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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Zovirax (acyclovir) injection in pediatric patients through 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious, unlabeled adverse events associated with acyclovir in pediatric patients.

Injectable acyclovir was first approved on October 22, 1982. Under Section 409I of the Best Pharmaceuticals for Children Act (BPCA) of 2002, the National Institutes of Health (NIH), in consultation with FDA, was directed to establish an annual list of drugs for which additional studies are needed in the pediatric population. Under BPCA amendment of 2007, NIH is required to publish a priority list of needs in pediatric therapeutics, including drugs or indications that require study. The intent of Section 409I is to obtain data on the safe and effective use of off-patent drugs that will result in pediatric labeling. Published in a 2005 Federal Register notice (FR 70:17 January 27, 2005), NIH identified acyclovir as a priority drug for which additional pediatric data is required to fill the labeling gap for dosing recommendation between the standard of care and the FDA approved label.

The investigational new drug application (IND) 106153 was submitted on July 30, 2009, to support changes in dosing regimens of IV acyclovir for the treatment of neonatal infection through the BPCA off-patent labeling change process. The Applicant submitted efficacy, safety and pharmacokinetic (PK) data to support labeling changes. On January 25, 2019, pediatric labeling was updated to include the proposed high-dose/longer duration IV acyclovir regimen in place of the standard dose.

DPV reviewed all U.S. serious FAERS reports with acyclovir use in the pediatric population (ages 0 through 17 years), received by FDA from October 22, 1982, through April 26, 2022. After exclusions, DPV identified seven non-fatal serious pediatric cases with unlabeled adverse events of tachycardia, hypertension, bradycardia, and renal colic. However, these cases were confounded by comorbidities, concomitant medications, or contained limited information for an adequate causality assessment. There were no new safety signals and no increased severity of any labeled events identified for injectable acyclovir at this time. DPV will continue to monitor all adverse events associated with acyclovir use through routine pharmacovigilance.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Zovirax (acyclovir) injection in pediatric patients through 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious, unlabeled adverse events associated with acyclovir in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Injectable Zovirax (acyclovir) was first approved on October 22, 1982. Acyclovir is a nucleoside analog antiviral drug approved for the treatment of herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV) infections.[1]

Acyclovir injection is available as a 500 mg and 1,000 mg vial. The calculated dose should then be removed and added to any appropriate intravenous (IV) solution at a volume selected for administration during each 1-hour infusion. Infusion concentrations of approximately 7 mg/mL or lower are recommended. Higher concentrations (e.g., 10 mg/mL) may produce phlebitis or inflammation at the injection site upon inadvertent extravasation. The recommended dosage of acyclovir for pediatric patients is described in **Table 1**.[1]

Table 1. Intravenous Acyclovir Recommended Dosage in Pediatric Patients	
Mucosal and cutaneous HSV-1 and HSV-2 infections in immunocompromised patients	- 3 months to 12 years: 10 mg/kg IV every 8 hours for 7 days - 12 years and older: 5 mg/kg IV every 8 hours for 7 days
Severe initial clinical episode of herpes genitalis	- 12 years and older: 5 mg/kg IV every 8 hours for 5 days
Herpes simplex encephalitis	- 3 months to 12 years: 20 mg/kg IV every 8 hours for 10 days - 12 years and older: 10 mg/kg IV every 8 hours for 10 days
Neonatal herpes simplex virus infections (all types – mucosal, cutaneous, disseminated or CNS)[*]	- PMA of at least 34 weeks: 20 mg/kg IV every 8 hours for 21 days - PMA of less than 34 weeks: 20 mg/kg IV every 12 hours for 21 days

Table 1. Intravenous Acyclovir Recommended Dosage in Pediatric Patients	
Varicella zoster infections in immunocompromised patients	- 12 years of age and older: 10 mg/kg IV every 8 hours for 7 days - < 12 years of age: 20 mg/kg IV every 8 hours for 7 days
* In neonates with ongoing medical conditions affecting their renal function beyond the effect of prematurity, the doses recommended should be used with caution. Abbreviations: HSV = herpes simplex virus, IV = intravenous, CNS = central nervous system, PMA = post-menstrual age	

Under Section 409I of the Best Pharmaceutical Children Act (BPCA) of 2002, the National Institute of Health (NIH), in consultation with the FDA, was directed to establish an annual list of drugs for which additional studies are needed in the pediatric population. NIH is required to publish a priority list of needs in pediatric therapeutics, including drugs or indications that require study. This priority list is updated every three years. The intent of Section 409I is to obtain data on the safe and effective use of off-patent drugs that will result in pediatric labeling.

On May 6, 2021, the Applicant submitted a request for withdrawal of Zovirax (acyclovir) injection new drug application (NDA) 18603 due to discontinued marketing of the drug product. The Federal Register published FDA's determination that NDA 18603 was withdrawn from marketing for reasons unrelated to safety or effectiveness.[2]

Published in a 2005 Federal Register notice (FR 70:17 January 27, 2005),[3] NIH identified acyclovir as a priority drug for which additional pediatric data are required to fill the labeling gap for dosing recommendation between the standard of care and the FDA approved label. The initial approved dosing regimen of acyclovir for neonatal HSV infection was 10 mg/kg IV every 8 hours for 10 days. However, a higher dose and longer duration (20 mg/kg IV every 8 hours for 21 days) is commonly used in clinical practice based on a publication where superiority of the high dose/longer duration regimen to the FDA approved dosing regimen was observed.[4] The trial was conducted through the Collaborative Antiviral Study Group (CASG), an NIH funded multi-center clinical trials group.

The investigational new drug application (IND) 106153 was submitted on July 30, 2009, to support changes in dosing regimens of IV acyclovir for the treatment of neonatal infection through the BPCA off-patent labeling change process. Efficacy, safety, and PK data were submitted to support labeling changes. This review was prompted by pediatric labeling approved on January 25, 2019, which was updated to include the proposed high-dose/longer duration IV acyclovir regimen in place of the standard dose.

The following regulatory history was reproduced from Drs. Yodit Belew and Fraser Smith's combined clinical and statistical review, Dr. Su-Young Choi's clinical pharmacology review, and Dr. Ethan Hausman's, Division of Pediatric and Maternal Health (DPMH), clinical review for IND 106153.[5,6,7]

Study ACY01, an open-label study, was conducted to describe the pharmacokinetics of acyclovir in preterm infants. This study provided pharmacokinetic and safety data on acyclovir in infants with suspected or confirmed HSV. Dosing group assignments were based on gestational age (GA) and postnatal age (PNA). Thirteen subjects were enrolled under version 1.0 of the protocol (GA 23-42 weeks and PNA up to 60 days; 500 mg/m^2 IV every 8 hours) and 19 subjects were enrolled under version 2.0 of the protocol (GA 23-34 weeks and PNA < 45 days; 10-20 mg/kg IV every 8-12 hours). The review team concluded that dosing based on PMA (post-menstrual age) rather than GA or PNA was acceptable, and a PMA cutoff of 34 weeks is more acceptable to produce similar exposures across the age groups.

Study ACY02 was a retrospective review of safety data related to acyclovir use in neonates. Pediatrix Medical Group (PMG) administrative database, and retrospective chart reviews were conducted to assess the safety of standard and high dose acyclovir. Additional safety data were available from studies conducted by Kimberlin et al. and Whitely et al.

The primary data source for the safety assessment of acyclovir included the Pediatrix Medical Group administrative database, and the Medical Chart Review. The most common adverse events from the Pediatrix Medical Group database were hypotension requiring support with inotropes, seizures, leukopenia, thrombocytopenia, and mild elevated serum liver biochemistries. The most common adverse events from the Medical Chart Review were rash, hypotension seizures, intraventricular hemorrhage, renal failure, mild serum electrolyte abnormalities, mild complete blood cell count abnormalities, and mild liver dysfunction. In general, the adverse events reported were consistent with symptoms associated with systemic neonatal HSV infection, or these events are known/labeled adverse events (e.g., seizures, renal failure, bone marrow suppression) associated with use of acyclovir. The clinical-statistical review stated that due to overlapping toxicities/adverse events between HSV infection and its complications vs. use of acyclovir, and the limitations with retrospective data collection, the adverse events/laboratory toxicities reported are difficult to interpret and attribute causality for the events. Overall, no new or unexpected adverse events were reported.

The efficacy of the high dose acyclovir was supported primarily by the data generated from the Kimberlin et al study, titled “Safety and Efficacy of High-Dose Intravenous Acyclovir in the Management of Neonatal Herpes Simplex Virus Infections”. The study was an open-label trial with an objective of establishing the safety and efficacy (mortality, morbidity) of high-dose acyclovir for the treatment of neonatal HSV disease. Two doses were evaluated during the trial: a high dose (20mg/kg/q8; n=66) and an intermediate dose (15mg/kg/q8; n=13). The primary time point for the assessment of the efficacy outcomes (mortality, morbidity) was at Month 24. The FDA analysis also evaluated mortality at 6- and 12-months to minimize the amount of missing data. The results from these treatment arms were then compared to the results from the clinical trial that led to FDA’s original approval of the 10mg/kg/q8 dose, which was based on the study conducted by Whitely et al.

The review team concluded that that there were differences in the mortality outcome among the three doses, favoring the high dose acyclovir arm across multiple time points over the standard dose and intermediate dose, supporting the high dose with respect to efficacy for the treatment of systemic HSV infection in neonates.

DPV has not previously presented an evaluation of postmarketing adverse event reports for acyclovir in pediatric patients to the Pediatric Advisory Committee (PAC).

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The injectable acyclovir labeling includes the following safety information (excerpted from the pertinent sections). For further acyclovir labeling, including dosage and administration for adult patients, please refer to full prescribing information.

----------CONTRAINDICATIONS----------

- ZOVIRAX for Injection is contraindicated for patients who develop hypersensitivity to acyclovir or valacyclovir.

----------WARNINGS----------

- ZOVIRAX for Injection is intended for intravenous infusion only, and should not be administered topically, intramuscularly, orally, subcutaneously, or in the eye. Intravenous infusions must be given over a period of at least 1 hour to reduce the risk of renal tubular damage (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).
- Renal failure, in some cases resulting in death, has been observed with acyclovir therapy (see ADVERSE REACTIONS: Observed During Clinical Practice and OVERDOSAGE).
- Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), which has resulted in death, has occurred in immunocompromised patients receiving acyclovir therapy.

----------PRECAUTIONS----------

- Precipitation of acyclovir crystals in renal tubules can occur if the maximum solubility of free acyclovir (2.5 mg/ml at 37°C in water) is exceeded or if the drug is administered by bolus injection. Ensuing renal tubular damage can produce acute renal failure.
- Abnormal renal function (decreased creatinine clearance) can occur as a result of acyclovir administration and depends on the state of the patient's hydration, other treatments, and the rate of drug administration. Concomitant use of other nephrotoxic drugs, pre-existing renal disease, and dehydration make further renal impairment with acyclovir more likely.
- Administration of ZOVIRAX by intravenous infusion must be accompanied by adequate hydration.
- When dose adjustments are required, they should be based on the estimated creatinine clearance (see DOSAGE AND ADMINISTRATION).
- Approximately 1% of patients receiving intravenous acyclovir have manifested encephalopathic changes characterized by either lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures, or coma. ZOVIRAX should be used with caution in those patients who have underlying neurologic abnormalities and those with serious renal, hepatic, or electrolyte abnormalities, or significant hypoxia.

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

Adult and Pediatric Clinical Trials:

- The adverse reactions listed below have been observed in controlled and uncontrolled clinical trials in approximately 700 patients who received ZOVIRAX at ~ 5 mg/kg (250 g/m^2) 3 times daily, and approximately 300 patients who received ~ 10 mg/kg (500 mg/m^2) 3 times daily.
- The most frequent adverse reactions reported during administration of ZOVIRAX were inflammation or phlebitis at the injection site in approximately 9% of the patients, and transient elevations of serum creatinine or BUN in 5% to 10% (the higher incidence occurred usually following rapid [less than 10 minutes] intravenous infusion). Nausea and/or vomiting occurred in approximately 7% of the patients. Itching, rash, or hives occurred in approximately 2% of patients. Elevation of transaminases occurred in 1% to 2% of patients.
- The following hematologic abnormalities occurred at a frequency of less than 1%: anemia, neutropenia, thrombocytopenia, thrombocytosis, leukocytosis, and neutrophilia. In addition, anorexia and hematuria were observed.

Neonatal Clinical Trial

- In Study 2, 72 of the 88 enrolled neonates received 60 mg/kg/day. Among subjects with recorded normal baseline values, the following laboratory abnormalities were reported: 6% (4/64) with Grade 3 or 4 increase in creatinine; 4% (2/52) with total bilirubin Grade 3 or 4 toxicity; 13% (8/64) with hemoglobin <8 gm%; 16% (10/64) and 3% (2/64) with absolute neutrophil count 500 to 1,000 cells/mm^3 and < 500 cells/mm^3, respectively; 10% (6/63) and 5% (3/63) with platelet count 50,000 to 100,000 and < 50,000, respectively.

Observed During Clinical Practice

- ***General:*** Anaphylaxis, angioedema, fatigue, fever, headache, pain, peripheral edema.
- ***Digestive:*** Abdominal pain, diarrhea, gastrointestinal distress, nausea.
- ***Cardiovascular:*** Hypotension.
- ***Hematologic and Lymphatic:*** Disseminated intravascular coagulation, hemolysis, leukocytoclastic vasculitis, leukopenia, lymphadenopathy.
- ***Hepatobiliary Tract and Pancreas:*** Elevated liver function tests, hepatitis, hyperbilirubinemia, jaundice.
- ***Musculoskeletal:*** Myalgia.
- ***Nervous:*** Aggressive behavior, agitation, ataxia, coma, confusion, delirium, dizziness, dysarthria, encephalopathy, hallucinations, obtundation, paresthesia, psychosis, seizure, somnolence, tremor (see PRECAUTIONS).
- ***Skin:*** Alopecia, erythema multiforme, photosensitive rash, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria. Severe local inflammatory reactions, including tissue necrosis, have occurred following infusion of ZOVIRAX intro extravascular tissues.
- ***Special Senses:*** Visual abnormalities.
- ***Urogenital:*** Renal failure, elevated blood urea nitrogen, elevated creatinine (see WARNGINGS).

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 2**.

Table 2. FAERS Search Strategy*	
Date of search	April 27, 2022
Time period of search	October 22, 1982† - April 26, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	PAI: acyclovir
MedDRA search terms (Version 24.1)	All PT terms
* See Appendix A for a description of the FAERS database. † U.S. approval date Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term, PV = pharmacovigilance, PAI= product active ingredient	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 3 presents the number of adult and pediatric FAERS reports from October 22, 1982 through April 26, 2022, with acyclovir.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA From October 22, 1982 through April 26, 2022 With Acyclovir			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	4,359 (644)	4,188 (592)	392 (70)
Pediatrics (0 - <18 years)	784‡ (122)	770‡ **(104)**	**61**‡ (10)
* 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, or other serious important medical events. ‡ See Figure 1. Seven additional U.S. reports of pediatric deaths were identified among reports not reporting an age. These reports are reflected in the counts of pediatric reports.			

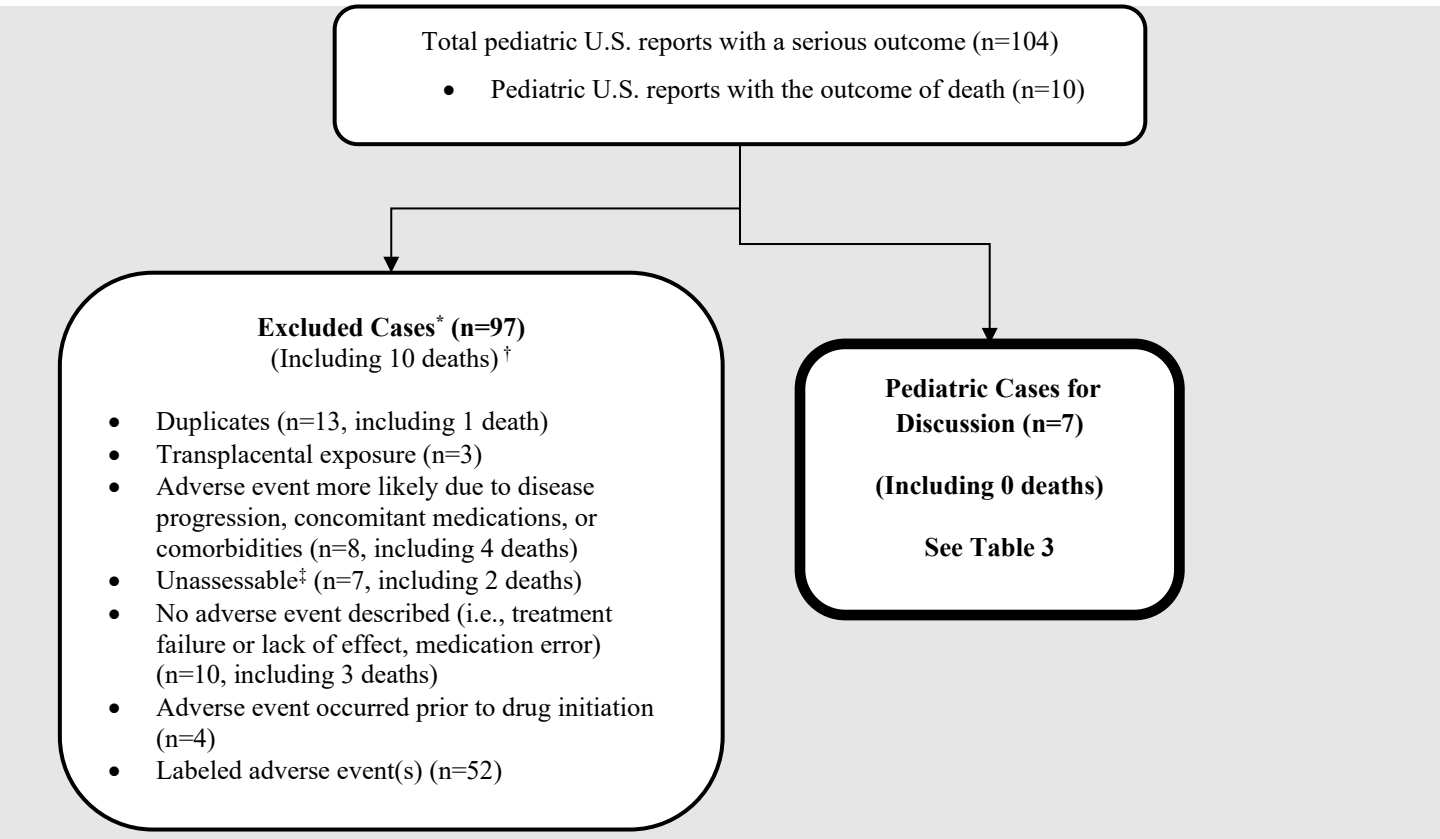
3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 104 U.S. serious pediatric reports from October 22, 1982 (U.S. approval date) through April 26, 2022.

We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded reports from the case series for various reasons, such as duplicate reporting (n=13), labeled adverse events (n=52), if the adverse event was unlikely to be causally related to the use of acyclovir (e.g., the report was confounded by disease progression, co-morbid diseases, or concomitant medications) (n=8), reporting lack of efficacy (n=9), described transplacental exposure (n=3), event occurred prior to acyclovir exposure (n=4), unassessable (n=7), and no adverse event described (n=1). We summarize the remaining cases in the sections below.

Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious U.S. Pediatric Cases with Acyclovir



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

† Ten excluded reports described fatal outcomes, including one duplicate report. No deaths were attributed to acyclovir, but were due to progression or complications of underlying medical condition or were unassessable. These reports are not remarkable given the serious medical conditions of the patient population using the drug. Three reports described HSV or VZV resistance to acyclovir and drug ineffectiveness. Four reports described fatal events considered due to disease progression, including a 9-day-old female with disseminated HSV infection and methicillin-sensitive Staphylococcus aureus bacteremia who developed disseminated intravascular coagulation and multiple organ system failure, a 15-year-old male with T-cell lymphoblastic leukemia on chemotherapy who developed hepatitis and multiple organ system failure, a 17-year-old with Hodgkin's lymphoma status post allogenic hematopoietic cell transplantation and myeloablative autologous stem cell transplantation who died due to graft versus host disease and VZV infection, and a 5-day-old female with severe herpes encephalitis who developed seizures prior to and after acyclovir administration and died of an unknown cause. Two reports had limited information and were considered unassessable; in both of these reports the cause of death was not reported.

‡ Unassessable: Case cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome) or the information is contradictory or information provided in the case cannot be supplemented or verified.

3.1.3 Characteristics of Pediatric Cases

Appendix B contains a line listing of the seven pediatric cases.

Table 4 summarizes the seven FAERS cases in U.S. pediatric patients with acyclovir reporting a serious outcome received by FDA from October 22, 1982 through April 26, 2022.

Table 4. Characteristics of the FAERS U.S. Serious Pediatric Cases With Acyclovir Received by FDA From October 22, 1982 through April 26, 2022 (N=7)		
Age	0 - < 1 month	2
	1 month - <2 years	2
	2 - < 6 years	2
	6 - <12 years	1
Sex	Male	3
	Female	3
	Not reported	1
Reported reason for use	Meningitis (unspecified)	3
	HSV infection	2
	HSV encephalitis	1
	VZV infection	1
Serious outcome*	Life-threatening	1
	Hospitalization	2
	Required Intervention	1
	Other Serious	4
* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome.		
Abbreviations: HSV = Herpes Simplex Virus, VZV = Varicella-Zoster Virus		

3.1.4 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for further discussion.

3.1.5 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=7)

We identified seven cases of serious, unlabeled adverse events with acyclovir in the U.S. pediatric population reporting a non-fatal serious outcome. These seven cases are summarized below.

FAERS Case #4443743, United States, 1985, Serious Outcome: Hospitalization

A 2-day-old infant was exposed to herpes genitalis at birth and was started on intravenous acyclovir 1,500 mg/m^2 (first dose; then reduced to 750 mg/m^2) and developed **tachycardia** within 30 minutes following administration. The patient received a total of 11 doses and experienced the same adverse event after each dose. The patient's heart rate ranged from 150-190 beats per minute (bpm). Concomitant medications included ampicillin, gentamicin, and vidarabine ophthalmic.

FAERS CASE #7888812, United States, 2011, Serious Outcome: Other Serious

A 4-week-old female infant received intravenous acyclovir 60 mg every 8 hours (18 mg/kg/dose) for possible meningitis. Concomitant medications included cefotaxime and ampicillin. The patient became **tachycardic** (heart rate up to 209 bpm) on day 2 and 3 of acyclovir treatment. Her electrocardiogram (EKG) was significant for sinus tachycardia with no other cardiac anomalies. Acyclovir was discontinued and the patient's heart rate returned to normal sinus rhythm (161-165 bpm).

FAERS CASE #7888082, United States, 2011, Serious Outcome: Other Serious

A 7-week-old female infant received intravenous acyclovir 80 mg every 8 hours (20 mg/kg/dose) for possible meningitis. Concomitant medications included ceftriaxone. The patient became **tachycardic** on day 3 of acyclovir treatment, heart rate up to 215 bpm. EKG was significant for sinus tachycardia, T-wave flattening, and ST depression. An echocardiogram was evaluated by the Pediatric Cardiologist who noted no cardiac abnormalities. The patient's mother also reported lethargy during the course of treatment. All symptoms resolved after acyclovir was discontinued.

Reviewers' comment: The three cases above describe a possible temporal association with acyclovir and tachycardia with a positive dechallenge. However, these cases are confounded by the patients' underlying infection, which is a risk factor for the development of tachycardia.

FAERS Case 5001877, United States, 1993, Serious Outcome: Life-threatening, Other Serious

A 4-day-old male (weight: 4 kg) was admitted for evaluation of fever and started on treatment with intravenous ampicillin, gentamicin, and acyclovir (38 mg every 8 hours) for possible herpes meningitis. Blood and urine cultures were positive for Group B streptococci. A lumbar puncture revealed 4,160 white blood cells with 79% segmented neutrophils, 2% lymphocytes, and 19% monocytes, 290 red blood cells, protein of 210 mg/dL, and glucose of 41. The cerebral spinal fluid (CSF) culture was negative; however, the infant received one dose of antibiotics prior to lumbar puncture. The infant experienced **seizure** activity in the first 24 hours of admission and was treated with intravenous phenobarbital. He had rhythmic jerking and apnea during the seizure episodes. The infant required Oxyhood on days 4-6 of life. On approximately day 3 of acyclovir, 30 minutes after the infusion, the infant developed "splotchy" areas on buttocks, **decreased pulses in the left leg, pallor, and a heart rate in the 60s**. There was no evidence of seizure activity during this event. The infant was treated with an intravenous bolus of normal saline and shortly after his heart rate increased to 200 bpm. His blood pressure remained normal during this time. After several minutes, the heart rate slowly returned to normal and perfusion to lower extremities improved. The electroencephalography (EEG), echocardiogram, and CT of the head were normal. Subsequent doses of acyclovir were given with no problem. Acyclovir was continued until the viral cultures were negative at 72 hours.

Reviewers' comment: Seizures is a labeled adverse event for acyclovir; however, this patient's underlying infection (i.e., meningitis) and concomitant medications are confounding factors. Although this case describes a possible temporal association with acyclovir and bradycardia, the

case is confounded by the patient's underlying infection, which is a risk factor for the development of bradycardia. In addition, dehydration may have been another possible contributing factor since the patient responded to intravenous fluids.

FAERS Case #10540801, United States, 2014, Serious Outcome: Hospitalization
Kocak O, Yarar C, Yakut A, et al. Akathisia in association with herpes simplex encephalitis relapse and opercular syndrome in children. *Brain and Development* 2014;36(2):167-170.

A literature case described a 2-year-old male who was hospitalized with fever and focal seizures and diagnosed with HSV-1 encephalitis and opercular syndrome. He received intravenous acyclovir 30mg/kg/day, a benzodiazepine, phenytoin, and flumazenil. His consciousness normalized after 3 days. On hospital day 10, a neurological examination revealed that his deep tendon reflexes were hyperactive. The Babinski sign was positive bilaterally, his muscle tonus was slightly decreased, and involuntary movements developed on his left side. He was unable to sit and walk. There were partial recurrent seizures on his left arm, which were treated with midazolam, levetiracetam, and clobazam. On hospital day 21, he developed **hypertension**, which was suspected to be due to acyclovir. A renal ultrasound and renal scintigraphy were normal. Acyclovir was discontinued. It is unknown if the hypertension resolved after discontinuation of acyclovir.

Reviewers' comment: This case is missing important clinical information to assess for causality, including objective blood pressure measurements, EEG information, renal function tests and the outcome of the event.

FAERS Case #5637800, United States, 1983, Serious Outcome: Other Serious

A 2-year-old female with acute myeloid leukemia (AML) received intravenous acyclovir for VZV and developed **hypertension** for 3 days starting on day 1 of acyclovir treatment. The patient received acyclovir for 7 days. Prior to acyclovir, the patient's blood pressure was 110/60 mmHg. The patient's blood pressure returned to normal and then again became elevated on the last day of therapy and then returned to normal when therapy was stopped. On day 1 of acyclovir treatment, blood pressure measurements ranged from a systolic of 102-140 mmHg and a diastolic of 64-90 mmHg. On day 2, blood pressure measurements ranged from a systolic of 120-136 mmHg and a diastolic of 54-70 mmHg. On day 3, blood pressure measurements ranged from a systolic of 90-130 mmHg and a diastolic of 62 mmHg. Concomitant medications included intravenous morphine, oral chloral hydrate and oral acetaminophen.

Reviewers' comment: Although this case describes a possible temporal association with acyclovir and hypertension and a positive dechallenge, causality is difficult to interpret due to limited clinical context, such as blood pressure measurement technique.

FAERS Case #3683314, United States, 2001, Serious Outcome: Required Intervention

A 6-year-old male received intravenous acyclovir (15 mg/kg/dose every 8 hours) for the treatment of herpes meningitis. On day 4 of treatment, the patient developed abdominal

cramping, which the physician considered likely **drug-induced renal colic**. The patient was treated with intravenous hydration with dextrose and normal saline. No other information was provided.

Reviewers' comment: This case is missing important clinical information to assess for causality, such as concomitant medication, diagnostic tests, and renal function tests.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with acyclovir use in the pediatric population (ages 0 through 17 years), received by FDA from October 22, 1982 through April 26, 2022, and identified seven non-fatal serious pediatric cases with unlabeled adverse events of tachycardia, hypertension, bradycardia, and renal colic. However, these cases were confounded by comorbidities, concomitant medications, or contained limited information for an adequate causality assessment. There were no new safety signals identified and no increased severity of any labeled events.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for acyclovir at this time.

6 RECOMMENDATION

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

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8 APPENDICES

8.1 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 FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council 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.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=7)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	4/23/1985	4443743	1	PMSZOV1	Expedited	0.006	Unknown	U.S.	HO
2	6/11/1993	5001877	1	ZOVIRAX1765	Periodic	0.011	Male	U.S.	LT, OT
3	3/23/2011	7888812	1	N/A	Direct	0.077	Female	U.S.	OT
4	3/23/2011	7888082	1	N/A	Direct	0.135	Female	U.S.	OT
5	10/22/2014	10540801	1	2014HINLIT0931	Expedited	2	Male	U.S.	HO
6	12/13/1983	5637800	1	83	Periodic	2	Female	U.S.	OT
7	7/18/2001	3683314	1	N/A	Direct	6	Male	U.S.	RI

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: HO=hospitalization, LT=life-threatening, OT=other medically significant, RI=required intervention, N/A = not applicable

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/s/

KIMBERLEY A SWANK
10/24/2022 02:33:14 PM

IVONE E KIM
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RACHNA KAPOOR
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IDA-LINA DIAK
10/25/2022 07:55:55 AM