference has already been disclosed in D1, any special technical feature has not been found among both the classified group. Hence, the authority considers that

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

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.:

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.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ 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.

☐ No protest accompanied the payment of additional search fees.

International application No.
PCT/IB2016/053391

Continuation of Observations where unity of invention is lacking(Box III)

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the present claims are not meeting the requirement of PCT Rule 13.2 (a posteriori).