CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-257s000

21-304s007

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER**:**	22-257
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	4/30/08
PRODUCT:	VALCYTE
INTENDED CLINICAL POPULATION:	Treatment of CMV retinitis in AIDS patients
SPONSOR:	Roche Pharmaceuticals
DOCUMENTS REVIEWED:	Label Revisions
REVIEW DIVISION:	Division of Antiviral Products (HFD-530)
PHARM/TOX REVIEWER:	Anita Bigger, Ph.D.
PHARM/TOX SUPERVISOR:	Hanan Ghantous, Ph.D., DABT
DIVISION DIRECTOR:	Debra Birnkrant, M.D.
PROJECT MANAGER:	David Araojo, Pharm.D.

Date of review submission to Division File System (DFS): 11/24/08

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-257
Review number: 1
Sequence number/date/type of submission: 000/4-30-08/Label revision
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Roche Palo Alto LLC, Hoffman-La Roche Inc., 340 Kingsland St., Nutley, NJ 07110

Reviewer name: Anita Bigger, Ph.D.
Division name: Division of Antiviral Products
HFD #: 530
Review completion date: 10-23-08

Drug:

Trade name: Valcyte™

Generic name: Valganciclovir hydrochloride

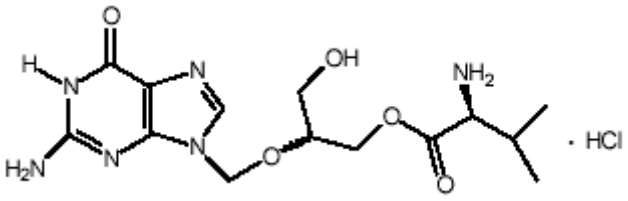
Code name: Ro 107-9070/F01

Chemical name: L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9yl) methoxy]-3- hydroxypropyl ester, monohydrochloride

CAS registry number: 175865-59-5

Molecular formula/molecular weight: $C_{14}H_{22}N_6O_5 \cdot HCl$/ 390.82

Structure:



Relevant INDs/NDAs/DMFs: NDAs 19-661, 20-460, 21-304, (b) (4) ; DMFs (b) (4) (b) (4)

Drug class: Antiviral

Intended clinical population: Treatment of CMV retinitis in patients with AIDS and prevention of CMV disease in transplant patients at high risk.

Clinical formulation: Powder for oral solution.

Route of administration: Oral.

Background: Valcyte is a valyl ester prodrug of ganciclovir and is rapidly hydrolyzed to ganciclovir and valine after oral administration. Once ganciclovir is phosphorylated, it exerts antiviral activity by inhibiting human cytomegalovirus DNA polymerase.

The current submission proposes an oral solution formulation that will provide greater flexibility in dosing than the marketed tablet formulation and allows once-daily dosing that may facilitate compliance, leading to fewer CMV infections and greater protection against development of resistance to ganciclovir.

No new pharmacology/toxicology data were submitted to this NDA; pharmacology/toxicology data were reviewed under previous NDAs.

Suggested Labeling:

5.2 Impairment of Fertility

Animal data indicate administration of ganciclovir causes inhibition of spermatogenesis and subsequent infertility. These effects were reversible at lower doses but irreversible at higher doses *[see Nonclinical Toxicology (13.1)]*. In human males, Valcyte at the recommended doses may cause temporary or permanent inhibition of spermatogenesis. Animal data also indicate suppression of fertility in females may occur.

5.3 Teratogenesis and Mutagenesis

Animal data indicate ganciclovir is teratogenic and mutagenic. Therefore, Valcyte should be considered to have the potential to cause birth defects and cancers in humans. Women of childbearing potential should be advised to use effective contraception during treatment. Similarly, men should be advised to practice barrier contraception during, and for at least 90 days following, treatment with Valcyte *[see Dosage and Administration (2.6), Use in Specific Populations (8.1), Nonclinical Toxicology (13.1, 13.3)]*.

5.4 Carcinogenesis

Animal data indicate that administration of ganciclovir is carcinogenic. Valcyte should, therefore, be considered a potential carcinogen in humans *[see Dosage and Administration (2.6), Nonclinical Toxicology (13.1)]*.

8.1 Pregnancy

Pregnancy Category C.

After oral administration, valganciclovir (pro-drug) is converted to ganciclovir (active drug) and, therefore, is expected to have reproductive toxicity effects similar to ganciclovir. There are no adequate and well-controlled studies of valganciclovir or

ganciclovir use in pregnant women. In animal studies of ganciclovir, embryo-fetal toxicity and structural malformations occurred. Valganciclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In animal studies, pregnant mice and rabbits received ganciclovir at doses that produced 2 times the human exposure (based on AUC comparison). Treated rabbits had increased rates of fetal resorption, fetal growth retardation, embryolethality, maternal toxicity, cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. In mice, increased fetal resorptions and embryolethality occurred in the presence of maternal/fetal toxicity.

Daily intravenous doses of approximately 1.7 times the human exposure (based on AUC) administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach.

Data from an ex-vivo human placental model showed that ganciclovir crosses the human placenta. The transfer occurred by passive diffusion and was not saturable over a concentration range of 1 to 10 mg/mL *[see Nonclinical Toxicology 13.3)]*.

8.3. Nursing Mothers

It is not known whether valganciclovir (pro-drug) or ganciclovir (active drug) are excreted in human milk. Because valganciclovir caused granulocytopenia, anemia and thrombocytopenia in clinical trials and ganciclovir was mutagenic and carcinogenic in animal studies, serious adverse events may occur from ganciclovir exposure in nursing infants *[see Boxed Warning, Warnings and Precautions (5.4)]*. Because of the potential for serious adverse events in nursing infants, a decision should be made whether to discontinue nursing or discontinue drug, taking into consideration the importance of the drug to the mother. The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term carcinogenicity studies have been conducted with Valcyte. However, upon oral administration, valganciclovir is rapidly and extensively converted to ganciclovir. Therefore, like ganciclovir, valganciclovir is a potential carcinogen.

Ganciclovir was carcinogenic in the mouse at oral doses that produced exposures approximately 0.1x and 1.4x, respectively, the mean drug exposure in humans following the recommended intravenous dose of 5 mg/kg, based on area under the plasma concentration curve (AUC) comparisons. At the higher dose there was a significant increase in the incidence of tumors of the preputial gland in males, forestomach

(nonglandular mucosa) in males and females, and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland and vagina) and liver in females. At the lower dose, a slightly increased incidence of tumors was noted in the preputial and harderian glands in males, forestomach in males and females, and liver in females. Ganciclovir should be considered a potential carcinogen in humans.

Valganciclovir increases mutations in mouse lymphoma cells. In the mouse micronucleus assay, valganciclovir was clastogenic. Valganciclovir was not mutagenic in the Ames Salmonella assay. Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes in vitro. In the mouse micronucleus assay, ganciclovir was clastogenic. Ganciclovir was not mutagenic in the Ames Salmonella assay.

Valganciclovir is converted to ganciclovir and therefore is expected to have similar reproductive toxicity effects as ganciclovir *[see Warnings and Precautions (5.2)]*. Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryolethality in female mice following intravenous doses that produced an exposure approximately 1.7x the mean drug exposure in humans following the dose of 5 mg/kg, based on AUC comparisons. Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or intravenous administration. Systemic drug exposure (AUC) at the lowest dose showing toxicity in each species ranged from 0.03 to 0.1x the AUC of the recommended human intravenous dose. Valganciclovir caused similar effects on spermatogenesis in mice, rats, and dogs. It is considered likely that ganciclovir (and valganciclovir) could cause inhibition of human spermatogenesis.

13.3 Reproductive and Developmental Toxicology

Valganciclovir is converted to ganciclovir and therefore is expected to have reproductive toxicity effects similar to ganciclovir. Ganciclovir has been shown to be embryotoxic in rabbits and mice following intravenous administration, and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered doses that produced 2x the human exposure based on AUC comparisons (all dose comparisons presented are based on the human AUC following administration of a single 5 mg/kg infusion of intravenous ganciclovir). Effects observed in rabbits included: fetal growth retardation, embryolethality, teratogenicity and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. In mice, effects observed were maternal/fetal toxicity and embryolethality.

Daily intravenous doses administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in the month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach *[see Warnings and Precautions (5.3)]*. The drug exposure in mice as estimated by the AUC was approximately 1.7x the human AUC.

Data obtained using an ex vivo human placental model show that ganciclovir crosses the placenta and that simple diffusion is the most likely mechanism of transfer. The transfer was not saturable over a concentration range of 1 to 10 mg/mL and occurred by passive diffusion.

Reviewer's Recommendation:

The suggested labeling is acceptable and approval of the NDA is recommended.

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/s/

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11/24/2008 03:23:45 PM
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