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

# Pediatric Postmarketing Pharmacovigilance Review

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| **Date:** | November 6, 2023 |
| **Reviewer:** | Ivone Kim, MD, Medical Officer<br>Division of Pharmacovigilance I |
| **Team Leader:** | Carmen Cheng, PharmD<br>Division of Pharmacovigilance I |
| **Division Director:** | Monica Muñoz, PharmD, PhD<br>Division of Pharmacovigilance I |
| **Product Name:** | Nuvessa (metronidazole) vaginal gel |
| **Pediatric Labeling Approval Date:** | August 3, 2018 |
| **Application Type/Number:** | NDA 205223 |
| **Applicant:** | Chemo Research SL |
| **TTT Record ID:** | 2023-6501 |

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## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Nuvessa (metronidazole) vaginal gel in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Nuvessa vaginal gel in pediatric patients.

Nuvessa (metronidazole) vaginal gel is a topical antibiotic initially approved in the U.S. on March 24, 2014. Nuvessa vaginal gel is currently indicated for the treatment of bacterial vaginosis in females 12 years of age and older.

This pediatric postmarketing safety review was prompted by pediatric labeling on August 3, 2018, that extended the indication to include pediatric patients aged 12 years and older. Safety and effectiveness in pediatric patients below the age of 12 years have not been established. A postmarketing pharmacovigilance review for Nuvessa vaginal gel has not been previously presented to the Pediatric Advisory Committee.

DPV reviewed all serious FAERS reports with Nuvessa vaginal gel in pediatric patients less than 18 years of age through September 18, 2023, and identified two reports. However, DPV excluded all reports from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Nuvessa vaginal gel in pediatric patients less than 18 years of age.

DPV did not identify any new pediatric safety concerns for Nuvessa vaginal gel at this time and will continue routine pharmacovigilance monitoring for Nuvessa vaginal gel.

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Nuvessa (metronidazole) vaginal gel in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Nuvessa vaginal gel in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY[1]

Nuvessa (metronidazole) vaginal gel is a topical antibiotic initially approved in the U.S. on March 24, 2014. Nuvessa vaginal gel is currently indicated for the treatment of bacterial vaginosis in females 12 years of age and older.

This pediatric postmarketing safety review was prompted by pediatric labeling on August 3, 2018, that extended the indication to include pediatric patients aged 12 years and older. Safety and effectiveness in pediatric patients below the age of 12 years have not been established. A postmarketing pharmacovigilance review for Nuvessa vaginal gel has not been previously presented to the Pediatric Advisory Committee.

## 1.2 RELEVANT LABELED SAFETY INFORMATION

The Nuvessa vaginal gel labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Nuvessa vaginal gel labeling information, please refer to the full prescribing information.[1]

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

- History of hypersensitivity to metronidazole, parabens, other ingredients of the formulation, or other nitroimidazole derivatives (4.1)
- Concomitant use of disulfiram or within 2 weeks of disulfiram (4.2, 7.1)
- Concomitant use of alcohol (4.3, 7.2)

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

- Central and peripheral nervous system effects: Convulsive seizures and peripheral neuropathy have been reported in patients treated with oral or intravenous metronidazole. Discontinue promptly if abnormal neurologic signs develop. (5.1)
- Interference with laboratory tests: Metronidazole may interfere with certain serum chemistry laboratory values. (5.3)

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

The most common adverse reactions observed in adult clinical studies (incidence ≥1%) were vulvovaginal candidiasis, headache, vulvovaginal pruritus, nausea, diarrhea, and dysmenorrhea. The most common adverse reactions observed in pediatric clinical studies (incidence ≥1%) was vulvovaginal discomfort. (6.1)

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

- Warfarin and other coumarin anticoagulants: Prolonged anticoagulant effects of warfarin and other coumarin anticoagulants have been reported with co-administration of oral metronidazole. (7.3)
- Lithium: Elevated plasma lithium concentrations have been reported with oral metronidazole. (7.4)

**8.4 Pediatric Use**

The safety and effectiveness of NUVESSA have been established in pediatric subjects between the ages of 12 and less than 18 years old. Use of NUVESSA in this age group is supported by evidence from a multicenter, open-label safety and tolerability study in 60 pediatric patients with bacterial vaginosis [see Adverse Reactions (6.1)] and, evidence from adequate and well-controlled studies in adult women.

The safety and effectiveness of NUVESSA in pediatric subjects below the age of 12 years have not been established.

# 2 METHODS AND MATERIALS

## 2.1 FAERS SEARCH STRATEGY

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

| **Table 1. FAERS Search Strategy*** | |
|---|---|
| Date of search | September 19, 2023 |
| Time period of search | All dates through September 18, 2023 |
| Search type | Drug Safety Analytics Dashboard (DSAD) Quick Query |
| Product terms | Product name: Nuvessa<br>NDA: 205223 |
| MedDRA search terms (Version 26.0) | All Preferred Terms |
| * See Appendix A for a description of the FAERS database.<br>Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, NDA=New Drug Application | |

# 3 RESULTS

## 3.1 FAERS

### *3.1.1 Total Number of FAERS Reports by Age*

**Table 2** presents the number of adult and pediatric FAERS reports received through September 18, 2023, with Nuvessa vaginal gel.

| **Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA Through September 18, 2023, With Nuvessa Vaginal Gel** | | | |
|---|---|---|---|
| | **All Reports (U.S.)** | **Serious† (U.S.)** | **Death (U.S.)** |
| Adults (≥ 18 years) | 25 (9) | 18 (3) | 1 (0) |
| Pediatrics (0 - < 18 years) | 2 (2) | 2 (2) | 0 (0) |
| * May include duplicates and transplacental exposures, and have not been assessed for causality<br>† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. | | | |

### *3.1.2 Selection of Serious Pediatric Cases in FAERS*

Our FAERS search retrieved two serious pediatric reports through September 18, 2023. We reviewed all FAERS pediatric reports with a serious outcome. We excluded both reports from the case series as neither report described exposure to Nuvessa vaginal gel.

### *3.1.3 Summary of U.S. Fatal Pediatric Cases (N=0)*

There are no fatal pediatric adverse event cases for discussion.

#### *3.1.4 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)*

There are no non-fatal pediatric adverse event cases for discussion.

## 4 DISCUSSION

DPV reviewed all serious FAERS reports with Nuvessa vaginal gel in pediatric patients less than 18 years of age through September 18, 2023, and identified two reports. However, DPV excluded all reports from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Nuvessa vaginal gel in pediatric patients less than 18 years of age.

## 5 CONCLUSION

DPV did not identify any new pediatric safety concerns for Nuvessa vaginal gel at this time and will continue routine pharmacovigilance monitoring for Nuvessa vaginal gel.

## 6 REFERENCES

1. Nuvessa (metronidazole) vaginal gel 1.3%. [Prescribing information]. Florham Park, NJ; Exeltis USA, Inc.: February, 2022.

## 7 APPENDICES

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

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities 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 an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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