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

**Pediatric Postmarketing Pharmacovigilance**

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| **Application Type/Number:** | NDAs 021085, 021334, 021227 |
| **Applicant/Sponsor:** | Bayer Pharmaceuticals Healthcare Inc. |
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## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for moxifloxacin (tablets, injection) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on unlabeled adverse events (AEs) associated with moxifloxacin (tablets, injection) in U.S. pediatric patients reporting a serious outcome. Although the focus of this review is on unlabeled AEs, labeled AEs were also reviewed and summarized because we anticipate there may be interest in off-label pediatric use of moxifloxacin (tablets, injection), especially since it has no approved indication in pediatric patients.

Avelox (moxifloxacin) is a fluoroquinolone antibiotic available as an oral tablet (approved December 10, 1999) and injection (approved November 30, 2001). It is indicated for use in adults, age 18 years and older, to treat infections caused by designated susceptible bacteria in the following conditions: community acquired pneumonia, skin and skin structure infections (uncomplicated and complicated), complicated intra-abdominal infections, plague, acute bacterial sinusitis, and acute bacterial exacerbation of chronic bronchitis. Moxifloxacin (tablets, injection) is not approved for pediatric use. A labeling change in September 2016 updated the moxifloxacin (tablets, injection) labeling to include safety information for pediatric patients derived from a trial in pediatric patients with complicated intra-abdominal infection. This PREA review is triggered by the pediatric labeling change.

DPV reviewed all U.S. serious FAERS reports with moxifloxacin use (tablets, injection) in the pediatric population (ages 0 to < 18 years), received by FDA through May 8, 2018. In the 19 years since approval of moxifloxacin in the U.S., three cases with unlabeled AEs and 19 cases with labeled AEs associated with adult indications were reported with moxifloxacin (tablets, injection) in the pediatric population. There were no deaths directly associated with moxifloxacin (tablets, injection), and of the three reports which described unlabeled AEs, there were no new safety signals identified. Among the 19 cases describing one or more labeled AEs, no apparent increased severity was reported. The labeled AEs in these reports are adequately described in the moxifloxacin labeling. There was no indication that the labeled AEs were occurring at increased frequency, although spontaneous databases are suboptimal for assessing frequency.

In summary, moxifloxacin (tablets, injection) is not approved for use in the pediatric population. This FAERS review of AEs associated with off-label use of moxifloxacin (tablets, injection) among U.S. pediatric patients did not identify any unpredicted pediatric safety signals. DPV recommends no regulatory action specific to pediatric patients at this time, and will continue to monitor all AEs associated with the use of moxifloxacin (tablets, injection).

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for moxifloxacin (tablets, injection) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on unlabeled adverse events (AEs) associated with moxifloxacin (tablets, injection) in U.S. pediatric patients reporting a serious outcome. Although the focus of this review is on unlabeled AEs, labeled AEs were also reviewed and summarized because we anticipate there may be interest in off-label pediatric use of moxifloxacin (tables, injection), especially since it has no approved indication in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY

Avelox (moxifloxacin) is a fluoroquinolone antibiotic available as an oral tablet (approved December 10, 1999) and injection (approved November 30, 2001).[1] It is indicated for use in adults, age 18 years and older, to treat infections caused by designated susceptible bacteria in the following conditions: community acquired pneumonia, skin and skin structure infections (uncomplicated and complicated), complicated intra-abdominal infections, plague, acute bacterial sinusitis, and acute bacterial exacerbation of chronic bronchitis.[2]

Moxifloxacin (tablets, injection) is not approved for use in pediatric patients, and its effectiveness in pediatric patients less than 18 years of age has not been established.[2,3] Postmarketing requirement (PMR) 2898-2 established the data needed to fulfill the requirements of the Pediatric Research Equity Act (PREA) (21 U.S.C.355c). PMR 2898-2 states, "Submit data to assess the pharmacokinetics and safety of Avelox (moxifloxacin hydrochloride) Tablets and IV in pediatric patients 3 months to less than 18 years of age" (see sNDA approval letter dated May 8, 2015[1]). DPV has not previously conducted a pediatric-specific review of FAERS data with moxifloxacin (tablets, injection) for the Pediatric Advisory Committee (PAC).

The moxifloxacin (tablets, injection) pediatric development program included two studies: a single-dose pharmacokinetic (PK) study (NCT01049022, hereafter study 1) and a randomized double blind active control multicenter PK and safety clinical trial for the treatment of complicated intra-abdominal infections (cIAI) including appendicitis with perforation, abscesses, and peritonitis (NCT01069900, hereafter study 2). The endpoints for study 1 included predominantly PK parameters; therefore, study 2 was used to evaluate pediatric safety for PMR 2898-2 due to the study size and multiple dosing regimen, according to the Medical/Clinical Review (dated February 12, 2016)[3].

The moxifloxacin-associated AEs observed in study 2 were similar to moxifloxacin-associated AEs that are observed in adults. In study 2, the most frequently occurring adverse reactions in pediatric patients treated with moxifloxacin were QT prolongation 9.3% (28/301), vomiting, 6.6% (20/301) diarrhea 3.7% (11/301), arthralgia 3.0% (9/301), and phlebitis 2.7% (8/301). These AEs are labeled in the Pediatric Use section of the moxifloxacin label. There were no pediatric deaths reported in study 2, or in the overall pediatric moxifloxacin development program. The incidence of AEs stratified by age group were similar between moxifloxacin and

comparator group (ertapenem followed by oral amoxicillin-clavulanate). Although the study enrolled patients ages 3 months to <18 years, there were only 15 subjects below the age of 6 years treated with moxifloxacin. As such there are insufficient data in this study to evaluate the safety profile of moxifloxacin in children younger than 6 years.[3]

Study 2 fulfilled PMR 2898-2, as noted in a supplement approval letter dated September 27, 2016.[1] A pediatric labeling change occurred on September 27, 2016 to incorporate information on the safety of moxifloxacin in pediatric patients derived from clinical data in study 2.[1,4] This PREA review is triggered by the pediatric labeling change.

### 1.1 RELEVANT LABELED SAFETY INFORMATION

The moxifloxacin (tablets, injection) labeling provides the following safety information and pediatric information (excerpted from the pertinent sections). For further moxifloxacin labeling information, including dosage and administration for adult patients, please refer to full prescribing information.[2]

**WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRIAL NERVOUS SYSTEM EFFECTS and EXACERBATION OF MYASTHENIA GRAVIS**

***See full prescribing information for complete boxed warning***

- **Fluoroquinolones, including AVELOX, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together (5.1) including:**
  - **Tendinitis and tendon rupture (5.2)**
  - **Peripheral Neuropathy (5.3)**
  - **Central nervous system effects (5.4)**

  **Discontinue AVELOX immediately and avoid the use of fluoroquinolones, including AVELOX, in patients who experience any of these serious adverse reactions (5.1)**

- **Fluoroquinolones, including AVELOX, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid AVELOX in patients with known history of myasthenia gravis (5.5).**

- **Because fluoroquinolones, including AVELOX, have been associated with serious adverse reactions (5.1–5.13), reserve AVELOX for use in patients who have no alternative treatment options for the following indications:**
  - **Acute bacterial sinusitis (1.6)**
  - **Acute bacterial exacerbation of chronic bronchitis (1.7)**

----------CONTRAINDICATIONS----------
Known hypersensitivity to AVELOX or other quinolones (4, 5.8)

----------WARNINGS AND PRECAUTIONS----------
• Prolongation of the QT interval and isolated cases of torsade de pointes has been reported. Avoid use in patients with known prolongation, proarrhythmic conditions such as clinically significant bradycardia or acute myocardial ischemia, hypokalemia, hypomagnesemia, and with drugs that prolong the QT interval. (5.6, 7.5, 8.5)
• Hypersensitivity and other serious reactions: Serious and sometimes fatal reactions, including anaphylactic reactions, may occur after first or subsequent doses of AVELOX. Discontinue AVELOX at first sign of skin rash, jaundice or any other sign of hypersensitivity. (5.7, 5.8)
• Clostridium difficile-Associated Diarrhea: Evaluate if diarrhea occurs. (5.9)

----------ADVERSE REACTIONS----------
Most common reactions (3% or greater) were nausea, diarrhea, headache, and dizziness. (6)

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

| Interacting Drug | Interaction |
|---|---|
| Multivalent cation-containing products including: antacids, sucralfate, multivitamins | Decreased AVELOX absorption. Take AVELOX Tablet at least 4 hours before or 8 hours after these products. (2.2, 7.1, 12.3) |
| Warfarin | Anticoagulant effect enhanced. Monitor prothrombin time/INR, and bleeding. (6, 7.2, 12.3) |
| Class IA and Class III antiarrhythmics: | Proarrhythmic effect may be enhanced. Avoid concomitant use. (5.6, 7.5) |
| Antidiabetic agents | Carefully monitor blood glucose. (5.11, 7.3) |

# 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 | May 9, 2018 |
| Time Period of Search | All reports through May 8, 2018 |
| Search Type | Drug Safety Analytics Dashboard Quick Search |
| Product Terms | • Product Names: Avelox, Avelox ABC pack, Avelox IV<br>• Product Active Ingredients: Moxifloxacin, Moxifloxacin hydrochloride, Moxifloxacin hydrochloride monohydrate<br>• NDAs: 021085, 021334, 021277 |
| Search Parameters: | Age < 18 years, all outcomes, worldwide |
| * See Appendix A for a description of the FAERS database. | |

# 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 through May 8, 2018 with moxifloxacin identified by the search strategy.

| **Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA through May 8, 2018 with Moxifloxacin and identified by the search strategy** | | | |
|---|---|---|---|
| | **All reports (U.S.)** | **Serious† (U.S.)** | **Death (U.S.)** |
| Adults (≥18 years) | 11,238 (6,707) | 9,270 (4,851) | 811 (229) |
| Pediatrics (0 - <18 years) | 186 (85) | **144 (47)** | 17 (0) |

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

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

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

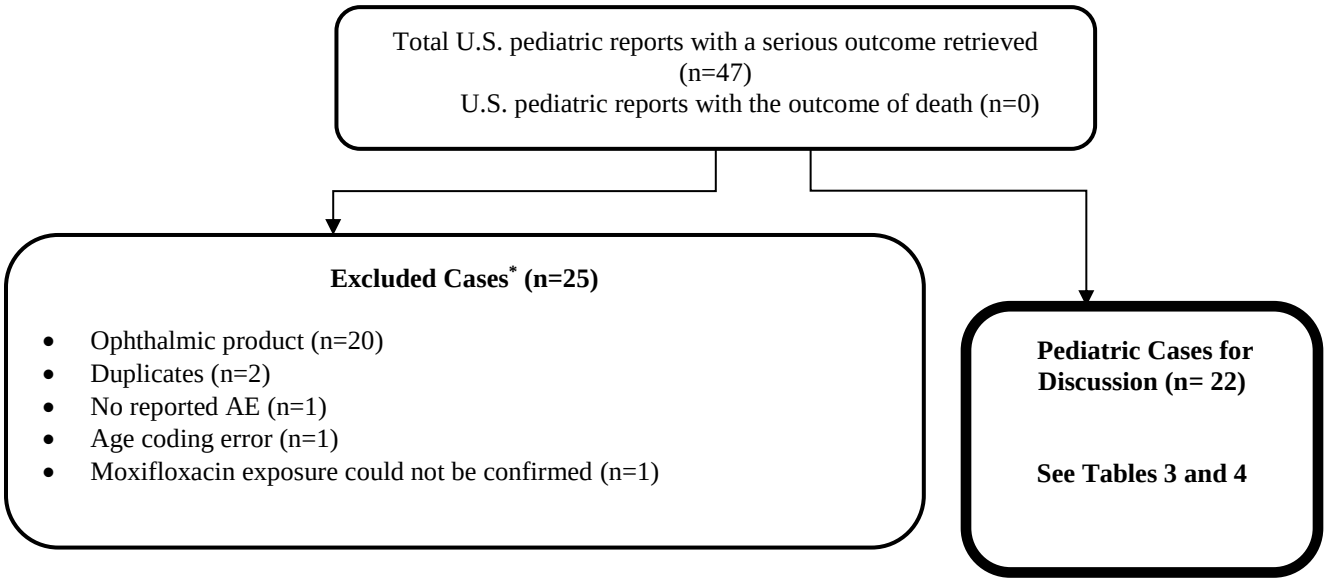
Our FAERS search retrieved 47 U.S. pediatric reports with a serious outcome associated with moxifloxacin use, received by FDA through May 8, 2018.

We reviewed all 47 U.S. FAERS pediatric reports with a serious outcome. Our primary focus was identifying and discussing unlabeled AEs associated with moxifloxacin (tablets, injection) to determine if these data contain new pediatric safety signals. However, in recognition that off-label moxifloxacin use has been reported, our secondary focus was on U.S. serious labeled pediatric cases.

We excluded reports from the case series for these reasons: moxifloxacin ophthalmic products (n=20), duplicate reports (n=2), no reported AE (n=1), age coding error (n=1), and moxifloxacin exposure could not be confirmed (n=1). We summarize the remaining 22 cases in Sections 3.1.4 and 3.1.5.

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

**Figure 1. Selection of U.S. Serious Pediatric Cases with Moxifloxacin (tablets, injection)**




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

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

We did not identify any U.S. fatal pediatric AE report associated with moxifloxacin among the 47 U.S. reports reviewed.[a]

### *3.1.4 Characteristics of Non-Fatal U.S. Serious Unlabeled Pediatric Cases (n=3)*

Appendix B contains a line listing of the three U.S. pediatric cases reporting a serious outcome describing an unlabeled AE in association with moxifloxacin (tablets, injection).

Table 3 summarizes the three U.S. pediatric cases reporting a serious outcome describing an unlabeled AE in association with moxifloxacin (tablets, injection), received by FDA through May 8, 2018.

[a] This review focuses on U.S. reports; however, DPV screened all fatal pediatric reports (i.e., non-U.S. reports) with moxifloxacin use identified by the search strategy and no signal was identified. Of the 17 fatal non-U.S. reports, twelve reports were duplicate. Among the remaining five reports, no signal was identified and no deaths could be directly attributed to moxifloxacin.

| **Table 3. Characteristics of the U.S. Serious Unlabeled Pediatric Cases with Moxifloxacin (tablets, injection), Received by FDA through May 8, 2018** (n=3) | | | |
|---|---|---|---|
| **FAERS Case #** | 3867655 | 6213836 | 14547304 |
| **Age** | 17 | 17 | 2 |
| **Sex** | F | F | F |
| **Reported Reason for Use** | Bronchitis and sinusitis | Respiratory infection | Multi-drug resistant pulmonary tuberculosis |
| **Serious Outcome*** | Other serious | Hospitalization | Hospitalization |
| **Preferred Terms** | *Urinary Tract Infection* | *Speech disorder; Seizure; Gait inability; Fall; Extrasystoles; Depersonalisation/ derealisation disorder* | *Hepatitis A; Drug administered to patient of inappropriate age* |

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. Reports may have more than one outcome.

### 3.1.4.1 Summary of Non-Fatal U.S. Serious Unlabeled Pediatric Cases (n=3)

We identified three U.S. pediatric cases reporting a serious outcome and describing an unlabeled AE in association with moxifloxacin (tablets, injection).

**FAERS Case: 3867655**

- Summary: A 17-year-old female (140 pounds) treated with moxifloxacin PO 400 mg daily prescribed by allergist for bronchitis and sinusitis, presented to a second physician (reporter) with a urinary tract infection (unlabeled AE). Cocomitant medications, past medical history, and dates of moxifloxacin therapy were not reported. The urinary tract infection was treated with sulfamethoxazole/trimethoprim and resolved.

*Reviewer Comment: Urinary tract infection (UTI) is unlikely to be causally related to moxifloxacin. Although moxifloxacin is an antibiotic, it is not indicated for the treatment of urinary tract infection and has a low excretion in the urine (~20% as unchanged drug[2]), so it is plausible that a patient could incidentally develop UTI while on moxifloxacin, especially given the variability in the pathogens that may cause UTI and the potential for fluoroquinolone resistance among these pathogens. Although the use of moxifloxacin and potential for subsequent development of moxifloxacin-resistant pathogens may ultimately influence the pathogens that can cause UTI in a patient, it is unlikely that the pathogenesis of UTI would be directly attributable to moxifloxacin use (instead, the pathogenesis would be attributable to bacteria). This case is also missing dates of therapy relative to presentation with UTI, as well as information about past medical history and other possible risk factors for UTI that may explain the observed UTI.*

**FAERS Case: 6213836**

- Summary: A 17-year-old female (110 pounds) was treated concurrently with moxifloxacin (route and dose not reported) and ciprofloxacin (route and dose not reported) for a respiratory infection and UTI, respectively. The patient also had a concurrent mono (sic) infection. The patient received four days of both ciprofloxacin and moxifloxacin. Two to three weeks later the patient *"started falling down, feeling depersonalized, started talking like a little baby in 11$^{th}$ grade. Had missed heart beats, seizure like activity-eeg normal, lost ability to walk"*. The patient's evaluation included spinal tap, electrocardiograms, multiple magnetic resonance imaging (MRI) studies, unspecified laboratory tests, and an evaluation by a neurologist; all diagnostic evaluations were reported as "normal" and no diagnoses were made. The patient was hospitalized at an unspecified time, discontinued all her medications, and her *"legs returned- but very debilitated".*

*Reviewer Comment: The majority of AEs in this case occur within the spectrum of currently labeled AEs for moxifloxacin, and the events may have been exacerbated by concurrent ciprofloxacin use or possibly related to Epstein-Barr virus infection (mononucleosis) if the CNS was involved.*[5] *Further, the musculoskeletal, neuropsychiatric, and cardiac AEs are consistent with fluoroquinolone associated disability (FQAD), a labeled AE. Additional labeled AEs reported in the case include palpitations and CNS/psychiatric AEs; CNS effects are labeled in the WARNINGS AND PRECAUTIONS* section and *palpitations is labeled in the ADVERSE REACTIONS section.*

*The unlabeled AEs included falling down, depersonalization, changes in speech pattern, and apparent infantile regression occurring two to three weeks following combined moxifloxacin and ciprofloxacin use for four days, though these AEs may ultimately be consistent with an FQAD presentation. The case lacks sufficient detail, such as psychiatric and sociodevelopmental history, specific results for the diagnostic workup, and physicians' assessments, thereby limiting our ability to evaluate the unlabeled AEs and rule out possible alternative etiologies (e.g., conversion disorder, psychosis, delirium, transverse myelitis, aseptic meningitis). The report indicates that the patient's walking improved ("legs returned – but very debilitated"), though moxifloxacin and ciprofloxacin were stopped two to three weeks before symptom onset began so this return of function did not correspond to specific medication discontinuation. The report was also not explicit about the nature of the patient's rehabilitation. Furthermore, the outcome of the other AEs is unknown which precludes our ability for a thorough dechallenge evaluation. There is no rechallenge information in the report.*

**FAERS Case: 14547304**

- Summary: A 2-year-old female (11.2 kg) started therapy for multi-drug resistant pulmonary tuberculosis (MDR-TB), including moxifloxacin PO 150 mg daily, on an unknown date. Concurrent medications included clofazimine PO 50 mg daily, cycloserine PO 150 mg daily, linezolid PO 90 mg daily, and delamanid (dosing information not reported). While on therapy, the patient experienced hepatitis A infection resulting in a five-day hospitalization and necessitating interruption of MDR-TB therapy until

resolution of the hepatitis A infection. Approximately one month later, the hepatitis A infection resolved, and MDR-TB therapy was resumed.

- At the time of hepatitis A diagnosis, reported labs included:
    - ALT 1381 U/L (ref 0 – 34.0 U/L), AST 1770 U/L (ref 15 – 37 U/L), bilirubin (conjugated) 0.4 mg/dL (ref 0.0 – 0.2 mg/dL), calcium 8.4 mg/dL (ref 9.0 – 11.0 mg/dL), creatinine 0.27 mg/dL (0.30 – 0.70 mg/dL)
    - Hepatitis A virus immunoglobulin M antibody 11.45 S/CO ratio (reactive; upper limit of normal reported as 1.2), hepatitis A virus immunoglobulin G antibody 4.06 index (reactive; upper limit of normal reported as 1.0)

*Reviewer Comment: Moxifloxacin is labeled for hepatotoxicity AEs (including hepatitis), but hepatitis A is unlabeled. The laboratory evidence for hepatitis A supports viral hepatitis as a diagnosis and contributing factor to the patient's liver toxicity, although concurrent hepatotoxicity due to moxifloxacin cannot be excluded. MDR-TB therapy (including moxifloxacin) was resumed following resolution of hepatitis A infection; however, the case lacks information about the clinical events following the re-initiation of moxifloxacin and concomitant medications.*

### *3.1.5 Characteristics of Non-Fatal U.S. Serious Labeled Pediatric Cases (n=19)*

Appendix C contains a line listing of the 19 U.S. pediatric cases reporting a serious outcome describing a labeled AE in association with off-label moxifloxacin (tablets, injection) use.

FDA received 19 U.S. pediatric cases reporting a serious outcome that describe one or more *labeled* AEs associated with moxifloxacin (tablets, injection) use since moxifloxacin approval in 1999 through May 8, 2018. The focus of this review is U.S. serious unlabeled pediatric cases; however, since moxifloxacin is not indicated for use in pediatric patients, characteristics of the 19 cases reporting labeled AEs are of interest. Age, sex, year of FAERS report, reason for off-label use, and AEs are summarized in Table 4.

**Table 4 Characteristics of the U.S. Serious Labeled Pediatric Cases with Moxifloxacin (tablets, injection), Received by FDA through May 8, 2018**
(n=19)

| | | |
|---|---|---|
| **Age** | Median | 16 years |
| | Mean | 14.6 years |
| | Range | 1 day – 17 years |
| **Sex** | Female | 10 |
| | Male | 7 |
| | Not reported | 2 |

| **Table 4 Characteristics of the U.S. Serious Labeled Pediatric Cases with Moxifloxacin (tablets, injection), Received by FDA through May 8, 2018** (n=19) | | | | |
|---|---|---|---|---|
| **Initial FDA Received Date** | 2000<br>2001<br>2002<br>2003<br>2005<br>2008 | 1<br>2<br>3<br>1<br>1<br>2 | 2009<br>2010<br>2011<br>2013<br>2016 | 2<br>3<br>1<br>2<br>1 |
| **Reported Reason for Use** | Sinusitis<br>Bronchitis, sinusitis<br>Pneumonia<br>Bronchitis<br>Tonsillitis, pharyngitis (*Streptococcus*, not group A)<br>Upper respiratory tract infection<br>Not reported | | | 9<br>2<br>2<br>2<br>1<br>1<br>2 |
| **Labeled AEs** | • Hypersensitivity (n=7)<br>• Hypersensitivity and peeling skin rash AE (n=1)<br>• Central Nervous System (e.g., CNS, including presyncope, seizure, night terrors, hallucinations) (n=3)<br>• Musculoskeletal pain (n=1)<br>• Hepatotoxicity and red raised rash (n=1)<br>• Hypersensitivity (e.g., swelling in throat), musculoskeletal (e.g., myalgias), CNS (e.g., headache, dizziness) (n=1)<br>• Musculoskeletal/Neuropathy (e.g., severe weakness, "losing feeling" in legs and finger tips) and CNS (e.g., dizziness, syncope, headache) (n=2)<br>• Hypersensitivity (e.g., hives), CNS (e.g., syncope), gastrointestinal (e.g., vomiting, abdominal cramps (n=1)<br>• Musculoskeletal pain and skin pain (n=1)<br>• Musculoskeletal and possible hypersensitivity (e.g., tendonitis described as allergic reaction) (n=1) | | | |

## 4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with moxifloxacin use (tablets, injection) in the pediatric population (ages 0 to < 18 years), received by FDA through May 8, 2018. In the 19 years since approval of moxifloxacin in the U.S., three cases with unlabeled AEs and 19 cases with labeled AEs were reported with moxifloxacin (tablets, injection). There were no deaths directly associated with moxifloxacin (tablets, injection), and of the three reports which described unlabeled AEs, there were no new safety signals identified.

Although the focus of this review was identifying and evaluating unlabeled AEs, it is important to note that the most frequently reported AEs were consistent with known labeled AEs. Among the 19 cases describing one or more labeled AEs, no apparent increased severity was reported.

The labeled AEs in these reports are adequately described in the moxifloxacin labeling. There was no indication that the labeled AEs were occurring at increased frequency, although spontaneous databases are suboptimal for assessing frequency. Some cases were also limited by variable data quality or lack of long-term follow up; consequently, we were unable to adequately assess for persistence of outcomes associated with labeled AEs using the available data.

In summary, moxifloxacin (tablets, injection) is not approved for use in the pediatric population. This FAERS review of AEs associated with off-label use of moxifloxacin (tablets, injection) among U.S. pediatric patients did not identify any new pediatric safety signals.

## 5 CONCLUSION

DPV did not identify any pediatric safety concerns for moxifloxacin (tablets, injection) at this time.

## 6 RECOMMENDATION

DPV recommends no regulatory action specific to pediatric patients at this time, and will continue to monitor all AEs associated with the use of moxifloxacin (tablets, injection).

## 7 REFERENCES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# 8 APPENDICES

## 8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

**FDA Adverse Event Reporting System (FAERS)**

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

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

### 8.2 APPENDIX B. FAERS LINE LISTING OF UNLABELED PEDIATRIC CASES (N=3)

**Appendix B. U.S. Serious Unlabeled Pediatric Cases with Moxifloxacin (tablets, injection), Received by FDA through May 8, 2018**

(n=3)

| | Initial FDA Received Date | FAERS Case # | Version # | Manufacturer Control # | Case Type | Age (years) | Sex | Country Derived | Serious Outcomes* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 11/18/2002 | 3867655 | 2 | 200226652BWH | Expedited | 17 | F | USA | OT |
| 2 | 12/22/2006 | 6213836 | 1 | n/a | Direct | 17 | F | USA | HO |
| 3 | 02/19/2018 | 14547304 | 1 | US-BAYER-2018-026818 | Expedited | 2 | F | USA | HO |

*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. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome.
Abbreviations: HO=Hospitalization, OT=Other medically significant

### 8.3 APPENDIX C. FAERS LINE LISTING OF LABELED PEDIATRIC CASES (N=19)

**Appendix C. Line Listing of the U.S. Serious Labeled Pediatric Cases with Moxifloxacin (tablets, injection), Received by FDA through May 8, 2018**

(n=19)

| | Initial FDA Received Dated | FAERS ID | Ver-sion # | Manufacturer Control # | Case Type | Age (years) | Sex | Reported Reason for Use | Country Derived | Serious Outcomes * |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 11/04/2003 | 4025579 | 1 | n/a | Direct | 0.00274 (1 day) | M | sinusitis | USA | OT |
| 2 | 06/14/2013 | 9348394 | 1 | US-BAYER-2013-072013 | Non-Expedited | 6 | M | sinusitis | USA | DS |

**Appendix C. Line Listing of the U.S. Serious Labeled Pediatric Cases with Moxifloxacin (tablets, injection), Received by FDA through May 8, 2018**

(n=19)

| | Initial FDA Received Dated | FAERS ID | Ver-sion # | Manufacturer Control # | Case Type | Age (years) | Sex | Reported Reason for Use | Country Derived | Serious Outcomes * |
|---|---|---|---|---|---|---|---|---|---|---|
| 3 | 07/22/2016 | 12583747 | 2 | US-VERTEX PHARMACEUTICALS-2016-004422 | Expedited | 13 | F | NR | USA | HO |
| 4 | 12/27/2001 | 3754719 | 1 | 200114788BWH | Non-Expedited | 14 | NR | sinusitis | USA | OT |
| 5 | 10/25/2000 | 3570251 | 2 | 200002678BWH (2) | Expedited | 15 | F | bronchitis, sinusitis | USA | OT |
| 6 | 02/01/2005 | 5758730 | 1 | 200418138BWH | Non-Expedited | 15 | F | pneumonia | USA | OT |
| 7 | 05/15/2008 | 6641032 | 2 | US-BAYER-200821801NA | Expedited | 16 | M | sinusitis | USA | OT |
| 8 | 12/29/2009 | 7232448 | 1 | US-BAYER-200943390NA | Non-Expedited | 16 | M | NR | USA | OT |
| 9 | 04/06/2010 | 7349287 | 1 | n/a | Direct | 16 | F | pneumonia | USA | OT |
| 10 | 07/23/2010 | 7498760 | 2 | US-BAYER-201028234NA | Non-Expedited | 16 | M | acute recurrent sinusitis | USA | OT |
| 11 | 08/27/2010 | 7570921 | 1 | n/a | Direct | 16 | M | bronchitis, sinusitis | USA | OT |
| 12 | 03/02/2011 | 7836104 | 1 | US-BAYER-2011-016388 | Non-Expedited | 16 | F | bronchitis | USA | OT |
| 13 | 03/26/2001 | 3631542 | 1 | n/a | Direct | 17 | NR | sinusitis | USA | HO |
| 14 | 01/22/2002 | 3756185 | 2 | 200210274BWH | Expedited | 17 | F | sinusitis | USA | OT |
| 15 | 02/07/2002 | 3763325 | 1 | n/a | Direct | 17 | M | tonsillitis, pharyngitis (throat culture | USA | OT |

**Appendix C. Line Listing of the U.S. Serious Labeled Pediatric Cases with Moxifloxacin (tablets, injection), Received by FDA through May 8, 2018**

(n=19)

| | Initial FDA Received Dated | FAERS ID | Ver-sion # | Manufacturer Control # | Case Type | Age (years) | Sex | Reported Reason for Use | Country Derived | Serious Outcomes * |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | positive for *Streptococcus*, not group A) | | |
| 16 | 02/05/2013 | 9058488 | 1 | n/a | Direct | 17 | F | sinusitis | USA | HO, OT |
| 17 | 02/18/2008 | 6555319 | 3 | US-BAYER-200813527NA | Non-Expedited | 17 | F | sinusitis | USA | OT |
| 18 | 03/02/2009 | 6924787 | 2 | US-BAYER-200913876NA | Expedited | 17 | F | upper respiratory tract infection | USA | OT |
| 19 | 05/16/2002 | 3795340 (3843786 duplicate) | 1 | n/a | Direct | 17 | F | bronchitis | USA | LT |

*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. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome.

Abbreviations: HO=Hospitalization, LT= Life-threatening, DS= Disability, OT=Other medically significant, NR = Not reported

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