

**Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Pediatric Postmarketing Pharmacovigilance Review

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Product Name: Valcyte (valganciclovir)

**Pediatric Labeling
Approval Date:** August 28, 2009

Application Type/Number: NDA 021304 (valganciclovir tablets),
NDA 022257 (valganciclovir oral solution)

Applicant/Sponsor: Hoffman-La Roche, Inc.

OSE RCM #: 2017-1230

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for valganciclovir in pediatric patients.

Valganciclovir was first approved in 2001 and is indicated in adult patients for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS) and prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk. The approved pediatric labeling is for prevention of CMV disease in kidney transplant patients (4 months to 16 years of age) and heart transplant patients (1 month to 16 years of age) at high risk.

Although we reviewed all serious FAERS reports with valganciclovir in the pediatric population (ages 0 - < 17 years) during the period September 2, 2010 (date of the last DPV review) through June 13, 2017, only four cases were included in our case series. Of the overall reports reviewed, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths directly associated with valganciclovir. The majority of reports described adverse events that were likely due to comorbidities or concomitant medications (e.g., rejection in patients who had a solid organ transplant, increased serum creatinine with high tacrolimus levels, etc.), consistent with the known risks described in labeling (e.g., leukopenia, neutropenia, pancytopenia, etc.), or had limited information which precluded a meaningful causality assessment.

Of the four serious and unlabeled adverse event cases included in this series, no specific pattern of adverse events was noted; single reports of encephalopathy, medication error, drug interaction, and genital hemorrhage were reported.

We further explored encephalopathy as an adverse event of interest because valganciclovir is known to cause neurotoxic effects including hallucination. We searched for all age groups within the FAERS database for cases of encephalopathy with valganciclovir. Our search did not identify any compelling cases, as all eight cases (in adults) were confounded by concomitant medications or comorbidities more likely to have caused the event (e.g., voriconazole, chemotherapy, pre-existing liver failure). No safety signal of a causal association between encephalopathy and valganciclovir use was appreciated at this time.

There is no evidence from these data that there are new pediatric safety concerns with this drug at this time.

DPV recommends no regulatory action at this time, and will continue to monitor adverse events associated with the use of valganciclovir.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

NDA 021304 (valganciclovir tablets) was initially FDA approved March 29, 2001, for the treatment of CMV retinitis in adult patients with AIDS. The prevention of CMV disease in kidney, heart, and kidney-pancreas transplant at high risk was added in September 2003. On August 28, 2009, NDA 022257 (valganciclovir oral solution) was approved and an indication for the prevention of CMV disease in pediatric kidney and heart transplant recipients 4 months to 16 years of age was added. At this time, no new safety issues were identified and the most common adverse events noted in the studies were diarrhea, pyrexia, upper respiratory tract infection, vomiting, and hypertension. On April 23, 2015, the FDA approved extending the indication in pediatric heart transplant patients from 1 month to 16 years of age and extending the duration of dosing from 100 to 200 days for the prevention of CMV in pediatric kidney transplant patients 4 months to 16 years. At the time, no new safety concerns were identified. However, it was noted that there was a higher rate of severe neutropenia (30%) when valganciclovir was given for 200 days compared to what was observed in a previous pediatric study where patients were treated until 100 days (5%). Nevertheless, because the risk of neutropenia is well known, the benefit of extended treatment duration outweighed the risk. The current approved pediatric labeling is for prevention of CMV disease in kidney transplant patients (4 months to 16 years of age, treatment duration 200 days) and heart transplant patients (1 month to 16 years of age, treatment duration 100 days) at high risk.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

-----CONTRAINDICATIONS -----

Hypersensitivity to valganciclovir or ganciclovir (4)

-----WARNINGS AND PRECAUTIONS -----

- Hematologic toxicity: Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow depression, and aplastic anemia have occurred with the use of VALCYTE or ganciclovir. Avoid VALCYTE use if absolute neutrophil count is less than 500 cells/ μ L, platelet count is less than 25,000/ μ L, or hemoglobin is less than 8 g/dL. Use with caution in pre-existing cytopenias and when receiving myelosuppressive drugs or irradiation. Monitor with frequent testing of platelet and complete blood counts (5.1).
- Impairment of fertility: Based on animal studies, VALCYTE may cause temporary or permanent inhibition of spermatogenesis (5.2).
- Fetal toxicity: Based on animal studies, VALCYTE may cause fetal harm. Females of reproductive potential should use effective contraception during and following treatment and males should practice barrier contraception during and following treatment (5.3).
- Mutagenicity and carcinogenicity: Based on animal studies, VALCYTE is potentially mutagenic and carcinogenic (5.4).
- Acute renal failure: Acute renal failure may occur in elderly patients (with or without reduced renal function), patients who receive concomitant nephrotoxic drugs, or inadequately hydrated patients. Use with caution in elderly patients or those taking nephrotoxic drugs, reduce dosage in patients with renal impairment, and monitor renal function (2.5, 5.5, 8.5, 8.6, 12.3).

-----ADVERSE REACTIONS-----

- Adult patients: Most common adverse events and laboratory abnormalities (reported in at least one indication by greater than or equal to 20% of patients) are diarrhea, pyrexia, nausea, tremor, neutropenia, anemia, graft rejection, thrombocytopenia, and vomiting (6.1).
- Pediatric patients: Most common adverse events and laboratory abnormalities (reported in greater than or equal to 20% of pediatric solid organ transplant recipients) are diarrhea, pyrexia, hypertension, upper respiratory tract infection, urinary

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 2.1.1. See Appendix A for a description of the FAERS database.

Table 2.1.1 FAERS Search Strategy

Date of Search	June 13, 2017
Time Period of Search	September 2, 2010* - June 13, 2017
Search Type	Quick Search Mercado Drug Safety Analytics
Product Names	Valcyte, Valganciclovir, Valganciclovir hydrochloride
Search Parameters	All ages, all outcomes, worldwide

* End date of last DPV pediatric review

2.2 RESULTS

2.2.1 Total number of FAERS reports by Age

Table 2.2.1 Total Adult and Pediatric FAERS reports* September 2, 2010 - June 13, 2017 with Valganciclovir

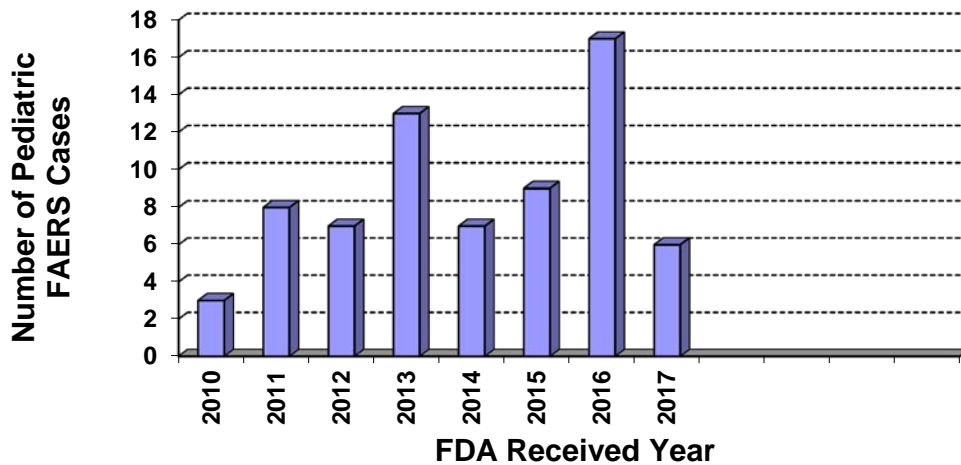
	All reports (U.S.)	Serious [†] (U.S.)	Death (U.S.)
Adults (≥ 17 years)	1,022 (287)	988 (256)	223 (99)
Pediatrics (0 - <17 years)	86 (28)	70[‡] (12)	4 (1)

* May include duplicates and transplacental exposures, and have not been assessed for causality

[†] For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

[‡] See Figure 2.2.2

Figure 2.2.1 Serious Pediatric Reports for Valganciclovir, by year of FDA receipt September 2, 2010 - June 13, 2017 (n=70)

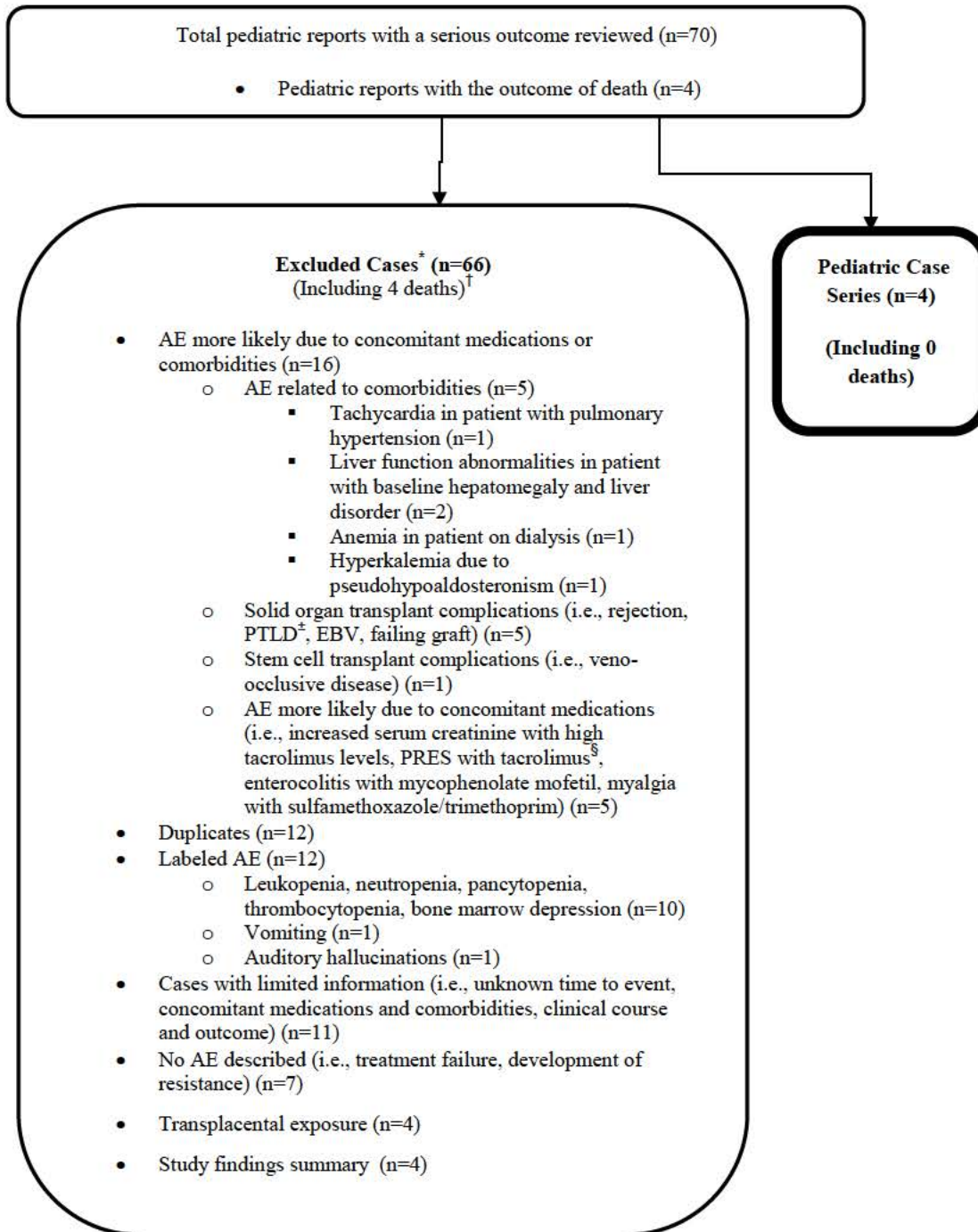


2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 70 pediatric reports with a serious outcome (See Table 2.2.1). See **Figure 2.2.2** below for the specific selection of cases to be summarized in **Sections 2.3 and 2.4**.

DPV assessed the 70 FAERS reports and excluded those where the adverse event was unlikely due to valganciclovir (i.e., cases not temporally related to the drug, other medications or underlying disease provide a more likely explanation), the case was unassessable (i.e., cases cannot be judged because information is insufficient or contradictory and the data cannot be supplemented or verified) or described labeled events, as well as any duplicate reports.

Figure 2.2.2 Selection of Serious Pediatric Cases with Valganciclovir



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above

† The 4 cases resulting in death were excluded because they contained limited information (n=1), described transplacental exposure to the drug (n=1), or described treatment failure/development of resistance (n=2)

‡ PTLD = post-transplant lymphoproliferative disease

§ PRES = posterior reversible encephalopathy syndrome

2.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

We did not include any fatal pediatric adverse event cases in our case series.

2.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=4)

2.4.1 Unlabeled Event: Ganciclovir-Induced Encephalopathy (n=1)

FAERS Case# 11121444 describes a 13-year-old male patient from a Japanese literature article that summarizes three patients (1 pediatric, 2 adults) who experienced ganciclovir-induced encephalopathy. The article postulates that ganciclovir causes encephalopathy based on ganciclovir levels in three patients that experienced confusion and disturbed consciousness. Information provided on the 13-year-old stem cell transplant patient is limited and he experienced visual hallucinations with slow waves on EEG after 14 days of ganciclovir treatment and 14 days of valganciclovir treatment but no imaging of brain was done. The drug was withdrawn and the patient improved two days later. Concomitant medications and concomitant disease states are unknown.

Reviewer's Comments: The literature article is lacking information that limits our assessment. Of note, neurotoxic effects including hallucinations are included in the valganciclovir label. DPV II searched the FAERS database for additional cases of encephalopathy associated with valganciclovir use in all age groups and retrieved eight cases. The reports provided limited information, were confounded by concomitant mediations or comorbidities more likely to have caused the event (e.g., voriconazole, chemotherapy, pre-existing liver failure).

2.4.2 Unlabeled Event: Medication Error (n=1)

FAERS Case# 9421012 describes a drug prescribing error in a 7-day-old female who was underdosed with oral valganciclovir for congenital CMV infection and received 16 mg twice a day instead of 16 mg/kg (41 mg total dose) twice a day. Additionally, there was a dispensing error in the outpatient pharmacy and the prescription was filled with valacyclovir instead of valganciclovir. The errors led to hospitalization of the patient due to seizures and reactivation/relapse of CMV infection. The clinical outcome at the time of the event is unknown.

2.4.3 Unlabeled Event: Drug Interaction (n=1)

FAERS Case# 10479888 describes a suspected drug interaction between valganciclovir and tacrolimus in a 1-year-old male patient leading to decreased levels of tacrolimus after two months of treatment with valganciclovir. His tacrolimus levels were low (unspecified values) but upon valganciclovir discontinuation they returned to therapeutic values. The patient was concomitantly receiving aspirin, famotidine, and prednisone. No further information provided.

Reviewer's comments: Many factors can contribute to variations in tacrolimus levels and since the clinical course information is limited, it is challenging to assess valganciclovir's contribution to the tacrolimus level changes especially considering the extended time to event.

2.4.4 Unlabeled Event: Genital Hemorrhage (n=1)

FAERS Case# 10760008 describes a prematurely born female patient with cerebral ventriculomegaly, cerebral calcifications, hepatomegaly, platelet count decrease, and severe deafness who was treated with valganciclovir for congenital CMV infection. After 25 days the patient had "small amount of genital hemorrhage" and this was again noted on days 36 to 41 of treatment. No aggravation of anemia was observed on laboratory values and on day 41 the event was resolved. After 54 days of treatment, valganciclovir was discontinued. She was monitored and no recurrence of events was noted within two weeks of monitoring. The patient was concomitantly receiving treatment with immune globulin, ferric pyrophosphate, and epoetin alfa. The event of genital hemorrhage was considered as not related to valganciclovir by the reporting physician.

Reviewer's comments: The extent of valganciclovir's contribution to the event is challenging to assess in light of the resolution of the hemorrhage while the treatment was ongoing.

3 DISCUSSION

Although we reviewed all serious FAERS reports with valganciclovir in the pediatric population (ages 0 - < 17 years) during the period September 2, 2010 (date of the last DPV review) through June 13, 2017, only four cases were included in our case series. Of the reports reviewed, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths directly associated with valganciclovir. The majority of reports described adverse events that were likely due to comorbidities or concomitant medications (e.g., rejection in patients who had a solid organ transplant, increased serum creatinine with high tacrolimus levels, etc.), consistent with the known risks described in labeling (e.g., leukopenia, neutropenia, pancytopenia, etc.), or had limited information which precluded a meaningful causality assessment.

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4 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with this drug at this time.

5 RECOMMENDATIONS

DPV recommends no regulatory action at this time, and will continue to monitor adverse events associated with the use of valganciclovir.

6 APPENDICES

6.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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/s/

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