CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212593Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 23, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 212593
Product Name and Strength:	Vasopressin Injection, 20 units per mL
Applicant/Sponsor Name:	American Regent Inc.
OSE RCM #:	2019-747-3
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling and Prescribing Information (PI) received on July 22, 2020 for Vasopressin. We review the revised container label and carton labeling for Vasopressin (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations made by Office of Product Quality to update the storage information in all labeling.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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MAXIMILIAN STRAKA
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 29, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 212593
Product Name and Strength:	Vasopressin Injection, 20 units per mL
Applicant/Sponsor Name:	American Regent Inc.
OSE RCM #:	2019-747-2
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

This review evaluates the proposed container label, carton labeling, and Prescribing Information (PI) for Vasopressin (NDA 212593) for areas of vulnerability that may lead to medication errors. We reviewed this as part of the evaluation of the 505(b)(2) Class I resubmission for Vasopressin injection. DMEPA provided recommendations during previous label and labeling reviews.[ab]

1.1 REGULATORY HISTORY

American Regent Inc. submitted Vasopressin Injection (NDA 212593) on March 29, 2019, a 505(b)(2) which relies upon the Listed Drug (LD), Vasostrict (Vasopressin Injection, USP) under NDA 204485. Vasostrict is currently marketed as 20 units/mL single dose vial and 200 units/10 mL (20 units/mL) multiple dose vial. The proposed product will only be available in the 20 units/mL single dose vial presentation.

[a] Thomas S. Label and Labeling Review for Vasopressin (NDA 212593). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 26. RCM No.: 2019-747.
[b] Thomas S. Label and Labeling Review for Vasopressin (NDA 212593). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 14. RCM No.: 2019-747-1

The application received a tentative approval letter dated January 28, 2020 with final approval being subject to expiration of a period of patent protection and/or exclusivity. American Regent submitted a request for final approval on June 4, 2020.

2 DISCUSSION

We note that Vasopressin Injection has the same active ingredient, strength (20 units/mL), dosage form (injection), route of administration (intravenous), storage requirements, dosing regimen, and administration as the reference listed drug, Vasostrict. As stated above the proposed product will only be available in the single-dose vial presentation.

The Listed Drug (LD), Vasostrict (Vasopressin Injection, USP) prescribing information indicates, "Vials may be held up to 12 months upon removal from refrigeration to room temperature storage conditions (20°C to 25°C [68°F to 77°F], USP Controlled Room Temperature), anytime within the labeled shelf life. Once removed from refrigeration, unopened vials should be marked to indicate the revised 12-month expiration date. If the manufacturer's original expiration date is shorter than the revised expiration date, then the shorter date must be used. Do not use Vasostrict beyond the manufacturer's expiration date stamped on the vial." Therefore, the applicant removed the statement (b) (4) from the container label and carton labeling to bring them in line with the LD.

We performed a risk assessment of the proposed container label, carton labeling, and PI to identify deficiencies that may lead to medication errors.

3 CONCLUSION

The proposed container label, carton labeling, and PI are acceptable from a medication error perspective. We have no recommendation at this time.

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MAXIMILIAN STRAKA
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HINA S MEHTA
06/30/2020 01:17:22 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 14, 2020
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 212593
Product Name and Strength:	Vasopressin Injection, 20 units per mL
Applicant/Sponsor Name:	American Regent Inc.
OSE RCM #:	2019-747-1
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on January 3, 2020 for Vasopressin. The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container label and carton labeling for Vasopressin (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 DISCUSSION

In discussion with the review team about the appropriate quantity expression to include in the chlorobutanol statement, the review team determined the appropriate statement should read "Contains 5 mg/mL chlorobutanol as a preservative." We find this determination acceptable from a medication safety perspective.

Also, American Regent commented in their January 3rd, 2020 submission that in order to fit important information regarding "chlorobutanol" the statement "(b) (4) See Prescribing Information" has been removed from the container label. We find this revision acceptable from a medication safety perspective.

[a] Thomas S. Label and Labeling Review for Vasopressin (NDA 212593). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 26. RCM No.: 2019-747.

3 CONCLUSION

Upon review of the revised container label and carton labeling, we note that the Applicant implemented all of our recommendations, and we have no additional recommendations at this time.

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01/14/2020 06:35:34 PM

CHI-MING TU
01/15/2020 09:47:39 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 18, 2019

To: Charu Gandotra, M.D.
Division of Cardiovascular and Renal Products (DCaRP)

Quynh Nguyen, Regulatory Project Manager, DCaRP

Michael Monteleone, MS, Associate Director for Labeling, DCaRP

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for VASOPRESSIN INJECTION

NDA: 212593

In response to DCaRP's consult request dated June 4,2019, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for VASOPRESSIN INJECTION.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DCaRP on December 4, 2019, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling accessed via SharePoint on December 17, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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/s/

DAVID F FOSS
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health PLLR Memorandum

Date: December 13, 2019 **Date Consulted:** June 4, 2019

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: Vasopressin Injection

NDA: 212593

Applicant: American Regent, Inc (ARI)

Subject: Pregnancy and Lactation Labeling

Drug Class: Anti-hypotensive

Indication: To increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.

Materials Reviewed:

- March 29, 2019 Applicant's submission for Vasopressin Injection, an original application, initial submission.
- June 4, 2019 DCRP's consult request to DPMH for Vasopressin Injection labeling review, DARRTS Reference ID: 4443586
- July 9, 2019 submitted proposed PLLR labeling with all supporting documentations

Consult Question: Assist with Pregnancy and Lactation Labeling Rule (PLLR).

INTRODUCTION AND BACKGROUND

On March 29, 2019, the applicant, ARI, submitted an original application for Vasopressin Injection, NDA 212593. The Division of Cardiovascular and Renal Products (DCRP) consulted the Division of Pediatric and Maternal Health (DPMH) on June 4, 2019, to provide input for appropriate labeling of the pregnancy and lactation subsections of Vasopressin Injection to comply

with the Pregnancy and Lactation Labeling Rule (PLLR) content and format.

Regulatory History

Vasopressin Injection, USP is an unapproved product marketed in the United States by American Regent, Inc. Since September 1993, Vasopressin Injection, USP, has been marketed for prevention and treatment of postoperative abdominal distention, use in abdominal roentgenography to dispel interfering gas shadows, and use in diabetes insipidus. The new application has a different indication, namely "Increase of blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines". It is filed as a 505(b)(2) and relies on the literature and the Agency's determination of safety and effectiveness for Vasostrict (vasopressin) (NDA 204485) by Par Pharmaceuticals.

Vasopressin Drug Characteristics[1]

- Molecular Weight is 1084.23 Daltons
- Terminal elimination Half-life is <10 min
- Protein binding is 1%
- Genotoxic/mutagenic: No
- Drug Class: Vasopressin analog, vasoconstrictor.

Current State of Labeling

Vasopressin Injection is not an approved drug. The listed drug relied upon Vasostrict (vasopressin) Injection, was approved on April 17, 2014. The current labeling of Vasostrict, approved on May 14, 2019, is in PLR and in a hybrid format, not PLLR. It states:

> FULL PRESCRIBING INFORMATION
>
> 8 USE IN SPECIFIC POPULATIONS
> 8.1 Pregnancy
> Pregnancy Category C
> Risk Summary: There are no adequate or well-controlled studies of Vasostrict in pregnant women. It is not known whether vasopressin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Animal reproduction studies have not been conducted with vasopressin *[see Clinical Pharmacology (12.3)]*.
> Clinical Considerations: Because of increased clearance of vasopressin in the second and third trimester, the dose of Vasostrict may need to be up-titrated to doses exceeding 0.1 units/minute in post-cardiotomy shock and 0.07 units/minute in septic shock.
> Vasostrict may produce tonic uterine contractions that could threaten the continuation of pregnancy.
>
> 8.3 Nursing Mothers
> It is not known whether vasopressin is present in human milk. However, oral absorption by a nursing infant is unlikely because vasopressin is rapidly destroyed in the gastrointestinal tract. Consider advising a lactating woman to pump and discard breast milk for 1.5 hours after receiving vasopressin to minimize potential exposure to the breastfed infant.

[1] Vasostrict (vasopressin) last approved labeling of May 14, 2019

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Vasopressin was found to be negative in the in vitro bacterial mutagenicity (Ames) test and the in vitro Chinese hamster ovary (CHO) cell chromosome aberration test. In mice, vasopressin has been reported to have an effect on function and fertilizing ability of spermatozoa.

REVIEW

Non Clinical Review

The applicant did not perform any non clinical studies and did not present any non clinical literature review.

Review of Literature

Applicant's Review

ARI conducted an evaluation of the medical literature on the effectiveness (efficacy) and safety of parenterally administered arginine vasopressin (AVP). The review focused on ARI's proposed indication of increasing blood pressure of individuals 18 years of age and older in vasodilatory shock (e.g. post-cardiotomy or sepsis) who remain hypotensive despite treatment with fluids and catecholamines. The search included all relevant articles published in English up to September 17, 2018 in the life sciences (Medline, PubMed,), biomedical (Medline, EMBASE, PubMed), and systematic reviews (Cochrane Library) literature. In addition, clinical practice guideline and clinical trials databases were searched. No relative publications on use of Vasopressin Injection during pregnancy were identified.

DPMH Review

In addition to the search of published literature performed by the applicant, DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases for Vasopressin Injection use in pregnancy.

- Reprotox/TERIS does not report any human literature. Endogenous vasopressin concentrations increase near term and in labor.[2] Vasopressin receptors are present in human uterine muscle and might not be distinguishable from oxytocin receptors.[3]
- GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation state: "No reports linking the use of vasopressin with congenital defects have been located." They cite the Robinson[2] publication that a "threefold increase of circulating levels of endogenous vasopressin" has been reported for women in the last trimester and in labor as compared with nonpregnant women. Induction of uterine activity in the 3rd trimester has been reported after IM and intranasal vasopressin use.[4]

This reviewer did not identify any additional publications on use of vasopressin in pregnancy.

Review of the Pharmacovigilance (PV)

The applicant identified 16 published safety-related case reports through their Pharmacovigilance department's literature. None of these case reports were considered relevant. The applicant states that "there were no cases reporting pregnancy, drug exposure in utero, exposures during breast feeding/lactation, and male infertility".

[2] Robinson KW, Hawker RW, Robertson PA. Antidiuretic hormone (ADH) in the human female. J Clin Endocrinol Metab 1957;17:320-2.

[3] Ivanisevic M, Behrens O, Helmer H, Demarest K, Fuchs AR. Vasopressin receptors in human pregnant myometrium and decidua: interactions with oxytocin and vasopressin agonists and antagonists. Am J Obstet Gynecol 1989;161:1637-43.

[4] Oravec D, Lichardus B. Management of diabetes insipidus in pregnancy. Br Med J 1972;4:114-5.

Drug Utilization Rates amongst Females of Reproductive Potential
No utilization rates have been presented by the applicant because it is not "available to them."

Summary
There is no published literature on the effects of vasopressin use in pregnancy to inform a drug-associated risk for major birth defects, miscarriage or adverse maternal or fetal outcomes.

LACTATION

Review of Literature
The applicant did not provide any literature animal or human with vasopressin use in lactation.

- TOXNET/LACTMED states that "No information is available on the clinical use of vasopressin during breastfeeding."
- GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation state:
  > Patients receiving vasopressin, desmopressin, or lypressin for diabetes insipidus have been reported to breastfeed without apparent problems in the infant.[5,6] Experimental work in lactating women suggests that suckling almost doubles the maternal blood concentration of vasopressin.[2]
- Thomas Hale in Medications and Mothers' Milk states:
  > Although [vasopressin] probably passes to some degree into human milk, it is rapidly destroyed in the gastrointestinal tract by trypsin and must be administered by injection or intranasally. Hence, oral absorption by a nursing infant is very unlikely.

Summary
There are no data on the presence of vasopressin injection in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The PLLR risk/benefit statement for breastfeeding should be included in the labeling for Subsection 8.2: "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VASOPRESSIN INJECTION and any potential adverse effects on the breastfed infant from VASOPRESSIN INJECTION or from the underlying maternal condition".

FEMALES and MALES of REPRODUCTIVE POTENTIAL

Neither the applicant nor this reviewer identified any literature on use of vasopressin in Females and Males of Reproductive Potential or on vasopressin's effects on Fertility. Because the drug is not genotoxic /mutagenic and is not associated with any malformations to the fetus, there is no need for contraception and pregnancy testing. Therefore, subsection 8.3 Females and Males of Reproductive Potential will be omitted.

LABELING RECOMMENDATIONS

DPMH attended the labeling meeting on December 2, 2019. DPMH discussed PLLR labeling recommendations with DCRP during the meeting and subsequent email exchanges. Subsections 8.1 and 8.2 of labeling were revised for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

[5] Hime MC, Richardson JA. Diabetes insipidus and pregnancy. Obstet Gynecol Surv 1978;33:375-9.
[6] Hadi HA, Mashini IS, Devoe LD. Diabetes insipidus during pregnancy complicated by preeclampsia. A case report. J Reprod Med 1985;30:206-8

HIGHLIGHTS

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

- **Pregnancy:** May induce tonic uterine contractions. (8.1)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on VASOPRESSIN INJECTION use in pregnant women to inform a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. (b) (4) Animal reproduction studies have not been conducted with vasopressin.

(b) (4)

Clinical Considerations

Dose Adjustments during Pregnancy and the Postpartum Period

Because of increased clearance of vasopressin in the second and third trimester, the dose of vasopressin injection may need to be (b) (4) *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

Maternal Adverse Reactions

Vasopressin injection may produce tonic uterine contractions. Vasopressin receptors are present in human uterine muscle and might not be distinguishable from oxytocin receptors.

8.2 Lactation

Risk Summary

There are no data on the presence of vasopressin in either human or animal milk, the effects on the breastfed infant, or the effects on milk production.*

* The PLLR Policy Working Group agreed (May 2019) that the standard risk/benefit (R/B) statement used in 8.2 Lactation "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Drug Name and any potential adverse effects on the breastfed infant from Drug Name or from the underlying maternal condition" was misleading for emergency situations and it is reasonable to delete the R/B statement from 8.2. Thus far, this approach was applied to Atropine sulfate and Glucagon labeling.

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CHRISTOS MASTROYANNIS
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TAMARA N JOHNSON
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 26, 2019
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 212593
Product Name and Strength:	Vasopressin Injection, 20 units per mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	American Regent Inc.
FDA Received Date:	July 9, 2019 and November 18, 2019
OSE RCM #:	2019-747
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As a part of the NDA review process, this review evaluates the proposed vasopressin container label, carton labeling, and prescribing information (PI) for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Vasopressin Injection, USP is an unapproved product that has been marketed in the United States by American Reagent (formerly Luitpold Inc.) from September 1993 through November 1, 2012 for the prevention and treatment of postoperative abdominal distention, in abdominal roentgenography to dispel interfering gas shadows, and in diabetes insipidus. Vasopressin is also used off-label for the treatment of esophageal varices, gastrointestinal hemorrhage, cardiac arrest, septic shock, and vasodilatory shock.

The sponsor submitted a 505(b)(2) application for Vasopressin Injection on March 29, 2019 with the proposed indication "to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines." The listed drug is Vasostrict (vasopressin), NDA 204485. The sponsor has also submitted published literature since April 17, 2014, the approval date for Vasostrict® (vasopressin), NDA 204485, to support the application.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters*	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Upon review of the proposed Vasopressin Injection, we note that the proposed storage instruction is different from the currently marketed Vasostrict (Vasopressin Injection, USP). Currently, healthcare professionals are used to storing Vasostrict refrigerated or unopened at room temperature for 12 months. (b) (4) We emailed the review team on August 13, 2019 to clarify the storage instruction for the proposed product. The review team responded on August 14, 2019 that the sponsor currently does not have the stability data to support that (b) (4) Given the lack of stability data at the time of this review, to prevent wrong storage errors, we will ensure the storage instructions are clearly visible on the proposed container label and carton labeling and clearly communicated in the proposed PI.

We also note that the proposed Vasopressin Injection 20 units/mL vials contain the preservative chlorobutanol, which differs from the currently marketed preservative-free Vasostrict 20 units/mL vials. Currently in practice, because the Vasostrict 200 units/10 mL vial contains chlorobutanol and is contraindicated in patients with known allergy to this preservative, healthcare professionals are used to selecting and administering the preservative-free Vasostrict 20 units/mL vial for use in patients with allergy to chlorobutanol. Due to the overlap in vial size (1 mL) between the proposed Vasopressin Injection 20 units/mL vial and currently marketed Vasostrict 20 units/mL vial, we are concerned for the risk of medication error associated with the use of the proposed Vasopressin Injection 20 units/mL vial in patients with known allergy to chlorobutanol. Therefore, we will ensure the proposed Vasopressin Injection 20 units/mL container label and carton labeling communicate the presence of chlorobutanol in the vials.

Our review of the proposed container label, carton labeling, and prescribing information (PI) for Vasopressin Injection identified areas where the label and labeling may be improved to promote the safe use of the product. Thus, we provide related recommendations below in Section 4.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container label, carton labeling, and prescribing information (PI) for Vasopressin Injection may be improved to promote the safe use of the product as described in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

1. Dosage and Administration Section, Highlights of PI

a. We recommend adding the units (e.g., units/minute) behind each dose numerical value (e.g., Post-cardiotomy shock: 0.03 units/minute to 0.1 units/minute).

b. Consider adding a statement similar to "See Full Prescribing Information for instructions on dilution and administration of vasopressin injection." after the last bullet in the Dosage and Administration section of the Highlights of PI.

2. Dosage Forms and Strengths, Highlights of PI

   a. Consider including limited packaging information that facilitates prescribing (e.g., Injection: 20 units per mL in single-dose vial).

4.2 RECOMMENDATIONS FOR AMERICAN REGENT INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container label & Carton Labeling)

1. Revise the storage statement "(b) (4) to improve readability, and because the storage instructions are different than the currently marketed Vasostrict product.
2. We note that the PI states "Do not freeze," but the container label and carton labeling do not contain this warning. If space allows, include the warning, "Avoid freezing," on the container label and carton labeling with the other storage information.
3. Consider revising the statements "1 mL Single Dose Vial" on the container label and "25 x 1 mL Single Dose Vials" on the carton labeling to read "1 mL Single Dose Vial- Discard Unused Portion" and "25 x 1 mL Single Dose Vials- Discard Unused Portion".[a]
4. Revise the statement "(b) (4) See Prescribing Information." to read "Recommended dosage: see prescribing information."
5. Consider relocating the manufacturer information to the side panel as it clutters the PDP and takes readers' attention away from important information such as strength and route of administration.[b]

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[a] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2018. Available from https://www.fda.gov/downloads/Drugs/Guidances/UCM468228.pdf.

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

6. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.
   The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.
7. Ensure the lot number and expiration date are clearly differentiated from one another.[c] Also ensure that the lot number and expiration date are not located in close proximity to other numbers where the numbers can be mistaken as the lot number or expiration date.[d]
8. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use for the expiration date. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date.[e]

B. Container Label

1. We recommend adding the statement in red text "Contains 0.5% chlorobutanol as a preservative.", in reverse lettering "Contains 0.5% chlorobutanol as a preservative.", or by another means with adequate color contrast and prominence to the side panel, in order to promote the safe use of your proposed Vasopressin Injection product. Currently in practice, because the Vasostrict 200 units/10 mL vial contains chlorobutanol and is contraindicated in patients with known allergy to this preservative, healthcare professionals are used to selecting and administering the preservative-free Vasostrict 20 units/mL single-dose vial for patients with known allergy to chlorobutanol. Due to the overlap in vial size (1 mL) between your proposed Vasopressin Injection product containing

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[c] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert A cute Care. 2014;19(23):1-4.

[d] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

[e] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf

chlorobutanol and the currently marketed preservative-free Vasostrict 20 units/mL single-dose vial, we are concerned for the risk of medication error associated with the use of the proposed Vasopressin Injection 20 units/mL vial in patients with known allergy to chlorobutanol.

C. Carton Labeling

1. We recommend adding the statement in red text "Contains 0.5% chlorobutanol as a preservative.", in reverse lettering "Contains 0.5% chlorobutanol as a preservative.", or by another means with adequate color contrast and prominence to the side panel, in order to promote the safe use of your proposed Vasopressin Injection product. Currently in practice, because the Vasostrict 200 units/10 mL vial contains chlorobutanol and is contraindicated in patients with known allergy to this preservative, healthcare professionals are used to selecting and administering the preservative-free Vasostrict 20 units/mL single-dose vial for patients with known allergy to chlorobutanol. Due to the overlap in vial size (1 mL) between your proposed Vasopressin Injection product containing chlorobutanol and the currently marketed preservative-free Vasostrict 20 units/mL single-dose vial, we are concerned for the risk of medication error associated with the use of the proposed Vasopressin Injection 20 units/mL vial in patients with known allergy to chlorobutanol.
2. Consider adding "Use normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) when diluting vasopressin injection." to one of the side panels.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vasopressin received on July 9, 2019 from American Regent Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Vasopressin and the Listed Drug		
Product Name	Vasopressin (NDA 212593)	Vasostrict (vasopressin)[f] (NDA 204485)
Initial Approval Date	N/A	April 17, 2014
Active Ingredient	vasopressin	vasopressin
Indication	Vasopressin injection is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.	Vasostrict is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	Injection
Strength	20 units per mL	20 units per mL 200 units per 10 mL (20 units per mL)
Dose and Frequency	• Dilute vasopressin injection with normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) to either 0.1 units/mL or 1 unit/mL for intravenous administration. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration. • Post-cardiotomy shock: 0.03 units/minute to 0.1 units/minute, with up-titration by 0.005 units/minute at 10- to 15-	• Dilute Vasostrict with normal saline or 5% dextrose in water to either 0.1 units per mL or 1 unit per mL for intravenous administration. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration. • Post-cardiotomy shock: 0.03 units per minute to 0.1 units per minute, with up-titration by 0.005 units per minute at ten to fifteen minute intervals • Septic shock: 0.01 units per minute to 0.07 units per minute, with up-titration by 0.005 units

[f] Vasostrict [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 AUG 14. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204485s009lbl.pdf.

	minute intervals • Septic shock: 0.01 units/minute to 0.07 units/minute, with up-titration by 0.005 units/minute at 10- to 15-minute intervals • After target blood pressure has been maintained for 8 hours without the use of catecholamines, taper vasopressin injection by 0.005 units/minute every hour as tolerated to maintain target blood pressure.	per minute at ten to fifteen minute intervals • After target blood pressure has been maintained for eight hours without the use of catecholamines, taper Vasostrict by 0.005 units per minute every hour as tolerated to maintain target blood pressure.
How Supplied	NDC 0517-1020-25: A carton of 25 single dose vials each containing vasopressin 1 mL at 20 units/mL.	NDC 42023-164-25: A carton of 25 single dose vials each containing vasopressin 1 mL at 20 units/mL. NDC 42023-190-01: A carton of 1 multiple dose vial containing vasopressin 10 mL at 200 units/10 mL (20 units/mL)
Storage	(b) (4)	Store between 2°C and 8°C (36°F and 46°F). Do not freeze. Vials may be held up to 12 months upon removal from refrigeration to room temperature storage conditions (20°C to 25°C [68°F to 77°F], USP Controlled Room Temperature), anytime within the labeled shelf life. Once removed from refrigeration, unopened vial should be marked to indicate the revised 12 month expiration date. If the manufacturer's original expiration date is shorter than the revised expiration date, then the shorter date must be used. Do not use Vasostrict beyond the manufacturer's expiration date stamped on the vial. Discard the 10 mL vial 30 days after first puncture.

Container Closure	2 mL, [redacted] glass, Type [redacted] 13 mm [redacted] vials	• Vial, 10 mL [redacted] d, 10 mm Type [redacted] USP • Stopper, 13 mm [redacted] Grey • Cap, 13 mm Flip-off [redacted]

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 14 and 15, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, vasopressin, Vasostrict, and NDA #s 212593 and 204485. Our search identified 10 previous reviews[g,h,i,j,k,l,m,n,o,p], and we considered our previous recommendations to see if they are applicable for this current review.

[g] DeFronzo K. Label, Labeling and Packaging Review for (b) (4) (NDA 204485). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 JUNE 7. OSE RCM No.: 2012-2808.

[h] Stewart J. Label and Labeling Review for Vasostrict (NDA 204485). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 FEB 12. OSE RCM No.: 2013-2864.

[i] Stewart J. Label and Labeling Review Memo for Vasostrict (NDA 204485). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 FEB 26. OSE RCM No.: 2013-2864-1.

[j] Stewart J. Label and Labeling Review Memo for Vasostrict (NDA 204485). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 APRIL 8. OSE RCM No.: 2013-2864-2.

[k] Stewart J. Label and Labeling Review for Vasostrict (NDA 204485/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JULY 28. OSE RCM No.: 2014-1283.

[l] Gao T. Label and Labeling Review for Vasostrict (NDA 204485/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MARCH 27. OSE RCM No.: 2015-563.

[m] Thomas, S. Label and Labeling Review for Vasostrict (vasopressin), NDA 204485/S-004. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUNE 22. RCM NO.: 2016-1060.

[n] Thomas, S. Label and Labeling Review Memo for Vasostrict (vasopressin), NDA 204485/S-004. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 OCT 25. RCM NO.: 2016-2236.

[o] Thomas, S. Label and Labeling Review Memo for Vasostrict (vasopressin), NDA 204485/S-004. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 DEC 15. RCM NO.: 2016-2236-1.

[p] Lowery, A. Memo for Vasopressin injection. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 17. RCM No.: 2017-2136.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[q] along with postmarket medication error data, we reviewed the following Vasopressin Injection label and labeling submitted by American Regent Inc.

- Container label received on November 18, 2019
- Carton labeling received on November 18, 2019
- Prescribing Information (Image not shown) received on July 9, 2019

G.2 Label and Labeling Images

Container Label

[q] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Memorandum

Date:	October 10, 2019
Reviewer:	Christine Chamberlain, PharmD, CDE, Safety Evaluator, Division of Pharmacovigilance I (DPV-I)
Team Leader:	Christian Cao, MPAS, PA-C Safety Evaluator Team Leader, DPV-I
Product Name:	Vasopressin Injection, USP
Subject:	All Adverse Events with Serious Outcome(s)
Application Type/Number:	NDA 212593
Applicant/Sponsor:	American Regent
OSE RCM #:	2019-1667

1 INTRODUCTION

The Division of Cardiovascular and Renal Products (DCaRP) requested a search of the FDA Adverse Event Reporting System (FAERS) for postmarket adverse event reports with a *serious* outcome for vasopressin injection in adult and pediatric patients. This information was requested to support the review of NDA 212593, vasopressin injection USP, a 505(b)(2) application referenced to NDA 204485 (Vasostrict). The proposed indication is to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. The Division of Pharmacovigilance I (DPV-I) provides a high-level analysis of recent (from January 1, 2013 to September 17, 2019) adverse events reported for vasopressin in FAERS to augment safety information being reviewed for NDA 212593 (vasopressin).

2 METHODS AND MATERIALS

DPV-I searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of Search	September 18, 2019
Time Period of Search	January 1, 2013† - September 17, 2019
Search Type	FBIS Product-Manufacturer Reporting Summary (Profile Report) and Quick Query
Product Terms	Product active ingredient: Vasopressin
MedDRA Search Terms (Version 22.0)	All Preferred Terms (PTs)
Regulatory Outcome	Serious‡
Age (Quick Query Search)	Search 1: all reports Search 2: 0-17.99 years of age (pediatrics) Search 3: 18 years of age and older (adults)
* See Appendix A for a description of the FAERS database. † Update to previous DPV-I review[1] completed on January 22, 2013 (time period of search was January 1, 1968 to January 2, 2013). ‡ For the purposes of this document, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A report may have one or more outcome.	

DPV-I conducted a disproportionality analysis of FAERS data using Empirica Signal with the strategy described in Table 2.

Table 2. Data Mining Search Strategy*	
Data Refresh Date	October 1, 2019†
Product Terms	Product active moiety: Vasopressin
Empirica Signal Run Name Description	Custom Run: PAM (S) by Age (pediatrics and adults), Product active moieties (PAM), Preferred Term (PT); Suspect drugs only; Restricted to serious reports; Subset for ages 0-17 years as Pediatrics and 18 years and older as Adults; Standard Stratification

Table 2. Data Mining Search Strategy*	
MedDRA Search Strategy (Version 22.0)	All PTs
* See Appendix A for description of Data Mining of FAERS using Empirica Signal. † Datamining scores are based on all reports in FAERS as of October 1, 2019, our FAERS search for this review is only from January 1, 2013 to September 17, 2019	

3 RESULTS

3.1 FAERS

An assessment of a causal relationship between the adverse events and vasopressin was not completed for this high-level analysis. The FAERS search strategy described in Table 1 retrieved 270 reports for vasopressin with a serious outcome. In the reports that provided the patient's age, there were 185 reports for adults and 35 pediatric reports with vasopressin use and serious outcome(s) (see Table 3).

Table 3. Total Number of Reports for Vasopressin with a Serious Outcome Received by FDA From January 1, 2013 to September 17, 2019, n=270*

	Serious† (US)‡	Death (US)
Adults (≥ 18 years)	185 (123)	48 (30)
Pediatrics (0-17.99)	35 (10)	6 (0)
Age Unknown	50 (31)	6 (3)
Total	270 (164)	60 (33)

* A report may contain more than one MedDRA PT.
† For the purposes of this document, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A report may have one or more outcomes.
‡ Counts of reports from the US are in parentheses

Table 4 lists the most frequently reported MedDRA Preferred Terms (PTs) in pediatric reports with a serious outcome. The nine reports with *Platelet count decreased*, are all from a Japanese retrospective study reporting on 17 neonatal cardiac patients who received intraoperative vasopressin infusion during cardiac surgery while under cardiopulmonary bypass.[2] The authors noted that intraoperative vasopressin infusion prolonged the need for peritoneal dialysis, reduced the platelet count, and delayed blood lactate normalization after complex neonatal cardiac surgery.

Table 4. Most Frequently Reported MedDRA Preferred Terms (PTs) with n ≥ 2 for Vasopressin in Reports of Pediatric Patients (0-17.99 years old) with a Serious Outcome Received by FDA from January 1, 2013 to September 17, 2019, Sorted by Decreasing Number of FAERS Reports per PT

MedDRA PT	Number of FAERS Reports*
Drug ineffective	13
Blood lactic acid increased	9
Blood urea increased	9
Platelet count decreased	9
Blood creatinine increased	6
Hypotension	4

Table 4. Most Frequently Reported MedDRA Preferred Terms (PTs) with n ≥ 2 for Vasopressin in Reports of Pediatric Patients (0-17.99 years old) with a Serious Outcome Received by FDA from January 1, 2013 to September 17, 2019, Sorted by Decreasing Number of FAERS Reports per PT	
MedDRA PT	**Number of FAERS Reports***
Cardiac arrest	3
Hyponatraemia	3
Acute kidney injury	2
Atrioventricular block complete	2
Haemophagocytic lymphohistiocytosis	2
Intentional overdose	2
Lethargy	2
Toxicity to various agents	2
*A report may contain more than one MedDRA PT.	

Table 5 lists the most frequently reported MedDRA PTs in adult reports with a serious outcome(s).

Table 5. Most Frequently Reported MedDRA Preferred Terms (PTs) with n ≥ 5 for Vasopressin in Adult (≥ 18 years) Reports with a Serious Outcome Received by FDA from January 1, 2013 to September 17, 2019, Sorted by Decreasing Number of FAERS Reports per PT	
MedDRA PT	**Number of FAERS Reports***
Drug ineffective	67
Hypotension	33
Diabetes insipidus	19
Shock	16
Cardiac arrest	14
Cardiac failure	14
Overdose	14
Pulmonary oedema	13
Toxicity to various agents	13
Cardiogenic shock	12
Condition aggravated	12
Metabolic acidosis	12
Multiple organ dysfunction syndrome	12
Ischaemia	11
Circulatory collapse	10
Intentional overdose	10
Off label use	10
Anuria	9
Hypoglycaemia	9
Hypokalaemia	9
Acute kidney injury	8
Cerebral infarction	8
Lactic acidosis	8
Reversible cerebral vasoconstriction syndrome	8
Altered state of consciousness	7
Optic atrophy	7

Table 5. Most Frequently Reported MedDRA Preferred Terms (PTs) with n ≥ 5 for Vasopressin in Adult (≥ 18 years) Reports with a Serious Outcome Received by FDA from January 1, 2013 to September 17, 2019, Sorted by Decreasing Number of FAERS Reports per PT	
MedDRA PT	**Number of FAERS Reports***
Sepsis	7
Septic shock	7
Tachycardia	7
Cyanosis	6
Death	6
Drug interaction	6
Hyperdynamic left ventricle	6
Renal impairment	6
Therapy non-responder	6
Ventricular tachycardia	6
Arteriospasm coronary	5
Atrial fibrillation	5
Blindness	5
Blindness cortical	5
Bradycardia	5
Colour blindness	5
CSF pressure increased	5
Cytotoxic oedema	5
Depressed level of consciousness	5
Electrocardiogram P wave abnormal	5
Electrocardiogram ST segment depression	5
Electrocardiogram T wave amplitude decreased	5
Electrocardiogram T wave inversion	5
Electrocardiogram U wave present	5
Embolism	5
Embolism arterial	5
Hypertension	5
Hypothermia	5
Myocardial infarction	5
Optic nerve injury	5
Renal tubular necrosis	5
Retinal ischaemia	5
Visual impairment	5
* A report may contain more than one MedDRA PT. See discussion of highlighted eye related terms in Reviewer's Comments section 4 below (page 8).	

Appendix B, lists the most frequently reported MedDRA preferred terms (PTs) with n ≥ 5 in the 270 FAERS reports with a serious outcome (includes all ages and reports without a reported age). Appendix C and D are FAERS line listings of the pediatric (n=35) and adult reports (n=185), respectively.

3.2 DATA MINING

DPV-I uses Empirica Signal software to perform disproportionality analyses on FAERS data and to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large

databases. If a drug-event combination has a score (EB05) of ≥ 2, this score indicates 95% confidence that a drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database. Data mining scores do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation.

Table 6 provides the disproportionality scores, sorted by descending EB05 scores for vasopressin reports with a serious outcome in pediatric reports as of October 1, 2019. We reviewed the labeling status and location of each PT using the Vasostrict (vasopressin injection) label.[3] Vasostrict is not indicated for pediatric use in the FDA approved label.

Table 6. Data Mining Results Using Empirica Signal for Events with EB05 ≥ 2 Reported with Vasopressin use and a Serious Outcome in Pediatrics (0 to 17.99 years) as of October 1, 2019, Sorted by Descending EB05 Scores

MedDRA PT	N	EB05	EBGM	EB95	Labeled (Yes/No), Location† or Other Category
Blood lactic acid increased	9	12.91	26.36	46.25	No, DR
Platelet count decreased	11	12.79	23.80	39.43	Yes, AR
Blood urea increased	9	12.73	26.16	45.95	No
Drug ineffective	17	3.66	5.56	8.25	No, U
Blood creatinine increased	6	3.00	7.97	25.16	Yes, AR as ARI
Hyponatraemia	4	2.14	7.74	37.23	Yes, AR

A score (EB05) of ≥ 2 indicates 95% statistical confidence that a drug-event combination has been reported at least twice the expected ratio relative to all other drugs and events in the database, considering the database as a background "expected."
Datamining of FAERS data in this table is through October 1, 2019
* A report may contain more than one MedDRA PT.
† If the event is included in multiple sections of labeling, only the section of highest importance is listed.
Abbreviations: AR = Adverse Reactions, ARI= acute renal insufficiency, DR = Disease-related, OD = Overdosage, U = Uninformative.

Table 7 provides the disproportionality scores, sorted by descending EB05 scores for vasopressin reports with a serious outcome in adult reports as of October 1, 2019. We reviewed the labeling status and location of each PT using the Vasostrict (vasopressin injection) label.[3]

Table 7. Data Mining Results Using Empirica Signal for Events with EB05 ≥ 2 Reported with Vasopressin use and a Serious Outcome in Adults (≥ 18 years) as of October 1, 2019, Sorted by Descending EB05 Scores

MedDRA PT	N	EB05	EBGM	EB95	Labeled (Yes/No), Location† or Other Category
Diabetes insipidus	25	172.68	243.36	335.22	No, IR, DI
Ischaemia	8	31.02	58.51	102.54	Yes, AR
Reversible cerebral vasoconstriction syndrome	5	30.11	70.58	146.27	No
Vasoconstriction	4	23.71	74.25	179.15	Yes, AR
Hypernatraemia	7	21.41	43.14	79.55	No

Table 7. Data Mining Results Using Empirica Signal for Events with EB05 ≥ 2 Reported with Vasopressin use and a Serious Outcome in Adults (≥ 18 years) as of October 1, 2019, Sorted by Descending EB05 Scores

MedDRA PT	N	EB05	EBGM	EB95	Labeled (Yes/No), Location† or Other Category
Vasoplegia syndrome	4	16.07	65.39	162.91	No, IR
Cardiogenic shock	11	15.96	27.57	44.88	No
Metabolic acidosis	15	9.49	17.38	27.22	No, DR
Anuria	8	6.39	22.47	43.76	No
Drug ineffective	77	5.58	6.78	8.20	No, U
Hypotension	41	4.79	6.27	8.15	No, IR, withdrawal
Shock	14	4.53	9.02	17.93	No, IR
Rhabdomyolysis	15	4.38	7.97	15.56	Yes, OD
Pulmonary oedema	16	4.31	7.37	13.86	No
Multiple organ dysfunction syndrome	14	4.16	7.66	15.53	Yes, DA
Optic atrophy	4	3.52	42.23	123.23	No
Cardiac arrest	20	3.44	5.04	7.23	Yes, W/P
Myopathy	7	3.36	12.68	35.20	No
Ventricular tachycardia	9	3.17	6.95	18.91	Yes, OD
Bradycardia	13	3.04	4.93	7.84	Yes, AR
Arteriospasm coronary	5	3.02	20.68	63.78	No
Lactic acidosis	9	2.99	6.04	15.84	No, DR
Cyanosis	8	2.86	6.40	19.09	No
Cardiac failure	13	2.83	4.54	7.07	Yes, W/P
Septic shock	10	2.76	4.84	8.59	No, IR
Wernicke-Korsakoff syndrome	3	2.75	68.96	253.24	No
Therapy non-responder	8	2.66	5.39	14.53	Yes, DI
Intestinal ischaemia	5	2.60	14.88	54.24	Yes, AR
Pulse absent	5	2.37	11.39	47.27	No, DR, IR
Circulatory collapse	7	2.37	4.97	14.28	No
Optic ischaemic neuropathy	4	2.33	21.62	87.79	No
Peripheral ischaemia	5	2.33	10.68	45.65	Yes, AR
Hyponatraemia	9	2.25	3.96	6.66	Yes, AR
Blood pressure decreased	9	2.15	3.78	6.31	Yes, IR
Blood creatine phosphokinase increased	8	2.12	3.88	6.72	No
Myocardial necrosis	3	2.09	43.66	200.37	Yes, AR as myocardial ischemia
Hypokalaemia	8	2.03	3.70	6.36	No

A score (EB05) of ≥ 2 indicates 95% statistical confidence that a drug-event combination has been reported at least twice the expected ratio relative to all other drugs and events in the database, considering the database as a background "expected."
Datamining of FAERS data in this table is through October 1, 2019
* A report may contain more than one MedDRA PT.
† If the event is included in multiple sections of labeling, only the section of highest importance is listed.
Abbreviations: W/P = Warnings/Precautions, AR = Adverse Reactions, DA = Dosage and Administration, DI = Drug Interactions, DR = Disease-related, IR = Indication-related, OD = Overdosage, U = Uninformative

4 REVIEWER'S COMMENTS

Results are crude counts of FAERS reports and may include duplicate reports submitted for the same events in the same patient. Duplicate reports may include additional information from one or more sources (e.g., manufacturer, physician, pharmacist, patient, etc.). A detailed case review was not performed for these crude count reports, and therefore, a drug-event causal association cannot be assessed based on these crude counts (See Appendix A for FAERS Limitations).

Decreased platelet count was identified in pediatric reports (see Table 4) and was attributed to a medical literature article reporting results of a Japanese retrospective study of intraoperative vasopressin during neonatal cardiac surgery.[2] The FAERS reports provided patient age but did not provide any other individual patient characteristics or individual laboratory results. There are several limitations in this study that include retrospective design, more severe illness at baseline, and lower pre-operative platelet counts in vasopressin treated patients. Decreased platelets is listed in Adverse Reactions section of the Vasostrict label.[3]

Potential confounders may exist in the adult reports. Many of the adverse events identified through data mining of FAERS data are potentially indication related (e.g., diabetes insipidus, hypotension), complications of vasodilatory shock and volume depletion (e.g., ischemia, cardiac arrest), related to the pharmacology of vasopressin (vasoconstriction) or are potentially refractory disease (drug ineffective). For the reports with the PT *Diabetes insipidus* (n=19, Table 5), eighteen cited six medical literature articles and abstracts that reported patients experienced diabetes insipidus after vasopressin discontinuation.[4,5,6,7,8,9] Many patients in these articles received vasopressin to treat hypotension, but vasopressin was also used in several reports for treatment of neurological conditions (e.g., intracranial hypertension). The diabetes insipidus was reported to be transient and some were managed with desmopressin. Transient diabetes insipidus is not an expected adverse event listed in the label for Vasostrict.[3] The medical literature articles have information on one or more patients and the FAERS report count for the PT *Diabetes insipidus* may include duplicates.

In adult patients, there were several PTs identified from the System Organ Class (SOC) Eye disorders (*Blindness cortical*, *Optic atrophy*, *Optic nerve injury*, *Retinal ischaemia, Visual impairment*) in FAERS (Table 5) and disproportional reporting was noted for the drug-event pair of vasopressin and *Optic atrophy* (Table 7). After presenting the FAERS information in this memorandum at a mid-cycle meeting for NDA 212593 on September 26, 2019, DPV-I reviewed these reports for duplicates and relatedness to vasopressin use at the request of the DCaRP review team. The five aforementioned PTs from the SOC *Eye disorders* were from seven reports (a report may contain more than one PT). Of these seven reports, six were duplicates and therefore, artificially inflated the data mining scores. This single case was also published in the medical literature[10] and is summarized below.

FAERS Case IDs 13893657, 13901387, 14523594, 15779138, 16254208, 16266075, 16721745; Canada; 2017: A healthcare professional in Canada reported that a 49-year-old female patient took an intentional overdose of amlodipine 150 mg, escitalopram 60 mg, and risperidone 6 mg and experienced an altered state of consciousness, hypotension, and bilateral cortical blindness. Medical history included hepatitis C, prior intravenous drug use, diverticulitis, hypertension, mild chronic obstructive pulmonary disease, gastroesophageal reflux disease, anxiety, and

depression. She also had a prior history of reduced visual acuity secondary to early optic atrophy. The patient was hospitalized, intubated, mechanically ventilated, and administered vasopressors (norepinephrine, epinephrine, and vasopressin). Hypotension persisted and intralipid emulsion therapy was subsequently administered; however, the patient did not initially respond. A chest X-ray showed diffuse pulmonary edema and intravenous diuresis as well as continuous renal replacement therapy was initiated. Oxygen requirements and urine output improved with this therapy, and 3 days later, mechanical ventilation was discontinued. Following extubation, she complained of new onset visual impairment, specifically seeing only red-green colors, but no objects. An ophthalmologist assessed that the visual impairment was due to bilateral optic atrophy from prolonged hypotension. The patient was hospitalized for a total of 8 days. Five months after hospital discharge, she underwent a follow-up ophthalmology examination and was diagnosed with irreversible complete optic atrophy.

Reviewer comments: In this report, the authors attribute bilateral cortical blindness and optic atrophy to prolonged hypotension during the first 24 hours after an amlodipine overdose. Additionally, the patient's medical history included early optic atrophy diagnosed approximately 10 years prior to the event confounding any further meaningful assessment. Information provided in this report does not constitute a new safety signal for eye disorders with vasopressin use.

5 CONCLUSION

In our high-level analysis of recent FAERS data (including a data mining analysis), DPV-I identified cases of transient diabetes insipidus occurring upon withdrawal of vasopressin as an unexpected adverse event and a potential safety signal for DCaRP's consideration for the purpose of review of NDA 212593 (vasopressin injection).

6 REFERENCES

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7 APPENDICES

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

FDA Adverse Event Reporting System (FAERS)

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 terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. “Data mining” refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., “potential signals”) in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FAERS database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

7.2 APPENDIX B. LIST OF ALL MEDDRA PREFERRED TERMS (PTS) WITH N ≥ 5 FOR VASOPRESSIN REPORTS WITH A SERIOUS OUTCOME RECEIVED BY FDA FROM JANUARY 1, 2013 TO SEPTEMBER 17, 2019, SORTED BY DECREASING NUMBER OF FAERS REPORTS PER PT

MedDRA PT	Number of FAERS Reports*
Drug ineffective	88
Hypotension	43
Cardiac arrest	21
Diabetes insipidus	20
Shock	20
Condition aggravated	19
Overdose	19
Toxicity to various agents	18
Cardiac failure	17
Pulmonary oedema	16
Cardiogenic shock	15
Intentional overdose	14
Off label use	14
Ischaemia	13
Multiple organ dysfunction syndrome	13
Circulatory collapse	12
Hypoglycaemia	12
Metabolic acidosis	12
Acute kidney injury	11
Anuria	11
Hypokalaemia	11
Hyponatraemia	11
Blood lactic acid increased	10
Cerebral infarction	10
Death	10
Reversible cerebral vasoconstriction syndrome	10
Tachycardia	10
Altered state of consciousness	9
Blood urea increased	9
Lactic acidosis	9
Optic atrophy	9
Platelet count decreased	9
Product use in unapproved indication	9
Septic shock	9
Bradycardia	8
Hyperdynamic left ventricle	8
Sepsis	8
Blindness	7
Blindness cortical	7
Blood creatinine increased	7
Colour blindness	7
CSF pressure increased	7
Cyanosis	7
Cytotoxic oedema	7
Depressed level of consciousness	7

MedDRA PT	Number of FAERS Reports*
Drug interaction	7
Electrocardiogram P wave abnormal	7
Electrocardiogram ST segment depression	7
Electrocardiogram T wave amplitude decreased	7
Electrocardiogram T wave inversion	7
Electrocardiogram u wave present	7
Embolism	7
Embolism arterial	7
Hypothermia	7
Optic nerve injury	7
Renal impairment	7
Renal tubular necrosis	7
Retinal ischaemia	7
Therapy non-responder	7
Ventricular tachycardia	7
Visual impairment	7
Blood pressure decreased	6
Foetal exposure during pregnancy	6
Haemorrhage	6
Hyperkalaemia	6
Intestinal ischaemia	6
Myocardial ischaemia	6
Renal failure	6
Vasoplegia syndrome	6
Anaemia	5
Arteriospasm coronary	5
Atrial fibrillation	5
Cardio-respiratory arrest	5
Hypertension	5
Maternal exposure during pregnancy	5
Myocardial infarction	5
Peripheral ischaemia	5
Rhabdomyolysis	5
Serotonin syndrome	5
Stress cardiomyopathy	5
A report may contain more than one MedDRA PT.	

7.3 APPENDIX C. FAERS LINE LISTING OF PEDIATRIC REPORTS WITH A SERIOUS OUTCOME, N=35

Row	Initial FDA Received Date	FAERS Case #	Version #	MFR Ctrl #	Case Type	Age in Years	Sex	Country	PTs	All Outcomes
1	5/19/2014	10184662	1	ADR-2014-00830	Expedited	8	M	AUS	Areflexia, arrhythmia supraventricular, autonomic nervous system imbalance, body temperature fluctuation, diabetes insipidus, disease progression, encephalopathy, hypoglycaemia, hypopituitarism, pupil fixed, seizure, sinus arrest, sinus node dysfunction	DE
2	6/11/2014	10231142	3	JP-PFIZER INC-2014115530	Expedited	0.06571	M	JPN	Acute kidney injury, gastrointestinal perforation, necrotising colitis	DE, DS, HO, LT
3	8/7/2014	10368143	6	JP-OTSUKA-JP-2014-15875	Expedited	0.06845	M	JPN	Cardiac failure, hypotension, off label use, pulmonary hypertension	DE, OT
4	12/23/2014	10671392	2	US-BAXTER-2014BAX075155	Expedited	16	M	USA	Arrhythmia, drug ineffective	OT
5	7/30/2015	11322999	1	GB-HOSPIRA-2863609	Expedited	17	NR	GBR	Acute kidney injury, hypophosphataemia, rhabdomyolysis	HO
6	12/22/2016	13055057	1	JP-PFIZER INC-2016501970	Expedited	3	M	JPN	Brain oedema, hyponatraemia	OT
7	8/31/2017	13926516	1	US-APOTEX-2017AP017349	Non-Expedited	5	F	USA	Drug ineffective	OT
8	10/20/2017	14111780	4	US-PFIZER INC-2017453504	Expedited	16	M	USA	Bradycardia, cardiac arrest, hypotension, pulseless electrical activity, tachycardia, trigemino-cardiac reflex	HO, OT
9	12/1/2017	14241485	3	AU-SUN Pharmaceutical Industries LTD-2017RR-155617	Expedited	15	M	AUS	Drug interaction, drug resistance, overdose, serotonin syndrome, vasoplegia syndrome	LT, OT
10	12/5/2017	14250502	1	US-AUROBINDO-AUR-APL-2017-44132	Expedited	0.23546	M	USA	Drug ineffective	LT, OT
11	1/2/2018	14343433	2	AU-PFIZER INC-2017555182	Expedited	6	M	AUS	Drug ineffective	DE, LT
12	1/2/2018	14343769	1	AU-GLAXOSMITHKLINE-AU2017201704	Expedited	6	M	AUS	Drug ineffective	LT
13	1/24/2018	14434738	2	US-BAXTER-2018BAX002513	Expedited	5	F	USA	Blister, cyanosis, device occlusion, hyperkalaemia, poor peripheral circulation, skin discolouration	OT
14	2/1/2018	14475185	12	JP-PFIZER INC-2018039742	Expedited	17	M	JPN	Haemophagocytic lymphohistiocytosis	HO, LT, OT
15	2/5/2018	14484329	1	JP-SUN PHARMACEUTICAL	Expedited	17	M	JPN	Haemophagocytic lymphohistiocytosis	HO, OT

Row	Initial FDA Received Date	FAERS Case #	Version #	MFR Ctrl #	Case Type	Age in Years	Sex	Country	PTs	All Outcomes
				INDUSTRIES LTD-2018R3-162323						
16	2/26/2018	14573962	1	IN-BAUSCH-BL-2018-004936	Expedited	0.5	M	IND	Drug ineffective	HO, LT, OT
17	3/3/2018	14595853	1	IN-GLENMARK PHARMACEUTICALS-2018GMK032643	Expedited	0.5	M	IND	Drug ineffective	HO, LT, OT
18	2/19/2019	15979800	1	DE-BAUSCH-BL-2019-004649	Expedited	17	F	DEU	Drug ineffective	DE, HO, LT, OT
19	2/22/2019	15994025	1	DE-TORRENT-00013337	Expedited	17	F	DEU	Drug ineffective	HO, LT, OT
20	3/14/2019	16072876	1	US-MYLANLABS-2019M1023845	Expedited	14	F	USA	Atrioventricular block complete, cardiac arrest, drug ineffective, hypotension, intentional overdose, lethargy, toxicity to various agents	HO, LT
21	3/28/2019	16127692	1	US-TEVA-2019-US-1030002	Expedited	14	F	USA	Atrioventricular block complete, cardiac arrest, drug ineffective, hypotension, intentional overdose, lethargy, toxicity to various agents	HO, LT
22	5/9/2019	16291317	1	IN-MYLANLABS-2019M1044591	Expedited	4	M	IND	Drug ineffective	LT
23	5/9/2019	16292442	1	IN-FRESENIUS KABI-FK201905281	Expedited	4	M	IND	Product use issue, pulmonary hypertensive crisis	DE
24	1/30/2013	9044222	1	JP-JHP PHARMACEUTICALS, LLC-JHP201300032	Expedited	0.03833	NR	JPN	Blood lactic acid increased, blood urea increased, platelet count decreased	OT
25	1/30/2013	9044223	1	JP-JHP PHARMACEUTICALS, LLC-JHP201300022	Expedited	0.01369	NR	JPN	Blood creatinine increased, blood lactic acid increased, blood urea increased, platelet count decreased	OT
26	1/30/2013	9044224	1	JP-JHP PHARMACEUTICALS, LLC-JHP201300030	Expedited	0.02464	NR	JPN	Blood creatinine increased, blood lactic acid increased, blood urea increased, platelet count decreased	OT
27	1/30/2013	9079485	1	JP-JHP PHARMACEUTICALS, LLC-JHP201300026	Expedited	0.00274	NR	JPN	Blood creatinine increased, blood lactic acid increased, blood urea increased, platelet count decreased	OT
28	1/30/2013	9079492	1	JP-JHP PHARMACEUTICALS, LLC-JHP201300025	Expedited	0.07118	NR	JPN	Blood creatinine increased, blood lactic acid increased, blood urea increased, platelet count decreased	OT
29	1/30/2013	9079500	1	JP-JHP PHARMACEUTICALS, LLC-JHP201300024	Expedited	0.06023	NR	JPN	Blood lactic acid increased, blood urea increased, platelet count decreased	OT
30	1/30/2013	9079508	1	JP-JHP PHARMACEUTICALS, LLC-JHP201300029	Expedited	0.03285	NR	JPN	Blood creatinine increased, blood lactic acid increased, blood urea increased, platelet count decreased	OT

Row	Initial FDA Received Date	FAERS Case #	Version #	MFR Ctrl #	Case Type	Age in Years	Sex	Country	PTs	All Outcomes
31	1/30/2013	9079515	1	JP-JHP PHARMACEUTICALS, LLC-JHP201300033	Expedited	0.02738	NR	JPN	Blood lactic acid increased, blood urea increased, platelet count decreased	OT
32	1/30/2013	9079522	1	JP-JHP PHARMACEUTICALS, LLC-JHP201300027	Expedited	0.05476	NR	JPN	Blood creatinine increased, blood lactic acid increased, blood urea increased, platelet count decreased	OT
33	6/7/2013	9337675	1	US-JHP PHARMACEUTICALS, LLC-JHP201300330	Expedited	1.33333	M	USA	Hyponatraemia	OT
34	6/14/2013	9349176	1	US-JHP PHARMACEUTICALS, LLC-JHP201300356	Expedited	1.83333	F	USA	Drug ineffective	OT
35	6/24/2013	9370198	1	20130307	Expedited	1.33333	M	USA	Hyponatraemia, urine output decreased	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, and 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: DE=Death, HO=Hospitalization, LT= Life-threatening, DS= Disability, CA= Congenital Anomaly, OT=Other Medically Significant, NR = not reported
Country Codes: AUS=Australia, DEU=Germany, IND=India, GBR=United Kingdom of Great Britain and Northern Ireland, JPN=Japan, USA=United States of America,

7.4 APPENDIX D. FAERS LINE LISTING OF ADULT REPORTS WITH A SERIOUS OUTCOME, N=185

Row	Initial FDA Received Date	FAERS Case #	Version #	MFR Ctrl #	Case Type	Age in Years	Sex	Country	PTs	All Outcomes
1	3/26/2014	10039676	1	CA-BAXTER-2014BAX014847	Expedited	48	F	CAN	Drug ineffective	OT
2	3/28/2014	10045803	2	GB-JHP PHARMACEUTICALS, LLC-JHP201400112	Expedited	74	F	GBR	Ischaemic cerebral infarction	DE
3	6/9/2014	10229672	1	FK201402236	Expedited	37	F	USA	Hypotension, kounis syndrome, stress cardiomyopathy	LT
4	6/24/2014	10265465	1	2014AMD00007	Expedited	37	F	USA	Stress cardiomyopathy	OT
5	9/4/2014	10431545	1	US-BAXTER-2014BAX052276	Expedited	43	F	USA	Cardiac arrest, haemodynamic instability, hypotension, therapy non-responder	DE, OT
6	9/5/2014	10439424	1	FK201403553	Expedited	76	F	JPN	Continuous haemodiafiltration, hyperkalaemia, multiple organ dysfunction syndrome, ventricular fibrillation	DE, LT

Row	Initial FDA Received Date	FAERS Case #	Version #	MFR Ctrl #	Case Type	Age in Years	Sex	Country	PTs	All Outcomes
7	9/11/2014	10448353	1	US-BAXTER-2014BAX053982	Expedited	28	F	USA	Cardiac arrest, cardiogenic shock, condition aggravated, respiratory failure, vasoplegia syndrome	DE, OT
8	9/12/2014	10450843	1	US-BAXTER-2014BAX053912	Expedited	46	F	USA	Acute kidney injury, drug ineffective, intestinal ischaemia, lactic acidosis, multiple organ dysfunction syndrome, sinus arrest	DE, LT, OT
9	11/13/2014	10585251	2	2617238	Expedited	33	F	COL	Cyanosis, drug ineffective, extremity necrosis, incorrect dose administered, product administration error, wrong technique in product usage process	OT
10	1/22/2015	10731256	2	CA-BAUSCH-BL-2015-000434	Expedited	51	M	CAN	Condition aggravated, hypotension, lactic acidosis	OT
11	1/23/2015	10741475	1		Direct	57	F	USA	Cyanosis, ischaemia, multiple organ dysfunction syndrome	OT
12	1/26/2015	10744157	2	20150014	Expedited	55	F	USA	Hyponatraemia	OT
13	2/16/2015	10798652	1	US-BAXTER-2015BAX007151	Expedited	67	M	USA	Blood lactic acid increased, blood pressure decreased	OT
14	2/27/2015	10875347	1	US-BAXTER-2015BAX009699	Expedited	55	M	USA	Anaemia, bacteraemia, cardiac failure acute, coagulopathy, disease recurrence, gastrointestinal haemorrhage, general physical health deterioration, heparin-induced thrombocytopenia, hypotension, malnutrition, mitral valve incompetence, pericarditis uraemic, pneumonia, respiratory failure, subarachnoid haemorrhage, tricuspid valve incompetence	HO, OT
15	3/25/2015	10951995	1	US-JNJFOC-20150309204	Expedited	63	M	USA	Abdominal pain, anaemia, atrial fibrillation, chest pain, dyspnoea, fall, gait disturbance, hyperglycaemia, lactic acidosis, muscular weakness	HO
16	4/1/2015	10984208	1	FK201501535	Expedited	67	F	NZL	Hyponatraemic seizure, malaise, nausea, urine output decreased	OT
17	4/21/2015	11058000	1	FK201501788	Expedited	60	F	USA	Breast necrosis, catheter site extravasation, chest wall necrosis, product use in unapproved indication, product use issue	OT
18	6/8/2015	11170418	2	US-LPDUSPRD-20150383	Expedited	60	F	USA	Extravasation, infusion site extravasation, infusion site ischaemia, infusion site necrosis, skin graft, skin necrosis	HO
19	6/12/2015	11184964	1	CA-ELI LILLY AND COMPANY-CA201506000722	Expedited	51	M	CAN	Hypotension, lactic acidosis	OT
20	7/13/2015	11266834	1	SI-BAYER-2015-375992	Expedited	66	M	SVN	Bradycardia, hypotension, left ventricular dysfunction, loss of consciousness, metabolic acidosis, overdose, suicide attempt	HO
21	7/15/2015	11273188	1	PHHY2015AT082802	Expedited	74	F	AUT	Diarrhoea, drug ineffective, drug interaction, endocarditis, overdose	DE, OT
22	7/30/2015	11323001	1	GB-HOSPIRA-2863602	Expedited	18	NR	GBR	Acute kidney injury, hypophosphataemia, rhabdomyolysis	HO

Row	Initial FDA Received Date	FAERS Case #	Version #	MFR Ctrl #	Case Type	Age in Years	Sex	Country	PTs	All Outcomes
23	7/30/2015	11323024	1	GB-HOSPIRA-2863596	Expedited	47	M	GBR	Acute kidney injury, arrhythmia, hypophosphataemia, multiple organ dysfunction syndrome, rhabdomyolysis	DE, HO
24	9/1/2015	11442812	4	JP-009507513-1508JPN013799	Expedited	48	F	JPN	Acute kidney injury	HO, OT
25	9/1/2015	11442813	3	JP-009507513-1508JPN013929	Expedited	41	F	JPN	Acute kidney injury	HO
26	9/16/2015	11515055	1	US-BAXTER-2015BAX050331	Expedited	38	F	USA	Abdominal compartment syndrome, anaemia, anaphylactoid syndrome of pregnancy, disseminated intravascular coagulation, exposure during pregnancy, general physical health deterioration, multi-organ disorder, premature delivery, pulmonary embolism, seizure like phenomena, shock	OT
27	1/28/2016	11971605	1	US-LPDUSPRD-20160056	Expedited	22	M	USA	Hyponatraemia	OT
28	1/28/2016	11971609	1	US-LPDUSPRD-20160057	Expedited	24	F	USA	Hyponatraemia	OT
29	3/18/2016	12192041	1	PHHY2016US033161	Expedited	54	M	USA	Aphasia, cerebral ischaemia, drug interaction, hemiparesis	DS, OT
30	3/21/2016	12195586	1	US-LPDUSPRD-20160229	Expedited	53	M	USA	Cardiac failure, cardiac ventricular disorder, mitral valve incompetence, myocardial reperfusion injury	OT
31	4/6/2016	12242370	1	US-SA-2015SA179485	Expedited	36	F	USA	Acidosis, acute right ventricular failure, cardiac failure, circulatory collapse, drug ineffective, echocardiogram abnormal, hypotension, ischaemic hepatitis, multiple organ dysfunction syndrome, oliguria, pulmonary hypertension, renal failure, respiratory gas exchange disorder, transplant failure, vasoconstriction, vasoplegia syndrome	DE, HO
32	4/14/2016	12269090	1	US-BAXTER-2016BAX018359	Expedited	43	F	USA	Drug ineffective, hyperlipidaemia	OT
33	5/16/2016	12372651	3	US-PFIZER INC-2016238594	Expedited	63	M	USA	Drug ineffective	DE
34	5/18/2016	12380837	1	JP-SCIEGEN PHARMACEUTICALS INC-2016SCILIT00121	Expedited	72	F	JPN	Anion gap increased, anuria, blood pH decreased, cardiomegaly, death, fall, hypoglycaemia, hypotension, metabolic acidosis, overdose, pulmonary oedema, vomiting	DE, OT
35	5/24/2016	12399086	1	US-LPDUSPRD-20160436	Expedited	48	F	USA	Dry gangrene, ischaemia	OT
36	6/15/2016	12468705	1	US-CONCORDIA PHARMACEUTICALS INC.-GSH201502-002322	Expedited	26	M	USA	Acute kidney injury, acute respiratory failure, bradycardia, death, drug ineffective, hypotension, intentional overdose	DE, OT
37	6/16/2016	12473800	2	US-VALIDUS PHARMACEUTICALS LLC-US-2016VAL002058	Expedited	36	F	USA	Acidosis, acute right ventricular failure, cardiac failure, circulatory collapse, drug ineffective, echocardiogram abnormal, hypotension, ischaemic hepatitis, multiple	DE, HO

Row	Initial FDA Received Date	FAERS Case #	Version #	MFR Ctrl #	Case Type	Age in Years	Sex	Country	PTs	All Outcomes
									organ dysfunction syndrome, oliguria, pulmonary hypertension, renal failure, respiratory gas exchange disorder, transplant failure, vasoconstriction, vasoplegia syndrome	
38	7/5/2016	12526762	2	US-ACTAVIS-2016-14517	Expedited	49	M	USA	BLOOD CREATININE INCREASED, LACTIC ACIDOSIS	DE, HO, OT
39	7/26/2016	12592475	3	JP-ROCHE-1789698	Expedited	59.30459	M	JPN	Castleman's disease, condition aggravated, gastrointestinal perforation, pancytopenia, sepsis	DE, HO
40	9/27/2016	12785556	1	US-PFIZER INC-2016452468	Expedited	21	F	USA	Abortion missed	OT
41	10/12/2016	12844331	1		Direct	65	M	USA	Cyanosis, dysphagia, gastrointestinal haemorrhage, hypoaesthesia, paraesthesia	LT
42	10/19/2016	12861311	1	CA-PAR PHARMACEUTICAL COMPANIES-2016SCPR015997	Expedited	51	M	CAN	Condition aggravated, hypotension, lactic acidosis, off label use	OT
43	10/21/2016	12872765	1	US-PAR PHARMACEUTICAL COMPANIES-2016SCPR016027	Expedited	65.62355	M	USA	Anaphylactic reaction, clostridium difficile infection	OT
44	10/27/2016	12887757	1	CN-INTERNATIONAL MEDICATION SYSTEMS, LIMITED-1058926	Expedited	35	M	CHN	Therapy non-responder	LT, OT
45	10/31/2016	12898253	1	US-PFIZER INC-3080065	Non-Expedited	57	F	USA	Hypertension	OT
46	11/8/2016	12922138	1	PHHY2016US149335	Expedited	25	F	USA	Maternal exposure during pregnancy, premature delivery	OT
47	12/13/2016	13023372	3	US-PFIZER INC-2016570462	Expedited	67	M	USA	Hypotension, shock	HO, LT, OT
48	1/17/2017	13123103	2	PHHY2017NL003902	Expedited	64	F	NLD	Aspartate aminotransferase increased, blood creatine phosphokinase increased, body temperature increased, hyperkalaemia, hypertonia, hypotension, mydriasis, neurological decompensation, nystagmus, renal impairment, serotonin syndrome, somnolence	HO, LT, OT
49	2/2/2017	13180423	1	US-ABBVIE-17K-163-1855412-00	Expedited	37.69	F	USA	Abdominal distension, chest pain, cholelithiasis, diaphragmatic rupture, gallbladder hypofunction, headache, heart rate decreased, hypotension, influenza, intra-abdominal fluid collection, intra-abdominal haemorrhage, jaundice, oxygen saturation decreased, pneumothorax, procedural haemorrhage, pulmonary oedema, staphylococcal sepsis, thyroid haemorrhage, unevaluable event	DE, HO, OT
50	2/22/2017	13260295	4	GB-PFIZER INC-2017074202	Expedited	63	M	GBR	Cardiac failure, colitis ischaemic, death, diabetes mellitus, hypertension, myocardial infarction, myocardial ischaemia, neutrophil count increased,	DE, HO, OT

Row	Initial FDA Received Date	FAERS Case #	Version #	MFR Ctrl #	Case Type	Age in Years	Sex	Country	PTs	All Outcomes
									peripheral vascular disorder, sepsis, white blood cell count increased	
51	2/24/2017	13269369	2	CH-PFIZER INC-2017074858	Expedited	27	F	CHE	Cardiogenic shock, pulmonary oedema, pulseless electrical activity, respiratory failure, sinus tachycardia, stress cardiomyopathy	OT
52	2/24/2017	13269467	1	US-LPDUSPRD-20170201	Expedited	63	F	USA	Vasospasm	OT
53	2/27/2017	13274473	3	GB-MYLANLABS-2017M1011449	Expedited	63	M	GBR	Cardiac failure, colitis ischaemic, diabetes mellitus, hypertension, myocardial infarction, myocardial ischaemia, neutrophil count increased, peripheral vascular disorder, sepsis, white blood cell count increased	DE, HO, OT
54	3/8/2017	13316182	2	GB-INTERNATIONAL MEDICATION SYSTEMS, LIMITED-1064013	Expedited	63	M	GBR	Cardiac failure, colitis ischaemic, death, hypertension, myocardial infarction, myocardial ischaemia, peripheral vascular disorder, sepsis	DE, HO, OT
55	3/23/2017	13366662	1	US-INTERNATIONAL MEDICATION SYSTEMS, LIMITED-1064600	Expedited	49	F	USA	Death, drug ineffective	DE, LT
56	3/28/2017	13377569	4	US-PFIZER INC-2017124250	Expedited	52	F	USA	Drug ineffective	DE, LT, OT
57	3/29/2017	13382148	1	US-LPDUSPRD-20170325	Expedited	49	F	USA	Death, drug ineffective	DE, LT
58	3/30/2017	13388958	1	US-TEVA-755236USA	Expedited	49	F	USA	Drug ineffective, hypotension	DE, LT, OT
59	3/30/2017	13389018	2	US-PFIZER INC-2017132069	Expedited	83	F	USA	Cardiac failure, stress cardiomyopathy	OT
60	4/13/2017	13438591	1	US-PFIZER INC-2017153731	Expedited	83	F	USA	Bradycardia, cardiac failure, hypotension	OT
61	5/1/2017	13500411	2	US-SA-2017SA052270	Expedited	60	F	USA	Blood pressure decreased, cardiac arrest, cardio-respiratory arrest, circulatory collapse, drug ineffective, hypotension, hypoxic-ischaemic encephalopathy, pulseless electrical activity, ventricular fibrillation, ventricular tachycardia	DE, HO, LT, OT
62	5/3/2017	13510985	1	US-SA-2017SA079006	Expedited	67	F	USA	Drug ineffective, hypotension	DE, HO
63	5/4/2017	13515640	2	US-BAUSCH-BL-2017-012711	Expedited	53	M	USA	Drug ineffective	LT, OT
64	5/8/2017	13525037	2	US-BAUSCH-BL-2017-013461	Expedited	67	F	USA	Drug ineffective	LT, OT
65	5/9/2017	13530437	1	US-INTERNATIONAL MEDICATION SYSTEMS, LIMITED-2020498	Expedited	52	F	USA	Drug ineffective, hypotension, hypoxic-ischaemic encephalopathy	DS, LT, OT

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66	5/10/2017	13534179	1	US-BAUSCH-BL-2017-014500	Expedited	74	M	USA	Drug ineffective	LT, OT
67	5/12/2017	13540428	1	US-FRESENIUS KABI-FK201703734	Expedited	48	M	USA	Atrial fibrillation, cardiac failure, diabetes insipidus, mental status changes	HO, LT
68	5/17/2017	13553600	1	US-FRESENIUS KABI-FK201703886	Expedited	48	M	USA	Diabetes insipidus	HO
69	5/17/2017	13553603	1	US-FRESENIUS KABI-FK201703885	Expedited	23	F	USA	Diabetes insipidus	HO
70	5/17/2017	13558441	1	US-JNJFOC-20170506129	Expedited	67	F	USA	Drug ineffective	LT, OT
71	5/23/2017	13573290	1	US-PFIZER INC-2016230273	Expedited	48	F	USA	Dry gangrene, peripheral ischaemia	HO, OT
72	5/23/2017	13574983	2	US-TEVA-770711USA	Expedited	23	F	USA	Diabetes insipidus, withdrawal syndrome	HO, OT
73	5/24/2017	13578304	1	US-TEVA-770710USA	Expedited	48	M	USA	Atrial fibrillation, cardiac failure, diabetes insipidus, mental disorder, withdrawal syndrome	HO, OT
74	5/31/2017	13597848	1	US-B. BRAUN MEDICAL INC.-2021417	Expedited	48	M	USA	Atrial fibrillation, cardiac failure, diabetes insipidus, hypernatraemia, mental status changes	LT
75	5/31/2017	13597906	1	US-B. BRAUN MEDICAL INC.-2021418	Expedited	23	F	USA	Diabetes insipidus	OT
76	6/21/2017	13674342	1	US-LPDUSPRD-20170808	Expedited	48	M	USA	Atrial fibrillation, cardiac failure, diabetes insipidus, mental status changes	OT
77	6/21/2017	13674650	1	US-LPDUSPRD-20170828	Expedited	43	F	USA	Diabetes insipidus	OT
78	6/21/2017	13674694	1	US-LPDUSPRD-20170829	Expedited	23	F	USA	Diabetes insipidus	OT
79	6/21/2017	13674716	1	US-LPDUSPRD-20170831	Expedited	57	M	USA	Diabetes insipidus	OT
80	6/21/2017	13674776	1	US-LPDUSPRD-20170833	Expedited	48	M	USA	Diabetes insipidus	OT
81	6/21/2017	13674799	1	US-LPDUSPRD-20170835	Expedited	58	M	USA	Diabetes insipidus	OT
82	7/5/2017	13717459	1	RU-GLAXOSMITHKLINE-RU2017GSK103039	Expedited	32	F	RUS	Cardiogenic shock, pulmonary embolism	DE, HO, OT
83	7/12/2017	13747534	1	US-IMPAX LABORATORIES, INC-2017-IPXL-01999	Expedited	67	F	USA	Drug ineffective, enteropathy-associated t-cell lymphoma, sepsis	DE, HO, OT
84	7/14/2017	13757018	1	KR-INTERNATIONAL MEDICATION SYSTEMS, LIMITED-2023403	Expedited	56	M	KOR	Drug ineffective	LT

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85	8/22/2017	13893657	5	CA-PFIZER INC-2017360842	Expedited	49	F	CAN	Anuria, hypoglycaemia, hypokalaemia, optic atrophy, overdose, pulmonary oedema, reversible cerebral vasoconstriction syndrome	DS, OT
86	8/23/2017	13900265	1	CA-IMPAX LABORATORIES, INC-2017-IPXL-02433	Expedited	49	F	CAN	Cerebral infarction, drug ineffective, hypoglycaemia, hypokalaemia, optic nerve infarction, pulmonary oedema	OT
87	8/24/2017	13901387	2	CA-APOTEX-2017AP017265	Expedited	49	F	CAN	Altered state of consciousness, anuria, blindness, blindness cortical, CSF pressure increased, cardiogenic shock, cerebral infarction, circulatory collapse, colour blindness, condition aggravated, cytotoxic oedema, depressed level of consciousness, electrocardiogram P wave abnormal, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased, electrocardiogram T wave inversion, electrocardiogram U wave present, embolism, embolism arterial, hyperdynamic left ventricle, hypoglycaemia, hypokalaemia, hypotension, hypothermia, intentional overdose, ischaemia, optic atrophy, optic nerve injury, overdose, pulmonary oedema, renal tubular necrosis, retinal ischaemia, reversible cerebral vasoconstriction syndrome, shock, tachycardia, toxicity to various agents, visual impairment	DS, HO, LT, OT
88	9/1/2017	13930853	1	CA-INTERNATIONAL MEDICATION SYSTEMS, LIMITED-2025495	Expedited	49	F	CAN	Reversible cerebral vasoconstriction syndrome	DS, OT
89	9/20/2017	13989721	1	US-WEST-WARD PHARMACEUTICALS CORP.-US-H14001-17-03464	Expedited	60	F	USA	Hyponatraemia, product preparation issue	OT
90	10/26/2017	14128866	2	US-GLAXOSMITHKLINE-US2017GSK164366	Expedited	22	F	USA	Bradycardia, circulatory collapse, drug interaction, end-tidal co2 decreased, heart rate increased, hypotension, myocardial ischaemia, rhythm idioventricular	HO, OT
91	11/16/2017	14196425	1	US-MYLANLABS-2017M1073043	Expedited	59	F	USA	Blood pressure decreased, drug ineffective	LT, OT
92	12/5/2017	14250683	2	JP-SUN PHARMACEUTICAL INDUSTRIES LTD-2017R1-156221	Expedited	32	F	JPN	Exposure during pregnancy, premature delivery	OT
93	12/5/2017	14251724	1	US-IMPAX LABORATORIES, INC-2017-IPXL-03439	Expedited	32	F	USA	Acute respiratory distress syndrome, drug ineffective, pancreatitis	OT
94	12/5/2017	14254129	3	KR-PFIZER INC-2017512070	Expedited	45	F	KOR	Peripheral ischaemia	OT
95	1/16/2018	14394563	1	US-FRESENIUS KABI-FK201800574	Expedited	55	F	USA	Arteriospasm coronary	LT

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96	1/17/2018	14401671	1	US-MYLANLABS-2018M1003513	Expedited	55	F	USA	Arteriospasm coronary, cardiac failure acute, ventricular hypokinesia	HO, OT
97	1/17/2018	14402238	2	US-PFIZER INC-2018018213	Expedited	55	F	USA	Arteriospasm coronary	HO, OT
98	1/19/2018	14409095	1	US-APOTEX-2018AP005282	Expedited	46	F	USA	Drug ineffective	HO, OT
99	1/19/2018	14413007	1	US-IMPAX LABORATORIES, INC-2018-IPXL-00129	Expedited	38	M	USA	Cardiomyopathy, drug ineffective	DE
100	1/22/2018	14421590	3	US-009507513-1801USA006858	Expedited	61	F	USA	Drug ineffective, metabolic acidosis, renal impairment	HO, LT, OT
101	1/25/2018	14441281	1	US-TEVA-2018-US-850243	Expedited	55	F	USA	Arteriospasm coronary, cardiac failure acute, ventricular hypokinesia	HO
102	1/26/2018	14447926	1	US-LPDUSPRD-20180055	Expedited	55	F	USA	Arteriospasm coronary, cardiac failure congestive	HO
103	1/29/2018	14455592	2	US-BAUSCH-BL-2018-001699	Expedited	61	F	USA	Drug ineffective, metabolic acidosis, renal impairment	HO, LT, OT
104	1/31/2018	14465484	2	GD-SUN PHARMACEUTICAL INDUSTRIES LTD-2018RR-161739	Expedited	61	F	GRD	Drug ineffective, intentional overdose, metabolic acidosis, renal impairment	HO, OT
105	1/31/2018	14466328	2	US-JNJFOC-20180121246	Expedited	61	F	USA	Drug ineffective, metabolic acidosis, renal impairment	HO, LT, OT
106	2/12/2018	14523594	1	CA-ENDO PHARMACEUTICALS INC-2018-016820	Expedited	49	F	CAN	Altered state of consciousness, anuria, hyperdynamic left ventricle, hypoglycaemia, hypokalaemia, hypotension, intentional overdose, off label use, optic atrophy, pulmonary oedema, reversible cerebral vasoconstriction syndrome, shock, tachycardia, toxicity to various agents	DS, OT
107	3/28/2018	14691246	1	US-FRESENIUS KABI-FK201803791	Expedited	54	M	USA	Diabetes insipidus	OT
108	3/29/2018	14693175	1	US-LPDUSPRD-20180420	Expedited	75	M	USA	Gangrene, off label use	HO
109	3/29/2018	14695608	1	US-TEVA-2018-US-874841	Expedited	75	M	USA	Gangrene	HO
110	4/9/2018	14734471	1	US-LPDUSPRD-20180475	Expedited	54	M	USA	Diabetes insipidus, off label use	HO
111	4/10/2018	14742507	1	US-LPDUSPRD-20180531	Expedited	34	M	USA	Diabetes insipidus	HO
112	4/12/2018	14752133	1	US-LPDUSPRD-20180535	Expedited	30	F	USA	Diabetes insipidus, off label use	HO
113	4/17/2018	14766758	2	PE-BEH-2018089695	Expedited	37	M	PER	Drug ineffective for unapproved indication	DE

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114	4/17/2018	14769006	1	US-LPDUSPRD-20180573	Expedited	47	M	USA	Diabetes insipidus, off label use	HO
115	4/17/2018	14769007	1	US-LPDUSPRD-20180570	Expedited	26	F	USA	Diabetes insipidus, off label use	HO
116	4/18/2018	14775960	1	PE-PFIZER INC-2018152806	Expedited	37	M	PER	Drug ineffective	DE
117	4/25/2018	14805132	1	US-FRESENIUS KABI-FK201804910	Expedited	32	F	USA	Anaphylactic reaction, intentional product use issue	LT
118	5/3/2018	14841823	1	US-LPDUSPRD-20180727	Expedited	32	F	USA	Anaphylactic reaction, off label use, rubber sensitivity	OT
119	5/3/2018	14843765	1	PE-MYLANLABS-2018M1028163	Expedited	37	M	PER	Drug ineffective, no adverse event	OT
120	7/19/2018	15165801	2	US-PFIZER INC-2018290349	Expedited	59	M	USA	Abdominal compartment syndrome, acute hepatic failure, disseminated intravascular coagulation, drug ineffective, intestinal ischaemia, multiple organ dysfunction syndrome, renal failure, septic shock, thrombosis mesenteric vessel	DE, LT
121	8/1/2018	15227015	1	KR-PFIZER INC-2018299688	Expedited	37	F	KOR	DRUG INEFFECTIVE, VENTRICULAR HYPOKINESIA	HO, OT
122	8/30/2018	15335445	1	JP-PFIZER INC-2018348613	Expedited	59	M	JPN	Drug ineffective	DE
123	9/11/2018	15372594	2	DE-BAXTER-2018BAX023211	Expedited	49	M	DEU	Multiple organ dysfunction syndrome, sepsis	DE
124	10/9/2018	15480482	1	US-BAXTER-2018BAX025393	Expedited	18	M	USA	Drug ineffective	OT
125	10/10/2018	15482069	1	US-BAXTER-2018BAX025394	Expedited	67	M	USA	Drug ineffective	OT
126	10/10/2018	15483607	1	US-BAXTER-2018BAX024850	Expedited	22	M	USA	Drug ineffective	OT
127	11/7/2018	15592182	2	IN-MYLANLABS-2018M1083831	Expedited	28	F	IND	Acute kidney injury, blood pressure decreased, circulatory collapse, drug ineffective, intentional overdose, metabolic acidosis, shock, suicide attempt, toxicity to various agents	HO, LT
128	11/6/2018	15593927	1	US-MYLANLABS-2018M1083824	Expedited	37	F	USA	Cardiac arrest, drug ineffective, overdose, toxicity to various agents	DE, HO, LT
129	11/9/2018	15603811	2	IN-PFIZER INC-2018461837	Expedited	28	F	IND	Drug ineffective	HO, LT
130	11/13/2018	15612370	1	US-MYLANLABS-2018M1083743	Expedited	53	M	USA	Cardiac arrest, drug ineffective, fluid overload, hypotension, overdose, shock, toxicity to various agents	DE, HO, LT

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131	11/15/2018	15622732	2	US-PFIZER INC-2018458960	Expedited	33	F	USA	Pneumonia	OT
132	11/20/2018	15638842	1	IN-ENDO PHARMACEUTICALS INC-2018-042882	Expedited	45	M	IND	Electrocardiogram qt prolonged, ventricular arrhythmia	OT
133	11/26/2018	15655249	1	JP-TEVA-2018-JP-980707	Non-Expedited	44	M	JPN	Drug ineffective	HO
134	11/27/2018	15662527	1	US-MYLANLABS-2018M1087981	Expedited	42	M	USA	Confusional state, delirium, drug interaction, serotonin syndrome	HO, LT
135	11/28/2018	15663799	1	US-TEVA-2018-US-980557	Expedited	42	M	USA	Confusional state, delirium, drug interaction, movement disorder, serotonin syndrome, therapy non-responder	HO, LT
136	11/29/2018	15672019	1	JP-MYLANLABS-2018M1088188	Expedited	44	M	JPN	Drug ineffective	HO
137	12/3/2018	15681570	1	BR-MYLANLABS-2018M1088122	Expedited	36	F	BRA	Drug ineffective, maternal exposure during pregnancy	OT
138	12/3/2018	15681638	1	US-BIODELIVERY SCIENCES INTERNATIONAL-2018BDSI0646	Expedited	42	M	USA	Confusional state, delirium, drug interaction, movement disorder, serotonin syndrome, therapy non-responder	HO, LT
139	12/12/2018	15715735	1	US-MYLANLABS-2018M1090331	Expedited	41	M	USA	Drug ineffective	HO, LT
140	12/19/2018	15740977	3	IS-SA-2018SA342386	Expedited	60	F	ISL	Acute myocardial infarction, cognitive disorder, cyanosis, electrocardiogram ST segment elevation, haemoglobin decreased, haemorrhage, ischaemia, myocardial necrosis, necrosis, peripheral coldness, septic shock, shock, thrombosis, ventricular tachycardia, vital functions abnormal, Wernicke-Korsakoff syndrome	HO, OT
141	12/20/2018	15745829	4	IS-MYLANLABS-2018M1095417	Expedited	60	F	ISL	Acute myocardial infarction, cognitive disorder, condition aggravated, cyanosis, drug tolerance, electrocardiogram ST segment elevation, extremity necrosis, gastrointestinal haemorrhage, haemoglobin decreased, haemorrhage, hypotension, ischaemia, myocardial necrosis, necrosis, necrosis ischaemic, peripheral coldness, septic shock, shock, thrombosis, ventricular tachycardia, vital functions abnormal, Wernicke-Korsakoff syndrome	HO, OT
142	12/21/2018	15750334	1	US-APOTEX-2018AP027330	Expedited	22	F	USA	Cardiac arrest, drug ineffective	HO, OT
143	12/30/2018	15774931	2	JP-BEH-2018098050	Expedited	74	M	JPN	Intestinal ischaemia, seizure	DE, HO, LT, OT
144	12/31/2018	15775863	1	AU-SUN PHARMACEUTICAL INDUSTRIES LTD-2018RR-194941	Expedited	55	F	AUS	Anuria, drug ineffective, hyperlactacidaemia, hypotension, intentional overdose, metabolic acidosis, renal failure	HO, OT

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145	1/1/2019	15779138	2	CA-ICU MEDICAL, INC.-ICU2018CA00241	Expedited	49	F	CAN	Altered state of consciousness, anuria, blindness, blindness cortical, CSF pressure increased, cardiogenic shock, cerebral infarction, circulatory collapse, colour blindness, condition aggravated, cytotoxic oedema, depressed level of consciousness, electrocardiogram P wave abnormal, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased, electrocardiogram T wave inversion, electrocardiogram U wave present, embolism, embolism arterial, hyperdynamic left ventricle, hypoglycaemia, hypokalaemia, hypotension, hypothermia, intentional overdose, ischaemia, optic atrophy, optic nerve injury, overdose, pulmonary oedema, renal tubular necrosis, retinal ischaemia, reversible cerebral vasoconstriction syndrome, shock, tachycardia, toxicity to various agents, visual impairment	DS, HO, LT, OT
146	1/3/2019	15786502	2	US-PFIZER INC-2018534599	Expedited	55	M	USA	Drug ineffective	LT
147	1/15/2019	15826324	4	PHHY2019IS005387	Expedited	60	F	ISL	Acute myocardial infarction, cognitive disorder, cyanosis, drug tolerance, electrocardiogram ST segment elevation, extremity necrosis, haemoglobin decreased, haemorrhage, hypotension, ischaemia, myocardial necrosis, necrosis, peripheral coldness, septic shock, shock, thrombosis, ventricular tachycardia, vital functions abnormal, Wernicke-Korsakoff syndrome	HO, OT
148	1/28/2019	15879931	2	KR-ENDO PHARMACEUTICALS INC-2019-100548	Expedited	31	F	KOR	Cardiac arrest, off label use	OT
149	2/5/2019	15920298	1	CA-MYLANLABS-2019M1010694	Expedited	22	F	CAN	Cardiac arrest, cardiogenic shock, cardiomyopathy, drug ineffective, metabolic acidosis, multiple organ dysfunction syndrome, pulmonary oedema	HO, LT
150	2/5/2019	15920678	1	CA-FRESENIUS KABI-FK201901251	Expedited	22	F	CAN	Drug ineffective	OT
151	2/14/2019	15959479	1	CA-TEVA-2019-CA-1010347	Expedited	22	F	CAN	Cardiac arrest, cardiogenic shock, cardiomyopathy, metabolic acidosis, multiple organ dysfunction syndrome, myocardial depression, pulmonary oedema, toxicity to various agents	HO, LT
152	2/14/2019	15963631	2	DK-MYLANLABS-2019M1013038	Expedited	62	M	DNK	Drug ineffective, hyperglycaemia, hypotension, metabolic acidosis, overdose, toxicity to various agents	HO, LT
153	3/20/2019	16094706	1	US-TEVA-2018-US-989083	Non-Expedited	41	M	USA	Drug ineffective	HO, LT
154	4/30/2019	16254208	2	PHHY2019CA095349	Expedited	49	F	CAN	Altered state of consciousness, anuria, blindness, blindness cortical, CSF pressure increased, cardiogenic	DS, HO, LT, OT

Row	Initial FDA Received Date	FAERS Case #	Version #	MFR Ctrl #	Case Type	Age in Years	Sex	Country	PTs	All Outcomes
									shock, cerebral infarction, circulatory collapse, colour blindness, condition aggravated, cytotoxic oedema, depressed level of consciousness, electrocardiogram P wave abnormal, electrocardiogram ST segment depression, electrocardiogram Tt wave amplitude decreased, electrocardiogram t wave inversion, electrocardiogram u wave present, embolism, embolism arterial, hyperdynamic left ventricle, hypoglycaemia, hypokalaemia, hypotension, hypothermia, intentional overdose, ischaemia, optic atrophy, optic nerve injury, overdose, pulmonary oedema, renal tubular necrosis, retinal ischaemia, reversible cerebral vasoconstriction syndrome, shock, tachycardia, toxicity to various agents, visual impairment	
155	5/2/2019	16266075	1	CA-TEVA-2019-CA-1042363	Expedited	49	F	CAN	Altered state of consciousness, anuria, blindness, blindness cortical, CSF pressure increased, cardiogenic shock, cerebral infarction, circulatory collapse, colour blindness, condition aggravated, cytotoxic oedema, depressed level of consciousness, electrocardiogram P wave abnormal, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased, electrocardiogram T wave inversion, electrocardiogram U wave present, embolism, embolism arterial, hyperdynamic left ventricle, hypoglycaemia, hypokalaemia, hypotension, hypothermia, intentional overdose, ischaemia, optic atrophy, optic nerve injury, overdose, pulmonary oedema, renal tubular necrosis, retinal ischaemia, reversible cerebral vasoconstriction syndrome, shock, tachycardia, toxicity to various agents, visual impairment	CA, DS, HO, LT, OT
156	5/8/2019	16285352	1	US-FRESENIUS KABI-FK201905221	Expedited	42	M	USA	Gastric ulcer, ischaemia, mucormycosis, product use in unapproved indication	HO
157	5/8/2019	16287362	1	US-MYLANLABS-2019M1043247	Expedited	42	M	USA	Anaemia, gastric ulcer, haematemesis, mucormycosis	HO
158	5/16/2019	16318483	1	US-TEVA-2019-US-1049608	Expedited	42	M	USA	Haematemesis, haemoglobin decreased, ischaemic skin ulcer, mucormycosis	HO
159	5/28/2019	16361310	1	US-MYLANLABS-2019M1049283	Expedited	70	M	USA	Drug ineffective	HO, LT
160	5/31/2019	16379797	1	US-SERB S.A.S.-2067673	Expedited	40	M	USA	Acidosis, complication associated with device, hyperkalaemia, product use in unapproved indication	HO
161	6/4/2019	16391278	1	PHHY2019US125336	Expedited	54	M	USA	Cardiac arrest, cardiac failure, cardio-respiratory arrest, disease progression, sepsis, shock, therapy non-responder, ventricular tachycardia	OT

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162	6/5/2019	16395780	1	US-MYLANLABS-2019M1052683	Expedited	54	M	USA	Drug ineffective	DE, HO
163	6/7/2019	16406568	1	US-TEVA-2019-US-1059251	Expedited	70	M	USA	Drug ineffective	HO, LT
164	6/11/2019	16414391	1	US-MYLANLABS-2019M1055062	Expedited	44	F	USA	Bacterial pericarditis, brain stem haemorrhage, catheter site erythema, cerebellar haemorrhage, cerebral haemorrhage, cerebral infarction, complication associated with device, device related infection, drug ineffective, encephalitis, expired product administered, exposure via contaminated device, myocardial infarction, renal haemorrhage, septic embolus, septic shock, staphylococcal sepsis	DE, HO, LT, OT
165	6/12/2019	16420165	1	US-ENDO PHARMACEUTICALS INC-2019-105443	Expedited	53	F	USA	Hypernatraemia, nephrogenic diabetes insipidus	OT
166	6/13/2019	16427107	1	US-TEVA-2019-US-1061376	Expedited	54	M	USA	Arrhythmia, cardiac arrest, cardiac failure, cardio-respiratory arrest, condition aggravated, drug ineffective, electrocardiogram QRS complex prolonged, liver function test abnormal, renal impairment, shock, toxicity to various agents, ventricular tachycardia	DE, HO
167	6/13/2019	16427261	2	US-PFIZER INC-2019249882	Expedited	44	F	USA	Bacterial pericarditis, brain stem haemorrhage, catheter site erythema, cerebellar haemorrhage, cerebral haemorrhage, cerebral infarction, complication associated with device, device related infection, drug ineffective, encephalitis, expired product administered, exposure via contaminated device, myocardial infarction, renal haemorrhage, septic embolus, septic shock, staphylococcal sepsis	DE, HO, LT, OT
168	6/20/2019	16456280	1	US-TEVA-2019-US-1064276	Expedited	44	F	USA	Drug ineffective	LT
169	6/20/2019	16457385	1	CA-PFIZER INC-2018302947	Expedited	51	M	CAN	Bradycardia, cardiac arrest, cardiogenic shock, coma scale abnormal, compartment syndrome, condition aggravated, hyperkalaemia, hypotension, ileus, lactic acidosis, overdose, pulse absent, rhabdomyolysis, vasoplegia syndrome	HO, LT, OT
170	6/25/2019	16471973	1	US-ALKEM LABORATORIES LIMITED-US-ALKEM-2018-05579	Expedited	22	F	USA	Overdose, therapy non-responder, toxicity to various agents	HO, OT
171	8/20/2019	16721745	1	CA-MYLANLABS-2019M1077239	Expedited	49	F	CAN	Altered state of consciousness, anuria, blindness, blindness cortical, CSF pressure increased, cardiogenic shock, cerebral infarction, circulatory collapse, colour blindness, condition aggravated, cytotoxic oedema, depressed level of consciousness, electrocardiogram P wave abnormal, electrocardiogram ST segment depression, electrocardiogram T wave amplitude	DS, HO, LT, OT

Row	Initial FDA Received Date	FAERS Case #	Version #	MFR Ctrl #	Case Type	Age in Years	Sex	Country	PTs	All Outcomes
									decreased, electrocardiogram t wave inversion, electrocardiogram u wave present, embolism, embolism arterial, hyperdynamic left ventricle, hypoglycaemia, hypokalaemia, hypotension, hypothermia, intentional overdose, ischaemia, optic atrophy, optic nerve injury, overdose, pulmonary oedema, renal tubular necrosis, retinal ischaemia, reversible cerebral vasoconstriction syndrome, shock, tachycardia, toxicity to various agents, visual impairment	
172	9/6/2019	16780998	1	US-MYLANLABS-2019M1083151	Expedited	58	M	USA	Drug ineffective	DE, HO
173	9/9/2019	16785021	1	US-MYLANLABS-2019M1083657	Expedited	66	F	USA	Cardiac arrest, cardiogenic shock, completed suicide, drug ineffective, ventricular fibrillation	DE, HO, OT
174	9/11/2019	16793267	2	US-DRREDDYS-USA/USA/19/0113921	Expedited	58	M	USA	Drug ineffective	DE, HO, OT
175	9/12/2019	16798516	1	US-MYLANLABS-2019M1084961	Expedited	57	F	USA	Drug ineffective	LT
176	1/7/2013	9001506	1	JP-JHP PHARMACEUTICALS, LLC-JHP201200588	Expedited	23	M	JPN	Pulmonary thrombosis	DE
177	6/14/2013	9349177	1	US-JHP PHARMACEUTICALS, LLC-JHP201300354	Expedited	47	F	USA	Drug ineffective	OT
178	6/27/2013	9371922	2	JP-PFIZER INC-HQWYE880219SEP06	Expedited	77	M	JPN	Acute respiratory distress syndrome, multiple organ dysfunction syndrome, rhabdomyolysis, septic shock, toxic epidermal necrolysis	DE, LT
179	6/27/2013	9379486	1	UCM201306-000032	Expedited	51	M	USA	Agitation, hypertension, hypokalaemia, hypoxic-ischaemic encephalopathy, tachycardia, ventricular fibrillation	DE, HO
180	6/28/2013	9380616	1	UCM201306-000033	Expedited	26	M	USA	Necrotising fasciitis, pulseless electrical activity	HO
181	8/29/2013	9489372	2	PHHY2013US092766	Expedited	56	M	USA	Abdominal tenderness, acute respiratory distress syndrome, altered state of consciousness, drug ineffective, general physical health deterioration, haemophagocytic lymphohistiocytosis, hyperferritinaemia, hypertriglyceridaemia, hypofibrinogenaemia, hypoxia, lactic acidosis, lethargy, metabolic acidosis, multiple organ dysfunction syndrome, pancytopenia, pyrexia, shock, splenomegaly	DE, OT
182	7/12/2013	9548199	1	1474029	Non-Expedited	23	F	USA	Anaesthetic complication, off label use	OT
183	1/7/2014	9801471	2	IL-JHP PHARMACEUTICALS, LLC-JHP201300767	Expedited	47	M	ISR	Acute kidney injury	DE, OT

Row	Initial FDA Received Date	FAERS Case #	Version #	MFR Ctrl #	Case Type	Age in Years	Sex	Country	PTs	All Outcomes
184	2/11/2014	9890517	1		Direct	60	M	USA	Post procedural haemorrhage, thoracic haemorrhage	HO
185	3/11/2014	9998942	1		Direct	76	F	USA	Cardiac arrest, cardio-respiratory arrest, device malfunction, hypotension	DE

*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, and 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: DE=Death, HO=Hospitalization, LT= Life-threatening, DS= Disability, CA= Congenital Anomaly, OT=Other Medically Significant, NR = not reported
Country Codes: AUS=Australia, BRA=Brazil, CAN=Canada, CHE=Switzerland, CHN=China, COL=Columbia, DEU=Germany, DNK=Denmark, GBR=United Kingdom of Great Britain and Northern Ireland, GRD=Grenada, IND=India, ISL=Iceland, ISR=Israel, JPN=Japan, KOR=Korea, NLD=Netherlands, NZL=New Zealand, PER=Peru, RUS=Russia, SVN=Slovenia, USA=United States of America,

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/s/

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10/10/2019 09:26:19 AM

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