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Pediatric Postmarketing Pharmacovigilance Review

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Product Name: Merrem[®] IV (meropenem for injection)
Meropenem for injection

**Pediatric Labeling
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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA), the Division of Pharmacovigilance (DPV) evaluated postmarketing adverse event reports with a serious outcome for Merrem® IV (meropenem for injection) in pediatric patients.

Meropenem was first approved in 1996 and is indicated for the treatment of complicated skin and skin structure infections (cSSSIs), complicated intra-abdominal infections (cIAIs), and bacterial meningitis. The approved Merrem® IV pediatric labeling is for cSSSIs (3 months of age and older), cIAIs (all ages, including less than 3 months of age), and bacterial meningitis (3 months of age and older).

Although we reviewed all serious FDA Adverse Event Reporting System (FAERS) reports from the U.S. with meropenem in the pediatric population (ages 0 - < 17 years) during the period June 21, 1996 (initial U.S. approval) through May 31, 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 meropenem. The majority of reports described adverse events that were likely due to comorbidities or concomitant medications (e.g., tinnitus and deafness with aminoglycosides, etc.), consistent with the known risks described in labeling (e.g., leukopenia, neutropenia, diarrhea, fever, rash, etc.), or had limited information which precluded a meaningful causality assessment.

Of the four serious and unlabeled adverse event cases included in this series, two cases of serum sickness and two cases of purpura (Henoch-Schönlein purpura [HSP]) were reported. We further explored serum sickness, serum sickness-like reaction, and HSP as adverse events of interest in all age groups and countries. We searched all reports within the FAERS database for cases of serum sickness, serum sickness-like reaction, or HSP. Our search identified two additional cases of serum sickness-like reaction; however, the first case was confounded by the recent administration of multiple antibacterial drugs and the second case was confounded by the concomitant administration of meropenem with vancomycin. Meropenem is labeled for hypersensitivity reactions and some of the components of serum sickness and serum-sickness like reaction such as fever and rash.

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

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

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY¹⁻³

Meropenem is a carbapenem antibacterial agent with a broad range of antimicrobial activity. Meropenem is indicated as a single antimicrobial agent for the treatment of complicated skin and skin structure infections (cSSSIs), complicated intra-abdominal infections (cIAIs), and bacterial meningitis.

Meropenem is indicated for pediatric patients and the label contains information from clinical studies in the pediatric population. In pediatric patients with serious bacterial infections (excluding meningitis), meropenem was studied in 515 patients (3 months to less than 13 years of age) at dosages of 10 to 20 mg/kg every 8 hours. The types of systemic and local adverse events seen in these patients were similar to adults. The most common adverse events reported as possibly, probably, or definitely related to meropenem were diarrhea (3.5%), rash (1.6%), and nausea and vomiting (0.8%). In pediatric patients with bacterial meningitis, meropenem was studied in 321 patients (3 months to less than 17 years of age) at a dosage of 40 mg/kg every 8 hours. The types of systemic and local adverse events seen in these patients were similar to adults. The most common adverse events reported as possibly, probably, or definitely related to meropenem were diarrhea (4.7%), rash (3.1%, mostly diaper area moniliasis), oral moniliasis (1.9%), and glossitis (1%). In the meningitis studies, in patients with no central nervous system abnormalities, the rates of seizure activity during therapy with meropenem were comparable with the rates observed in patients treated with comparator agents (either cefotaxime or ceftriaxone). In the group treated with meropenem, 12 of 15 patients with seizures had late onset seizures (defined as occurring on day 3 or later) versus 7 of 20 patients in the comparator arm. The meropenem group had a statistically higher number of patients with transient elevation of liver enzymes.

In December 2014, the Merrem IV indication was extended to pediatric patients less than 3 months of age with cIAIs after the completion of an open-label, non-comparative, multi-center, prospective, multiple-dose pharmacokinetic and safety study of meropenem in neonates and infants less than 91 days of age with suspected or definite cIAIs. Overall, meropenem was well tolerated in the studied population and out of the 11 deaths, none were attributed to the study medication. The majority of adverse events were reported in neonates less than 32 weeks gestational age and critically ill at baseline, making it difficult to assess the relationship of the adverse events to meropenem. Twenty-one patients (10.5%) had a treatment emergent adverse event (TEAE) considered to be possibly related to meropenem, and no patients had a TEAE that was considered to be probably or definitely related to meropenem. Of the TEAEs reported, sepsis (6%) and convulsions (5%) were the most frequently reported adverse events. Due to the limited evaluation of cerebrospinal fluid in patients who had seizures or seizure-like activity, it was not possible to determine if the seizure threshold changed due to possible underlying meningitis and the administration of meropenem. Other TEAEs reported and their rates of occurrence are as follows: hypokalemia (4.5%), increased conjugated bilirubin (4.5%), hypotension (3%), and patent ductus arteriosus (3%). Based on the safety results of this study, the use of meropenem was supported in neonates and infants less than 91 days of age for

cIAIs with dosing based on gestational and postnatal age. The recommended dosage of meropenem for pediatric patients 3 months of age and older with normal renal function is 10 mg/kg every 8 hours for cSSSIs, 20 mg/kg every 8 hours for cIAIs, and 40 mg/kg every 8 hours for meningitis. The recommended dosage for pediatric patients less than 3 months of age with cIAIs is listed in Table 1.1.1.

Age Group	Dose (mg/kg)	Dose Interval
Infants less than 32 weeks GA and PNA less than 2 weeks	20	Every 12 hours
Infants less than 32 weeks GA and PNA 2 weeks and older	20	Every 8 hours
Infants 32 weeks and older GA and PNA less than 2 weeks	20	Every 8 hours
Infants 32 weeks and older GA and PNA 2 weeks and older	30	Every 8 hours
There is no experience in pediatric patients with renal impairment		
Abbreviations: cIAI, complicated intra-abdominal infection; GA, gestational age; PNA, postnatal age		

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The current Merrem IV (meropenem for injection) product label provides the following information excerpted from the pertinent sections.³

-----CONTRAINDICATIONS-----

- Known hypersensitivity to product components or anaphylactic reactions to β -lactams.

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

- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving β -lactams.
- Seizures and other adverse CNS experiences have been reported during treatment.
- Co-administration of meropenem with valproic acid or divalproex sodium reduces the serum concentration of valproic acid potentially increasing the risk of breakthrough seizures.
- *Clostridium difficile*-associated diarrhea (ranging from mild diarrhea to fatal colitis) has been reported. Evaluate if diarrhea occurs.
- In patients with renal dysfunction, thrombocytopenia has been observed.

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

- Most common adverse reactions (2% or less) are: headache, nausea, constipation, diarrhea, anemia, vomiting, and rash.

-----DRUG INTERACTIONS-----

- Co-administration of MERREM IV with probenecid inhibits renal excretion of meropenem and is therefore not recommended.
- The concomitant use of meropenem and valproic acid or divalproex sodium is generally not recommended. Antibacterial drugs other than carbapenems should be considered to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium.

-----USE IN SPECIFIC POPULATIONS-----

- Renal Impairment: Dose adjustment is necessary, if creatinine clearance is 50 mL/min or less.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 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.

Date of Search	June 14, 2017
Time Period of Search	June 21, 1996* - May 31, 2017
Search Type	FAERS Business Intelligence Solution (FBIS) Profile Query Product-Manufacturer Reporting Summary
Product Name	Product Active Ingredient: Meropenem
Search Parameters	All ages, all outcomes, worldwide

* U.S. Approval date

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2.2.1 Total Adult and Pediatric FAERS Reports* from June 21, 1996 - May 31, 2017 with Meropenem

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	3,522 (449)	3,443 (388)	924 (93)
Pediatrics (0 - <17 years)	479 (94)	462 (80‡)	126 (9)

* 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

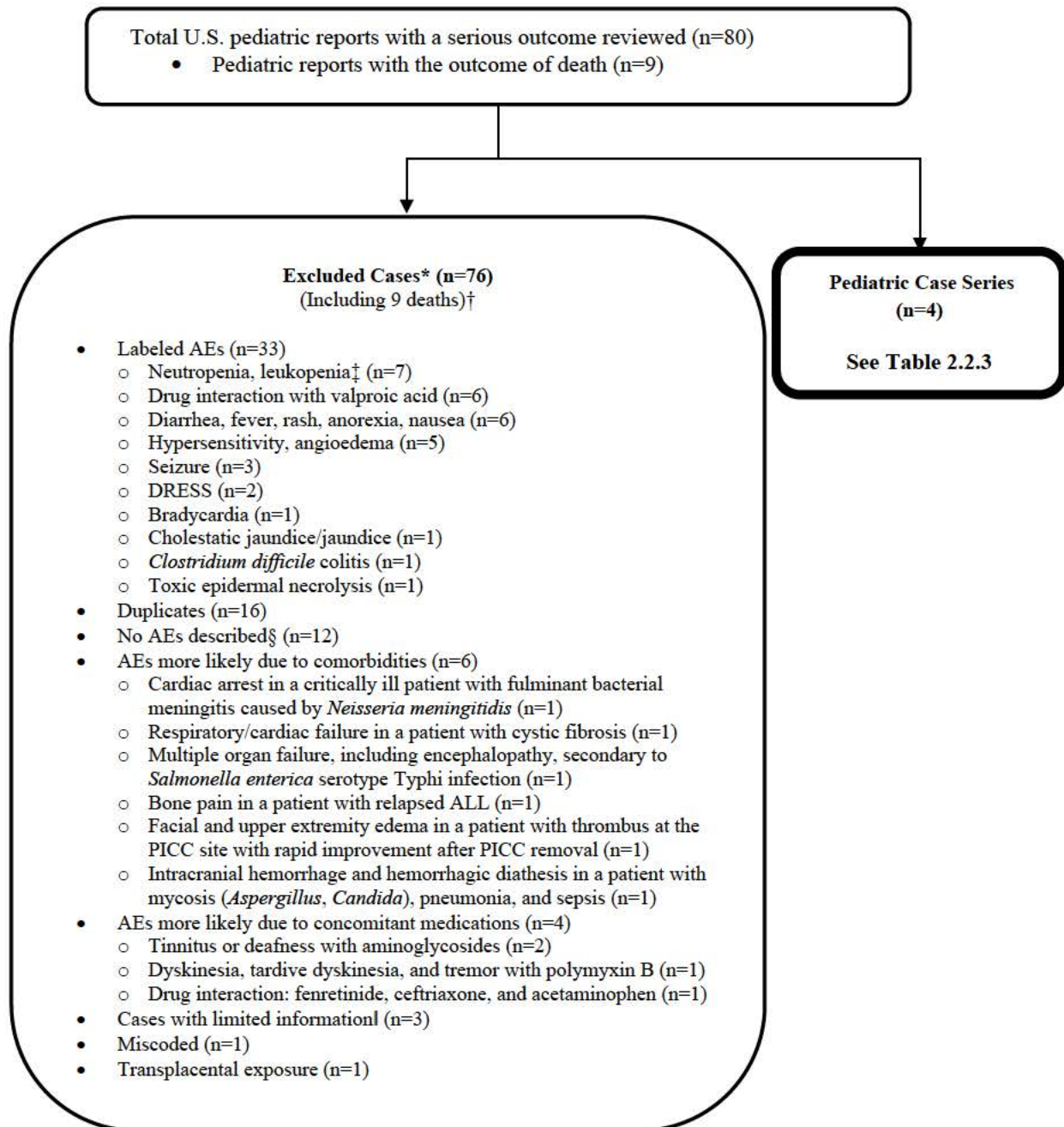
‡ See Figure 2.2.2

2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 80 pediatric U.S. 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 80 FAERS reports and excluded those where the adverse event was unlikely due to meropenem (i.e., cases not temporally related to the drug, other medications or underlying disease provide a more likely explanation), the case provided insufficient or contradictory information and the data cannot be supplemented or verified, described labeled events, and any duplicate reports.

Figure 2.2.2 Selection of Serious Pediatric Cases with Meropenem



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

† The nine cases resulting in death were excluded because they described treatment failure/development of resistance (n=3), were duplicates (n=2), described a case where death was attributed to *Clostridium difficile* sepsis (n=1), described a case of pneumonia and heart failure in a patient with cystic fibrosis and resistant *Pseudomonas aeruginosa* (n=1), described transplacental exposure (n=1), and described a fatal drug interaction between fenretinide, ceftriaxone, and acetaminophen (n=1)

‡ Three of the seven cases reported the concomitant administration of meropenem with drugs labeled for neutropenia or leukopenia (phenytoin and vancomycin [n=1], vancomycin [n=1], metronidazole [n=1]) and one of the seven cases reported neutropenia one day after starting meropenem (which was started after a 12-day course of cefazolin [labeled for neutropenia])

§ Indication related, treatment failure, development of resistance

¶ Unknown time to event, concomitant medications and comorbidities, clinical course and outcome

Abbreviations: AE, adverse event; ALL, acute lymphoblastic leukemia; DRESS, drug reaction with eosinophilia and systemic systems; PICC, peripherally inserted central catheter

2.2.3 Characteristics of Pediatric Case Series

Appendix B lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 2.2.3 Characteristics of Pediatric Case Series with Meropenem (N=4)

Age	6 - <12 years	2
	12 - < 17 years	2
Sex	Female	3
	Male	1
Reported Reason for Use	Cystic fibrosis/pulmonary infection	3
	Central nervous system infection	1
Coded Serious Outcomes*	Hospitalization	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, and other serious important medical events.

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: Serum Sickness (n=2)

FAERS Case Number **3699562 (version 1)**

Initial FDA Received Date August 20, 2001

Country USA

A 13-year-old male received intravenous meropenem (“40 mg/kg four times daily”) for cerebritis and left frontal and midline abscess; concomitant medications included carbamazepine and phenytoin. After receiving meropenem for 3 weeks, the patient was hospitalized and laboratory results revealed “increased liver functions tests” (results not reported), white blood count of 1.3 (baseline, normal range, units not reported), segmented neutrophils of 14% (baseline, normal range, units not reported), and an absolute neutrophil count of 273 (baseline, normal range, units not reported). Meropenem was discontinued for 4 days but was eventually restarted. Subsequently, the patient developed serum sickness with a rash and neutropenia on an unknown date. Meropenem and concomitant medications were discontinued and the patient recovered on an unknown date. The patient’s past medical history and other laboratory results were not reported.

Reviewer’s Comments: This case was confounded by the concomitant administration of meropenem with phenytoin and carbamazepine (and subsequent discontinuation at the same time) making it difficult to assess the extent of meropenem’s contribution to the reported events. Meropenem is labeled for rash, hypersensitivity reactions, and neutropenia³; phenytoin is labeled for granulocytopenia, rash, hypersensitivity reactions, and exfoliative or purpuric

dermatitis⁴; carbamazepine is labeled for agranulocytosis, rash, hypersensitivity reactions, and purpura.⁵

FAERS Case Number 12657679 (version 1)

Initial FDA Received Date August 16, 2016

Country USA

An 11-year-old female with cystic fibrosis received intravenous meropenem (dose and frequency not reported) for an unknown indication. Ten to 14 days after starting meropenem, “the patient experienced a rash and was hospitalized and told patient had serum sickness”. Meropenem was discontinued and the patient was initiated on other intravenous antibiotics. The outcome of the events of rash and serum sickness, past medical history, laboratory results, concomitant medications, and causality assessment were not reported.

Reviewer’s Comments: Limited case details preclude a meaningful causality assessment. Meropenem is labeled for rash and hypersensitivity reactions.³

2.4.2 *Unlabeled Events: Purpura and Vasculitis (n=1), Purpura (n=1)*

FAERS Case Number 5443486 (version 1)

Initial FDA Received Date July 26, 1996

Country USA

A 15-year-old female with cystic fibrosis received intravenous meropenem (3600 mg daily, frequency not reported) and fosfomycin (route, dose, and frequency not reported) for multidrug resistant organisms in the sputum. Three days after starting meropenem and fosfomycin, the patient developed cutaneous vasculitis as a manifestation of Henoch-Schönlein purpura (HSP). There was no renal or gut involvement and liver function tests were normal. Meropenem and fosfomycin were discontinued, and on an unknown date, it was reported there was a complete resolution of the event. On an unknown date, the patient was rechallenged with meropenem for 14 days and there were no signs of the previously reported event. No allergy testing or histological analysis was carried out and the only other reported concomitant medication was long-term prednisone.

Reviewer’s Comments: This case describes a positive dechallenge for meropenem and fosfomycin, and a negative rechallenge for meropenem with the reported event. HSP, also called immunoglobulin A vasculitis, is the most common form of systemic vasculitis in children; although microbiologic agents, vaccines, drugs, or genetics factors may play a causative role, the etiopathogenesis of HSP is not well defined.^{6,7}

FAERS Case Number 5607542 (version 1)

Initial FDA Received Date August 25, 1997

Country USA

An 11-year-old female with cystic fibrosis received intravenous meropenem (440 mg every 8 hours) and tobramycin (route, dose, and frequency not reported) for a pulmonary exacerbation. One to 2 days after starting meropenem and tobramycin, the patient experienced a palpable and purpuric rash in both feet which was diagnosed as HSP. The patient did not experience fever,

itching, or joint inflammation. Laboratory results, outcome, and causality assessment were not reported.

Reviewer's Comments: Tobramycin was initiated at the same time as meropenem making it difficult to assess the relationship of the event to meropenem. Meropenem is labeled for rash and erythema multiforme³; inhalational and intravenous tobramycin are labeled for rash.^{8,9} HSP, also called immunoglobulin A vasculitis, is the most common form of systemic vasculitis in children; although microbiologic agents, vaccines, drugs, or genetics factors may play a causative role, the etiopathogenesis of HSP is not well defined.^{6,7}

2.5 SUMMARY OF ADDITIONAL NON-FATAL ADVERSE EVENT CASES (N=2)

2.5.1 Unlabeled Event: Serum Sickness-like Reaction (n=2)

DPV searched the FAERS database for additional cases of serum sickness or serum sickness-like reaction associated with meropenem use in all age groups and countries using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms *Serum sickness* and *Serum sickness-like reaction*. Four additional cases were retrieved which included one case (age: 23 years) reporting serum sickness and three cases (age range: 3 – 34 years) reporting serum sickness-like reaction. The case of serum sickness and one case of serum sickness-like reaction were confounded by concomitant medications or comorbidities more likely to have caused the event (i.e., multiple concomitant anti-infective drugs, IgM-enriched polyclonal immunoglobulin, or infection). The remaining two cases of serum sickness-like reaction are described below:

<u>FAERS Case Number</u>	<u>3963196 (version 1)</u>
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Initial FDA Received Date	June 19, 2003
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Country	Canada
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A literature report¹⁰ described a 34-year old male with a past medical history of ventriculoperitoneal shunt placement for hydrocephalus secondary to a septum pellucidum cyst and no known drug allergies. The patient presented to the hospital with a suspected shunt infection and possible meningitis and he was subsequently started on intravenous vancomycin and cefotaxime. A cerebrospinal fluid culture grew *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, and the culture of the ventricular portion of the catheter grew *P. aeruginosa*, *Enterobacter cloacae*, and *Bacteroides fragilis*. Vancomycin and cefotaxime were discontinued and the patient was initiated on intravenous meropenem and oral ciprofloxacin. Meropenem was discontinued 11 days later and the patient was discharged on a planned two-month course of oral ciprofloxacin and metronidazole as his only medications. The following month, the patient was readmitted because of recurrent meningitis; ciprofloxacin and metronidazole were discontinued and he was started on intravenous vancomycin and cefotaxime (with intermittent ceftriaxone on a weekend leave) for 8 days. The remaining ventricular portion of the shunt was removed, the patient was then started on intravenous meropenem (2000 mg every 8 hours) for a planned 2-week course (vancomycin, cefotaxime, and ceftriaxone were discontinued), and he was discharged from the hospital with a home intravenous program. Six days later, the patient developed a pruritic rash and joint swelling.

The following day, the patient noticed erythematous macular lesions on his skin, accompanied by erythema and swelling of his fingers. The patient was seen in the emergency department and meropenem was discontinued because of a suspected serum sickness-like reaction. On physical examination, the patient was found to be mildly unwell with erythema multiforme and hand and finger edema; facial edema, mucosal lesions, lymphadenopathy, hepatomegaly and splenomegaly were not present. Laboratory values were within normal limits except for liver function test values which were moderately elevated. The following day, the patient was initiated on a 10-day course of prednisone 40 mg daily and a 1-week course of oral ciprofloxacin. Seven days later, the patient reported that his symptoms had improved and there was no evidence of skin or joint manifestations of the reaction; however, his liver transaminases and alkaline phosphatase levels had further increased but then decreased 2 weeks later. The patient subsequently reported mild persisting arthralgias of the hips, shoulders and hands. Approximately 5 weeks later, the arthralgias had resolved and liver profile improved. Serological tests for hepatitis B virus and hepatitis C virus and diagnostic tests for immune complexes were negative. An in vitro lymphocyte cytotoxicity assay was performed which indicated the patient's cells were markedly more sensitive to meropenem compared to control cells. The authors concluded the patient experienced a rare serum sickness-like reaction to meropenem because of the following factors: temporal relationship of meropenem to the development of events (ninth day of the patient's second course of meropenem), there were no other concomitant medications, the results of in vitro lymphocyte cytotoxicity assay, and medical work-up for other causes resulted in normal findings.

Reviewer's Comments: This case demonstrated a temporal onset of symptoms and positive dechallenge; however, it is confounded by the recent administration of multiple antibacterial drugs (cefotaxime, vancomycin, and ceftriaxone [labeled for serum sickness¹¹]). Meropenem is labeled for fever, rash, hypersensitivity reactions, anemia, agranulocytosis, neutropenia, leukopenia, thrombocytopenia, increased eosinophils, and increased creatinine.³

FAERS Case Number 8472615 (version 1)

Initial FDA Received Date March 22, 2012

Country Canada

A literature report¹² described a 3-year old male with a history of prematurity who was treated with intravenous vancomycin and meropenem for a ventriculoperitoneal shunt infection and brain abscess. On day 27 of vancomycin and day 14 of meropenem, the patient developed fever, bilateral knee swelling, and an erythematous maculopapular rash on his trunk and extremities. At the same time, the patient had elevated creatinine, elevated C reactive protein, eosinophilia, and hematuria. A sepsis workup and tests for autoimmunity were negative. On an unknown date, the patient developed transient coagulopathy and pancytopenia, which the authors attributed to vancomycin and meropenem. The patient was treated with 3 days of intravenous corticosteroids (methylprednisolone) and it was reported his symptoms improved soon after; the total duration of serum sickness-like symptoms was approximately 2 weeks. The authors considered this case as the first description of serum sickness-like symptoms with meropenem in the literature with a pediatric patient.

Reviewer's Comments: This case was confounded by the concomitant administration of meropenem with vancomycin making it difficult to assess the extent of meropenem's contribution to the reported events. Meropenem is labeled for fever, rash, hypersensitivity reactions, anemia, agranulocytosis, neutropenia, leukopenia, thrombocytopenia, increased eosinophils, and increased creatinine.³ Vancomycin is labeled for fever, drug fever, rash, agranulocytosis, neutropenia, thrombocytopenia, eosinophilia, and nephrotoxicity.¹³

2.5.2 Unlabeled Event: Serum Sickness-like Reaction

DPV searched the FAERS database for additional cases of HSP associated with meropenem use in all age groups and countries using the MedDRA preferred term *Henoch-Schonlein purpura*. Four adult cases (age range: 63 – 71 years) were retrieved; however, the cases were confounded by concomitant medications or comorbidities more likely to have caused the event (i.e., trimethoprim/sulfamethoxazole [labeled for HSP¹⁴], chemotherapy, or infection).

3 DISCUSSION

Although we reviewed all serious FAERS reports from the U.S. with meropenem in the pediatric population (ages 0 - < 17 years) during the period June 21, 1996 (initial U.S. approval) through May 31, 2017, only four cases were included in our case series. Of the reports reviewed, there were no new safety signals identified and no increased severity or frequency of any labeled adverse events. Most reports described adverse events that were likely due to comorbidities or concomitant medications (e.g., tinnitus and deafness with aminoglycosides, etc.), consistent with the known risks described in labeling (e.g., leukopenia, neutropenia, diarrhea, fever, rash etc.), or contained limited information which precluded a meaningful causality assessment.

Of the four serious and unlabeled adverse event cases included in this series, two cases of serum sickness and two cases of HSP were reported. We further explored serum sickness, serum sickness-like reaction, and HSP as adverse events of interest in all age groups and countries. Our search identified two additional cases of serum sickness-like reaction; however, the first case was confounded by the recent administration of multiple antibacterial drugs and the second case was confounded by the concomitant administration of vancomycin with meropenem. Meropenem is labeled for hypersensitivity reactions and some of the components of serum sickness and serum-sickness like reactions including fever and rash.³ The three other FDA-approved carbapenems (Primaxin® [imipenem and cilastatin], Invanz® [ertapenem], and Doribax® [doripenem]) are not labeled for serum sickness, serum sickness-like reaction, or HSP; however, they are all labeled for rash, fever, and hypersensitivity reactions.¹⁵⁻¹⁷

4 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with meropenem 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 meropenem.

6 REFERENCES

- 1) Development Resources for Medical, Statistical, and Clinical Pharmacology Reviews of Pediatric Studies Conducted under Section 505A and 505B of the Federal Food, Drug, and Cosmetic Act, as amended by the FDA Safety and Innovation Act of 2012 (FDASIA). Available at: <http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm316937.htm>. Accessed: July 2017.
- 2) U.S. Food & Drug Administration, New Pediatric Labeling Information Database. Available at: <https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase>. Accessed: July 2017.
- 3) Merrem® IV (meropenem for injection), NDA 05006 – Approved Product Label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/050706s037lbl.pdf. Accessed: July 2017.
- 4) Dilantin® (phenytoin sodium), NDA 084349 – Approved Product Label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/084349s080lbl.pdf. Accessed: September 2017.
- 5) Tegretol® (carbamazepine), NDA 016608 – Approved Product Label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/016608s097,018281s045,018927s038,020234s026lbl.pdf. Accessed: September 2017.
- 6) Barut K, Sahin S, Kasapcopur O. Pediatric vasculitis. *Curr Opin Rheumatol*. 2016;28:29-38.
- 7) Rigante D, Castellazzi L, Bosco A, Esposito S. Is there a crossroad between infections, genetics, and Henoch-Schönlein purpura? *Autoimmun Rev*. 2013;12:1016-21.
- 8) TOBI® (tobramycin inhalational solution), NDA 050753 – Approved Product Label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050753s018lbl.pdf. Accessed: September 2017.
- 9) Tobramycin for injection, NDA 050789 – Approved Product Label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050789s005lbl.pdf. Accessed: September 2017.
- 10) Ralph ED, John M, Rieder MJ, Bombassaro AM. Serum sickness-like reaction possibly associated with meropenem use. *Clin Infect Dis*. 2003;36:E149-51.
- 11) Rocephin® (ceftriaxone sodium), NDA 050624 – Approved Product Label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/50585s057,50624s027lbl.pdf. Accessed October 2017.
- 12) Leo SH, Chan ES. Serum sickness-like reaction associated with meropenem in a 3-year old child. *Allergy Asthma Clin Immunol*. 2010;6(Suppl 2):P31.
- 13) Vancomycin Injection, NDA 050671 – Approved Product Label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050671s024lbl.pdf. Accessed October 2017.
- 14) Bactrim™ (sulfamethoxazole and trimethoprim), NDA 017377 – Approved Product Label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/017377s074lbl.pdf. Accessed October 2017.
- 15) Primaxin® (imipenem and cilastatin), NDA 050587 – Approved Product Label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/050587s074lbl.pdf. Accessed October 2017.
- 16) Invanz® (ertapenem for injection), NDA 021337 – Approved Product Label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021337s042lbl.pdf. Accessed: October 2017.
- 17) Doribax® (doripenem for injection), NDA 022106 – Approved Product Label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022106s015lbl.pdf. Accessed October 2017.

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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 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 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.

7.2 APPENDIX B. LINE LISTING OF THE FAERS CASE SERIES FOR MEROPENEM

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome*
1	August 20, 2001	3699562	1	2001UW09993	Expedited (15-Day)	13	Male	USA	HO
2	August 16, 2016	12657679	1	US-ASTRAZENECA-2016SE87319	Expedited (15-Day)	11	Female	USA	HO
3	July 26, 1996	5443486	1	07171996U004	Expedited (15-Day)	15	Female	USA	HO
4	August 25, 1997	5607542	1	08131997M010	Expedited (15-Day)	11	Female	USA	HO
5	June 19, 2003	3963196	1	2003AP02180	Expedited (15-Day)	34	Male	Canada	RI
6	March 22, 2012	8472615	1	CA-ASTRAZENECA-2012SE17374	Expedited (15-Day)	3	Male	Canada	OT

*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, or a congenital anomaly/birth defect, required intervention and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome.

Abbreviations: HO, Hospitalization; OT, Other medically significant; RI, Required intervention

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/s/

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