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(54) Title: POWDER FORMULATION OF VALGANCICLOVIR

(57) Abstract: The present invention relates to the powder formulation of valganciclovir hydrochloride for oral administration after being reconstituted in water.

POWDER FORMULATION OF VALGANCICLOVIR

DESCRIPTION

Technical Field:

The present invention relates to the powder formulation of valganciclovir hydrochloride for oral administration after being reconstituted in water.

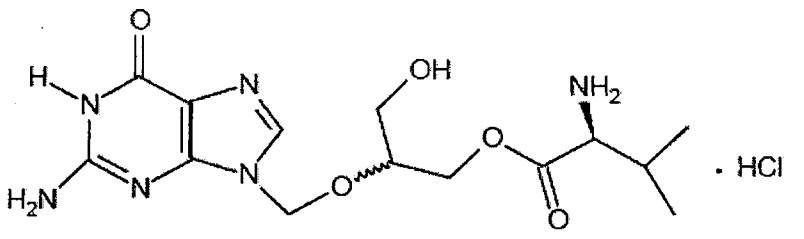
Prior Art:

Valganciclovir Hydrochloride is a strong antiviral agent which is used in the treatment of cytomegalovirus (CMV) retinitis in the patients with acquired immunodeficiency syndrome (AIDS) and in the prevention of cytomegalovirus (CMV) disease in patients with solid organ transplantation.

Valganciclovir is a prodrug which is L-valyl ester of ganciclovir,. It exists as the mixture of two diastereoisomers. When administered orally, both of these diastereoisomers rapidly turn into ganciclovir. Ganciclovir is a synthetic analogue of guanine.

The advantage of valganciclovir is that it shows a similar effect *in vivo* to that of the ganciclovir given by intravenous route, while it is more effective than ganciclovir capsules when it comes to oral administration. Ganciclovir was approved by FDA in March 2001 for use in the induction of CMV retinitis treatment, in maintenance treatment following the induction, or for use in the patients with inactive CMV retinitis. Furthermore, the use of Valganciclovir for CMV prophylaxis after heart, kidney or kidney-pancreas transplantation was approved.

The chemical name of valganciclovir hydrochloride is L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]-3-hydroxypropyl ester, monohydrochloride. (I)



(I)

Valganciclovir hydrochloride is commercially available under the trade name Valcyte® in tablet form or powder form for oral solution.

Molecular formula of Valganciclovir Hydrochloride is $C_4H_{22}N_6O_5.HCl$, while the molecular weight of the same is 390.83. Valganciclovir hydrochloride is a polar hydrophilic compound with a solubility of 70 mg/ml in water at 25°C at pH 7.0 and n-octanol-water partition coefficient of 0.0095 at pH 7.0. The pKa of valganciclovir hydrochloride is 7.6. Valganciclovir hydrochloride is freely soluble under acidic conditions with a maximum solubility higher than 200 mg/ml at a pH in the range of 4-6. Valganciclovir hydrochloride has maximum stability at a pH below 3.8.

Valganciclovir hydrochloride, in the solid form, shows acceptable physical, chemical, and light stability when stored under room temperature conditions. No special storage conditions are required except that excessive humidity must be avoided.

In the state of the art, PCT application No. WO2008/071573 (F.Hohhmann-LA Roche AG) regarding powder formulation of valganciclovir relates to a solid pharmaceutical dosage form for oral administration, after being constituted in water said formulation comprising therapeutically efficient amount of valganciclovir hydrochloride and fumaric acid which is a non-hygroscopic organic acid.

The use of citric acid or potassium acetate in acidic solutions in order to stabilize valganciclovir is disclosed (Stefanidis Dimitrios et al., "Reactivity of valganciclovir in aqueous solution" Drug Development and Industrial Pharmacy October 2005, Volume 31, no.9, pages 879-884, XP009105970 ISSN: 0363-9045).

Stability of valganciclovir in aqueous preparations under acidic conditions is disclosed (Henkin Carolyn C. et al., "Stability of valganciclovir in extemporaneously compounded liquid formulations" American Journal of Health-system Pharmacists April 1, 2003, Volume 60, no.7, April 1, 2003, pages 687-690, XP009105971 ISSN: 1079-2082). Short-term stability data has shown that liquid dosage forms are unstable for the anticipated shelf life of the product.

Therefore, efforts focused on powder dosage forms for later constitution with water, to provide a reasonable shelf life for the valganciclovir hydrochloride, and thus the liquid dosage form to be prepared therefrom.

Description of the Invention:

The present invention relates to the powder formulation of valganciclovir hydrochloride for oral administration after being reconstituted in water.

The present invention relates to the use of an organic acid in the formulation in order to increase the stability of the valganciclovir and to make the shelf life of the liquid dosage form prepared from the solid powder longer since valganciclovir hydrochloride is very soluble under acidic conditions. Tartaric acid is selected as the organic acid; wherein it lowers the pH of the solution to be prepared below 3.5, approximately to pH 3.0. The compound which is used is L-tartaric acid, which complies with European Pharmacopoeia specifications.

The present invention relates to the selection of the most appropriate formulation by analyzing the effect of the organic acid used in the formulation on degradation products of valganciclovir.

Test formulations are given in Table 1.

Table 1. Test formulations, Formula 1

	mg/120 mg	**g/bottle**	**Prepared Solution, mg/ml**
Valganciclovir HCl	55.15	5.515	55.15
Povidone K-30	2.0	0.2	2.0
L-Tartaric Acid	2.0	0.2	2.0
Sodium Benzoate	1.0	0.1	1.0
Sodium Saccharin	0.25	0.025	0.25
Mannitol	57.8	5.78	57.8
Tutti Frutti Flavor	1.8	0.18	1.8
Purified water	q.s.	q.s.	0.91 ml
Total	120 mg	12 g	1.0 ml

Table 2. Test formulations, Formula 2

	mg/120 mg	**g/bottle**	**Prepared Solution, mg/ml**
Valganciclovir HCl	55.15	5.515	55.15
Povidone K-30	2.0	0.2	2.0
Fumaric Acid	2.0	0.2	2.0
Sodium Bezoate	1.0	0.1	1.0
Sodium Saccharin	0.25	0.025	0.25
Mannitol	57.8	5.78	57.8
Tutti Frutti Flavor	1.8	0.18	1.8
Purified water	q.s.	q.s.	0.91 ml
Total	120 mg	12 g	1.0 ml

Wet granulation is used as the production process.

In the present invention, the powder formulation comprises sodium benzoate as preservative agent, sodium saccharin as sweetener, mannitol as bulking agent, tutti frutti as flavoring agent, and povidone K-30 as binder.

Stability study has been carried out for both of prepared formulations; and impurity results are analyzed in Table 3 and Table 4.

Table 3.

Comparison of the stability data of the powder prepared for the oral solution				
Formulation	Formula 1		Formula 2	
Storage Conditions	Quantitation % Valganciclovir	Total Impurity	Quantitation % Valganciclovir	Total Impurity
Starting	99.4%	0.63%	99.2%	1.45%
3 months 25°C / 60% RH	99.5%	0.64%	99.0%	1.53%
6 months 25°C / 60% RH	99.3%	0.65%	98.5%	1.57%
3 months 30°C / 65% RH	99.2%	0.66%	98.6%	1.67%
6 months 30°C / 65% RH	98.8%	0.69%	98.3%	1.73%

Table 4.

Comparison of the stability data of the solutions have been prepared				
Formulation	Formula 1		Formula 2	
Storage Conditions	Quantitation % Valganciclovir	Total Impurity	Quantitation % Valganciclovir	Total Impurity
Starting	100.7%	0.71%	102.1%	1.75%
1 month 5°C	100.5%	0.75%	101.6%	1.88%
2 months 5°C	100.4%	0.78%	99.4%	1.94%
3 months 5°C	100.4%	0.82%	98.6%	2.14%

As seen in the table, Formula 1 (the formulation comprising tartaric acid) has yielded better impurity results when compared to the Formula 2 (the formulation comprising fumaric acid).

CLAIMS

1. The powder formulation comprising valganciclovir hydrochloride for oral administration after being reconstituted in water, characterized in that it comprises L-tartaric acid as stabilizer.
2. The powder formulation comprising valganciclovir hydrochloride according to Claim 1, characterized in that the pH of the solution is below 3.5.
3. The powder formulation comprising valganciclovir hydrochloride according to Claim 1, characterized in that it is prepared by wet granulation.
4. The powder formulation comprising valganciclovir hydrochloride according to Claims 1 to 3, characterized in that it comprises sodium benzoate as the preservative agent.
5. The powder formulation comprising valganciclovir hydrochloride according to Claims 1 to 3, characterized in that it comprises sodium saccharin as the sweetener.
6. The powder formulation comprising valganciclovir hydrochloride according to Claims 1 to 3, characterized in that it comprises mannitol as the bulking agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2014/000124

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/12 A61K9/08 A61K9/00 A61K31/522
ADD.

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)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/071573 A2 (HOFFMANN LA ROCHE [CH]; BACHYNSKY MARIA OKSANA [US]; INFELD MARTIN HOW) 19 June 2008 (2008-06-19) page 8, line 1 - page 18, line 8; examples 1-3; tables 1-4	1-6

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[X] Further documents are listed in the continuation of Box C.

[X] 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)

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"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
23 July 2014	31/07/2014

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INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2014/000124

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STEFANIDIS DIMITRIOS ET AL: "Reactivity of valganciclovir in aqueous solution", DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, NEW YORK, NY, US, vol. 31, no. 9, 1 October 2005 (2005-10-01), pages 879-884, XP009105970, ISSN: 0363-9045, DOI: 10.1080/03639040500271951 abstract page 880, left-hand column, paragraph 2 page 881, right-hand column, paragraph 3 - page 884, column 1; figures 3,4 -----	1-6
A	HENKIN CAROLYN C ET AL: "Stability of valganciclovir in extemporaneously compounded liquid formulations", AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY, AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS, US, vol. 60, no. 7, 1 April 2003 (2003-04-01), pages 687-690, XP009105971, ISSN: 1079-2082 the whole document -----	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/TR2014/000124

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008071573 A2	19-06-2008	AR 065541 A1	17-06-2009
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