BEFORE THE CONTROLLER OF PATENTS
Patent Office, Chennai

In the matter of Patent Application No.3350/CHENP/2009 filed by M/s F.Hoffmann-La Roche AG, a Switzerland Company.

And

In the matter of section 15 of the Act.

DECISION

1. The applicant filed a national phase application 3 3 5 0 /CHENP/2009 on 2nd June, 2009 for the invention " POWDER FORMULATION FOR VALAGANCICLOVIR" with 25 claims at the time of filing the application. In response to the FER the applicant amended those originally filed claims into eight claims and subsequently restrict to one claim which as follows.

    1. A solid pharmaceutical dosage form for oral administration, after being constituted in water, comprising:
        a) valganciclovir hydrochloride in an amount from I 0% to 90%, by weight of the total composition; and
        b) fumaric acid an amount to lower the pH of the constituted solution of valganciclovir hydrochloride to a pH of about 3.8 or below, to stabilize the valganciclovir hydrochloride in water,

    wherein the dosage form has the following composition:

Components	Unit Weight mg/120 mg
Valganciclovir HCl	55.15[1]
Povidone K30	2.00
Fumaric Acid	2.00
Sodium Benzoate	1.00
Sodium Saccharin	0.25
Mannitol	57.80
Tutti-Frutti Flavor	1.80

Equivalent to 50 mg of valganciclovir (as free base) on a dry basis.

The applicant disclosed in the specification that the present invention is pertaining to improve the stability profile and manufacturability of the powder dosage form and the stability profile of the constituted liquid dosage form, the formulation procedure was changed from a dry mix granulation to a wet mix granulation. Since valganciclovir hydrochloride is readily soluble under acidic conditions, a solid pharmaceutical dosage form must contain an organic acid present in an amount sufficient to solubilize and stabilize the valganciclovir hydrochloride in a predetermined amount of water for the proposed shelf life of the resulting (constituted) liquid dosage form. The process as disclosed in the claimed invention, the active substance is pre-blended with Povidone K30, fumaric acid, and mannitol. Sodium benzoate and sodium saccharin were dissolved in purified water which served as the granulation solution. The granulation is prepared in a high shear mixer. The flavor is added to the dried and milled granulates during the final blending to form the filling mixture.

The applicant further disclosed in the specification that the present invention is to determine the bioequivalence of ganciclovir from the valganciclovir tutti-frutti oral solution (FO1-02) and Valcyte, the 450 mg marketed tablet formulation of valganciclovir hydrochloride, at a dose of 900 mg administered in the non-fasting state. The secondary objective was to compare the systemic exposure of ganciclovir from the valganciclovir strawberry flavored oral solution (J05) with the valganciclovir tutti-frutti flavored oral solution (FO1-02) at a dose of 900 mg. For both AUC 0-24 (area under the curve from 0-24 hours) and Cmax (maximum peak concentration), the 90% confidence interval (CI) for the mean ratios of the tablet relative to the tutti-frutti flavored oral solution lies entirely within the acceptance region of 80% to 125% ([96, 104] and [89, 101] for AUC 0-24 and Cmax, respectively). Bioequivalence of the tablet and the tutti-fruni flavored oral solution with respect to ganciclovir plasma levels can therefore be concluded. Based on the average ganciclovir AUC values, the tutti-frutti flavored oral solution delivers similar exposures known to be safe and efficacious. The ganciclovir PK comparing the tutti frutti flavored formulation vs. the strawberry flavored formulation is very similar in terms of Cmax and AUC resulting in 90% CI for the mean ratios of 96% to 109% and 94% to 101%, respectively.

2. The Agent for the applicant submitted during hearing that the present complete specification provides comparative stability data showing a better stability profile in terms of recovery of valganciclovir and amount of total impurities, when fumaric acid is employed instead of citric acid (pl. see page 12, table 3 of the complete specification). This evidences the synergistic effect or improved properties of the claimed solid dosage forms. Further, since the application of fumaric acid in solid dosage forms is not suggested in any of the prior art documents, the amended claim 1 of the instant invention is inventive over the cited documents.

3. It is observed from the prior art document D1 : Stefanidis Dimitrios et al: DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY OCT 2005, vol. 31, no. 9, October 2005 (2005-10), pages 879-884 which disclosed the rates of hydrolysis of valganciclovir to ganciclovir and L-valine and isomerization of the R and S diastereomers of valganciclovir in aqueous buffer solution from pH 3.8 to 11.5 were determined at 37°C. In acidic solutions where less than 10% degradation occurred, the rate of hydrolysis was determined assuming a first-order loss in drug. The maximum stability at the pH values studied occurred at pH 3.81 with a half life of 220 days. D2 : ANAIZI NASR H ET AL: OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS 1 JUL 2002, vol. 59, no. 13, 1 July 2002 (2002-07-01), pages 1267-1270 has also reported that in preliminary testing, valganciclovir was relatively unstable at a pH of 5 and most stable at or below pH 3.5 Valganciclovir 90 mg/mL is stable in an oral liquid prepared from valganciclovir tablets in a cherry-chocolate syrup vehicle at pH 3.2 for at least 125 days when stored at 2–8 °C in amber polyethylene terephthalate bottles. D3: HENKIN CAROLYN C ET AL: OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS 1 APR 2003, vol. 60, no. 7, 1 April 2003 (2003-04-01), pages 687-690 has reported that valganciclovir is unstable in alkaline solutions.

4. The problem solved as alleged by the applicant is the stability of the powder-product using the fumaric acid is better than product using citric acid. It is disclosed in the Examples 1-3 of the specification, method for preparing Type I formulation with citric acid and Type II formulation with fumaric acid. All the ingedirents along with active substance valganciclovir in Type I and Type II formulations are tabulated in Table 2 of the complete specification which is reproduced below;

Table 2

Powder for Oral Solution - Comparison of Formulations

Ingredients	**Type I** mg/250 mg (constituted = 1 mL)	**Type II** mg/120 mg (constituted = 1 mL)	
Formulation Number	J05	F01-03	F01-02
Valganciclovir Hydrochloride	55.15[1]	55.15[1]	55.15[1]
Citric Acid Anhydrous	9.50	-------	-------
Sodium Citrate	0.40	------	------
Sodium Benzoate	1.00	1.00	1.00
Fumaric Acid	------	2.00	2.00
Povidone K30	------	2.00	2.00
Sodium Saccharin	0.25	0.25	0.25
Strawberry Flavor #E187196	5.00	------	------
Tutti-Frutti Flavor #11900-31	------	1.80	1.80
Maltose, Crystalline	178.70	-------	-------
Mannitol	------	57.80	57.80
Purified Water	--------	[2]	[2]
Total weight per mL	250.00 mg	120.00 mg	120.00 mg
Bottle Fill Weight	15.00g	14.40g	12.00g
Amount of water to be added	51 mL	109 mL	91 mL
Total Constituted Volume	60 mL	120 mL	100 mL
Bottle: Type I amber glass	120 mL	120 mL	120 mL

The stability study data reported in the complete specification for solid powder in table 3 and for constituted solution in table 4 is reproduced below;

Table 3

Powder for Oral Solution -Comparison of Stability Data

Formulation	Type I Powder		Type II Powder	
Storage Conditions	Assay (% Label Claim) valganciclovir	Total Impurities	Assay (% Label Claim) valganciclovir	Total Impurities
Initial	100.4%	1.4%	102.1%	1.1%
12 months 25°C/60%RH	99.4%	2.0%	100.0%	1.2%
18 months 25°C/60%RH	98.9%	2.9%	100.0%	1.3%
24 months 25°C/60%RH	96.9%	4.3%	101.9%	1.4%

Table 4

Constituted Solution – Comparison of Stability Data

Formulation	Type I Constituted Solution		Type II Constituted Solution	
Storage Conditions	Assay (% Label Claim) valganciclovir	Total Impurities	Assay (% Label Claim) valganciclovir	Total Impurities
Initial	100.0%	1.42%	102.1%	1.1%
1 month 5°C	99.9%	1.69%	97.0%	1.1%
2 months 5°C	99.9%	2.20%	98.1%	1.2%
3 months 5°C	Not available	Not available	99.2%	1.3%

It is observed from the above table 3 and 4, the assay value for the compositions of Type I containing citric acid and Type II of fumaric acid in powder and constituted solution are conclusively very close and well within the acceptable range. The assay values and total impurities in the storage conditions as mentioned for powder oral solution and constituted solution for Type I and II are almost negligible difference in the acceptable range. There is no much drastic difference observed either in the % of active ingredient valganciclovir against the label claim and in the impurities range also. The prior art documents D1-D3 have already suggested that decomposition of valganciclovir is stable below pH 3.8, whereas in the basic condition the rate of decomposition is more. Therefore, the stability of the valganciclovir in powder and constituted solution is almost similar and there is no much difference in assay as well as in the decomposition product because pH of both citric acid and fumaric acid are below pH3.8. Thus, stability profile in terms of recovery of valganciclovir and amount of total impurities, when fumaric acid or citric acid is employed

in the powder or liquid solution are almost very close values according to stability data in Table 3 and 4. There is a teaching in the prior art that valganciclovir is stable at pH less than 3.8 and using a organic acid i.e., citric acid having pH less than 3.8 has also been reported in the prior art. The pH value of fumaric acid is 3.19 which is less than the suggested pH 3.8. Fumaric acid is an alternate organic acid having the pH well within the prior art suggested range below pH 3.8. Since fumaric acid is not reported in the prior art, the applicant claimed this as a technical advancement achieved to obtain patent. Therefore using fumaric acid in place of citric acid which exhibits similar stability profile in terms of recovery of valganciclovir and amount of total impurities is a choice of alternate organic acid available within the reported pH range. Thus there is no technical advancement achieved from the present invention. It is, therefore, claim of the claimed invention do not involve an inventive step u/s 2(1)j(a) of the Patents Act.

5. In view of the discussion in the preceding paragraphs, considering the relevant oral submissions made by the agent for the applicant and all the circumstances of the case, refusing the grant of patent under section 15 of the Patents Act without any order as to costs.

Dated this 30th day of January, 2019.

(Dr. S.P.SUBRAMANIYAN)
Deputy Controller of Patents & Designs