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 Review

Date:	April 17, 2013
Reviewers:	Debra Boxwell, PharmD, Safety Evaluator Jane Gilbert, MD, PhD, Medical Officer Division of Pharmacovigilance
Team Leaders:	Kelly Cao, PharmD, Team Leader Allen Brinker, MD, MS Team Leader Division of Pharmacovigilance
Acting Division Director:	Min Chu Chen, RPh, MS Division of Pharmacovigilance
Product Names/Sponsors:	Fluoroquinolones (oral and parenteral formulations): Noroxin® (norfloxacin)—Merck and Co. Cipro® Cipro XR® (ciprofloxacin)—Bayer HealthCare Levaquin® (levofloxacin)—Janssen Pharmaceuticals Avelox® (moxifloxacin)—Bayer HealthCare Factive® (gemifloxacin)—Cornerstone Therapeutics Ofloxacin—generic
Subject:	Disabling Peripheral Neuropathy Associated with Systemic Fluoroquinolone Exposure
Application Type/Numbers:	Norfloxacin: NDA 019384 Ciprofloxacin: NDA 019537, 019847, 020780 Levofloxacin: NDA 020634, 020635, 021721 Moxifloxacin: NDA 021085, 021334, 021277 Gemifloxacin: NDA 021158 Ofloxacin: ANDA 076182, 077098
OSE RCM #:	2011-4292
TSI #:	1270

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EXECUTIVE SUMMARY

OSE conducted this review of peripheral neuropathy associated with fluoroquinolone antibiotics as a result of consumer communications describing prolonged, disabling neuropathy thought to be associated with ciprofloxacin, ofloxacin and levofloxacin administration. OSE completed two previous reviews of fluoroquinolone-associated peripheral neuropathy, one in 2001 and the other in 2003. To focus this review to serious cases of prolonged, disabling neuropathy, the search criteria for this review were restricted to US cases with an outcome of disability from 2003 to 2012.

After reviewing the cases, we continue to find an association between fluoroquinolone antibiotic use and disabling peripheral neuropathy. Peripheral neuropathy appeared to be unrelated to the duration of therapy or the age of the patient. In addition, the onset of peripheral neuropathy after starting fluoroquinolone therapy was rapid, often within a few days. At the time the report was submitted to the FDA, 80% of patients had not recovered, and in 40%, the symptoms had been ongoing for over a year.

Based on this review, DPV recommends the following:

- Update the information in the Warnings and Precautions section:
    - Replace language suggesting that discontinuation of the drug may prevent an irreversible condition with language reflecting the rapid onset and possible permanence of peripheral neuropathy
    - Add language to discontinue the fluoroquinolone immediately with the first symptoms of peripheral neuropathy, unless the benefit of continued treatment with a fluoroquinolone outweighs the risk
- Make labeling consistent for all fluoroquinolones
- Update the patient education section of the label to reflect this information
- Consider a Drug Safety Communication (DSC) or other forums to communicate to health care professionals and patients that peripheral neuropathy may occur rapidly and potentially be permanent. If clinically appropriate, the drug should be discontinued immediately.

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1 INTRODUCTION

1.1 BACKGROUND

This review evaluates US cases of peripheral neuropathy with an outcome of disability associated with fluoroquinolones from 2003 to 2012 in the FDA's Adverse Event Reporting System (AERS), as well as reports of peripheral neuropathy in the published medical literature.

OSE conducted this review of peripheral neuropathy associated with fluoroquinolone antibiotics following continued inquiries from Congress and consumers regarding prolonged, disabling neuropathy associated with ciprofloxacin, ofloxacin and levofloxacin administration.

There are currently 6 systemic fluoroquinolones on the market in the US. Ciprofloxacin was approved in 1987 and the most recently approved fluoroquinolone was gemifloxacin in 2003 (see Appendix 8.1). Peripheral neuropathy was added to the Warnings and Precautions section of the fluoroquinolone labeling in July 2004.

OSE has written 2 previous reviews on fluoroquinolone-associated peripheral neuropathy, one in 2001 and the other in 2003. Both of these reviews were the result of a patient contacting the agency.

The first review, completed in 2001 (Singer, Sally. OSE Postmarketing Safety Review: Peripheral Neuropathy with Levofloxacin. 30 Apr 2001), identified 28 cases of peripheral neuropathy associated with levofloxacin use. It found that peripheral neuropathy lasted as long as two years after patients received levofloxacin.

A second review, completed in 2003 (Singer, Sally. OSE Postmarketing Safety Review: Prolonged Peripheral Neuropathies with Fluoroquinolones. 06 June 2003), described 108 cases of peripheral neuropathy associated with ciprofloxacin, levofloxacin, and/or ofloxacin use. Thirty-four of the 108 cases reported peripheral neuropathy at time periods of a year or more after the drug had been discontinued, suggesting potential irreversibility of the condition. The review recommended that peripheral neuropathy be added to the labeling for ciprofloxacin and levofloxacin (ofloxacin was already labeled).

1.2 PERIPHERAL NEUROPATHY SAFETY INFORMATION IN FLUOROQUINOLONE LABELING

Peripheral neuropathy was added to all labels in 2004. Depending upon the format of the label for each drug (Structured Product Labeling (SPL) or older format) the new information was placed either in the Warnings or Warnings and Precautions section. The locations of the labeling for all 6 of the commercially available fluoroquinolones can be found in Tables 1 and 2 below.

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Table 1: Peripheral Neuropathy Labeling in Fluoroquinolones with SPL Format

Fluoroquinolone	Label Version	Section 5 Warnings and Precautions	Section 6 Adverse Reactions	Section 17 Patient Counseling Information	FDA-Approved Medication Guide
Levofloxacin	4/2012	X	X	X	X
Moxifloxacin	10/2011	X	X	X	X

Table 2: Peripheral Neuropathy Labeling in Fluoroquinolones with Old Labels

Fluoroquinolone	Label Version	Warnings	Precautions	Adverse Reactions	FDA-Approved Medication Guide
Ciprofloxacin	11/2011	X	X	X	X
Ofloxacin	1/2011	X	X	X	
Gemifloxacin	10/2011	X			X
Norfloxacin	6/2012	X	X	X	X

The language found in these labels is as follows:

> Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones, including (drug name).

In addition, the levofloxacin, ciprofloxacin, ofloxacin, and norfloxacin labels also contain:

> (Drug name) should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense and vibratory sensation in order to prevent the development of an irreversible condition.

Complete peripheral neuropathy language in each of the 6 labels can be found in Appendix 8.2.

2 METHODS

2.1 CASE DEFINITION

A case definition was developed to determine whether there was an association between fluoroquinolone administration and disabling peripheral neuropathy. Each case must fulfill the following criteria:

- Peripheral neuropathy symptoms (defined as paresthesia, hypoesthesia, dysesthesia, weakness, numbness, pain, discomfort, burning, tingling, altered sensation [electric-like or otherwise]) occurred subsequent to fluoroquinolone exposure and was considered to be disabling.
- The reporter attributed fluoroquinolone exposure as a causative factor.

2.2 AERS Search Strategy

Narrow search criteria were used for this consult because the focus is prolonged, disabling neuropathy. Specifically, the search was restricted to US cases with an outcome of Disability from 2003 (date of the last review) to 2012, as described in Table 3. This search was conducted prior to September 2012 and the implementation of FAERS.

Table 3. AERS Search Strategy*	
Date of Search	August 1, 2012
Time Period of Search	January 1, 2003† - August 1, 2012
Product Terms	Avelox (moxifloxacin), Cipro, Cipro XR, Proquin XR (ciprofloxacin), Factive (gemifloxacin), Levaquin (levofloxacin), Noroxin (norfloxacin), Floxin (ofloxacin)
MedDRA Search Terms	HLGT Peripheral Neuropathies‡
Other Criteria	US cases only Outcome: Disability

* See Appendix 8.3 for description of the AERS database.
† Approximate date of the last review.
‡ See Appendix 8.4 for the PT terms included in the HLGT Peripheral Neuropathies.

2.3 Literature Search

2.3.1 Literature Search for Peripheral Neuropathy

The medical literature was searched with the strategy described in Table 4.

Table 4. Literature Search Strategy	
Date of search	November 12, 2012
Database	PubMed@FDA
Search Terms	Peripheral neuropathy AND Fluoroquinolone, Ciprofloxacin, Levofloxacin, Ofloxacin
Years included in search	January 1, 1980 to November 12, 2012

2.3.2 Literature Search for Possible Mechanism of Action

The medical literature was also searched for a possible mechanism of action with the strategy described in Table 5.

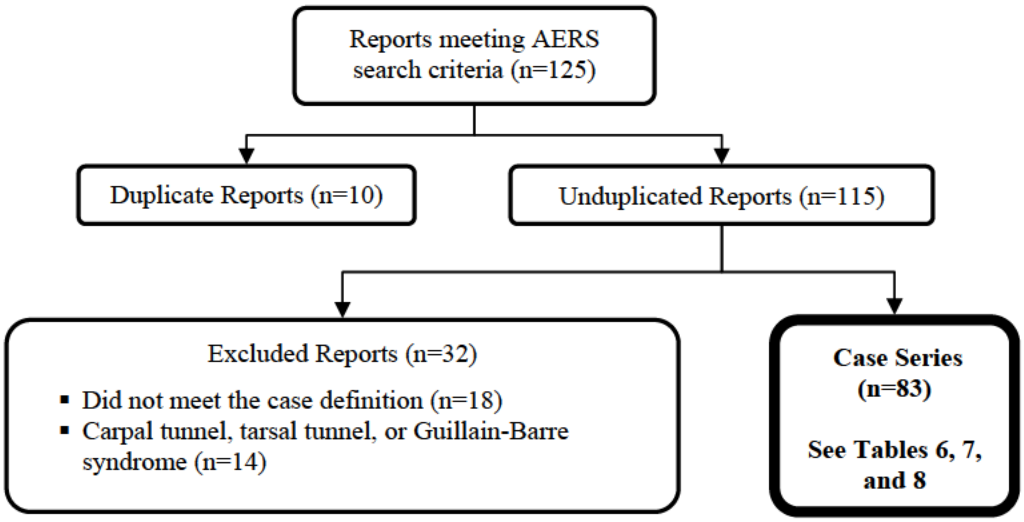
Table 5. Literature Search Strategy for Mechanism of Action	
Date of search	December 17, 2012
Database	PubMed@FDA
Search Terms	Fluoroquinolones AND topoisomerase, neuropathy, mitochondria, mtDNA, oxidative stress, Schwann, apoptosis, DNA gyrase
Years included in search	January 1, 1980 to December 17, 2012

3 RESULTS

3.1 AERS CASE SELECTION

The AERS search retrieved 125 reports. After applying the case definition in Section 2 and accounting for duplicate reports, 83 cases were included in the case series of domestic peripheral neuropathy cases reporting a outcome of disability with a currently marketed fluoroquinolone (see Figure A).

Figure A. AERS Case Selection



Tables 6, 7 and 8 summarize the 83 AERS cases of peripheral neuropathy reported with fluoroquinolone antibiotics for this case series.

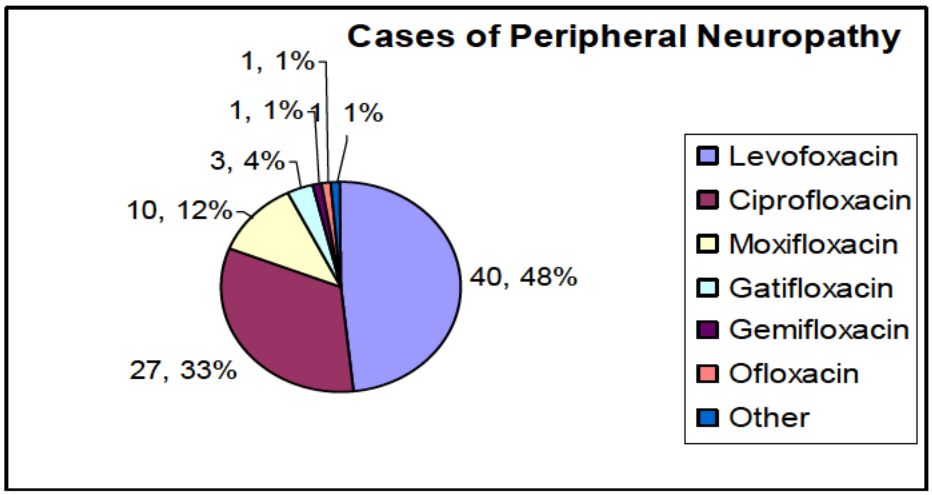
Appendix 8.8 lists all the AERS case numbers, AERS ISR numbers and Manufacturer Control numbers for the 83 cases in this case series.

Table 6: Demographic Characteristics of Peripheral Neuropathy Reported with Fluoroquinolone use, received by FDA from (January 1, 2003 - August 1, 2012) (N=83)		
Age (n=76)	Mean: 48.7 years Median: 46 years Range: 22-84 years	≤ 40 years: n=24 (32%) ≥ 65 years: n=11 (14%)
Sex	Female 50 (60%); Male 32 (39%); Unknown 1	
Reporter	Patient or other lay person: 49 Patient and MD: 11 MD: 9 Other health care professional (HCP): 5 Patient (who is a HCP): 7 (MD—1, RN—4, unspecified—2) Patient and lawyer/medical records: 2	

The age range was wide: from 22 to 84 years. Of interest was that only 14% of the patients were 65 years of age or older, while 32% of the patients were young (40 years of age or less).

Peripheral neuropathy was confirmed either by a healthcare provider or medical records information in 41% of cases. A layperson (patient, relative, or friend) reported the remaining cases.

Figure B: Cases of Peripheral Neuropathy with the Fluoroquinolones (FQs) (N = 83)



†Other = ciprofloxacin, ofloxacin and levofloxacin over 3 months

Figure C: Cases of Peripheral Neuropathy with FQs by Year of Event (N= 80)

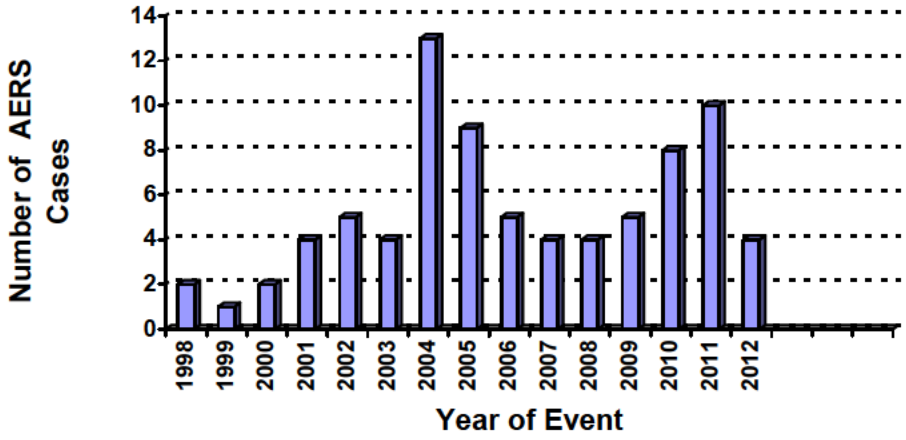


Table 7: Descriptive Characteristics of Peripheral Neuropathy Reported with Fluoroquinolone use, received by FDA from (January 1, 2003 - August 1, 2012) (N=83)	
Duration of FQ therapy (n=64)	Mean: 10.7 days, Median 10 days Range: 1-90 days Duration ≤ 5 days: n=22 (34%) Duration >14 days: n=10 (16%)
Onset of PN From Start of FQ Therapy (n=42)	Mean 17.4 days, Median 4 days Range: 1 – 104 days Onset ≤ 5 days of starting FQ: n=26 (62%)
Duration of PN *at the time of the report** (n=73)	1 day to 7 years < 1 year: 44 (60%) ≥ 1 year: 29 (40%)
Clinical Outcome	Death: 2 ("died in surgery to remove teeth"; died d/t hypersensitivity reaction after receiving a second course of FQ)—(2%) Not recovered, PN ongoing: 66 (80 %) Improvement/Recovering: 8 (10%) Not reported: 6 (7%)
Most Commonly Reported Indications for FQ Therapy (n=53)	Sinusitis—15 Urinary tract infection—15 Bronchitis—5 Pneumonia—6 Post-surgical/procedural prophylaxis—5 Prostatitis—5 Skin infection—2
Other Reported Adverse Events with 5 or More Occurrences (n=63)	Neuropsychiatric issues (i.e., hallucinations, memory loss, panic attacks, anxiety, depression, foggy feeling, insomnia)—20 Tendonitis/tendon rupture—19 Myalgia—19 Arthralgia—16 Vision problems—10 Hypersensitivity reactions (i.e., rash, fever)—9 Cardiac issues (i.e., tachycardia, bradycardia, arrhythmias)—6 Fatigue/weakness—6

There was no association seen between duration of therapy and toxicity. The mean and median duration of therapy was 10 days. However, 1/3 of patients received a fluoroquinolone for 5 days or less, with many stopping therapy because of side effects. Only 15% of patients received a fluoroquinolone longer than 14 days.

The onset of peripheral neuropathy from the time fluoroquinolone therapy was started was rapid. Approximately 60% of patients had an onset within 5 days of starting therapy. The mean onset was 17 days, while the median time to onset was 4 days.

Two of the 83 patients died but the cause of death was unrelated to peripheral neuropathy. According to the spouse, one patient "died in surgery to remove teeth". The other patient developed peripheral neuropathy and a hypersensitivity reaction while taking levofloxacin. After receiving one dose of a second course of levofloxacin, he was admitted to the ICU within 2 hours and he died 2 weeks later. Among the remaining patients, 80% reported that peripheral neuropathy was ongoing at the time the report was sent to the FDA. In 40% of the reports

received, the patient had been experiencing peripheral neuropathy for greater than 1 year. Only 10% of patients reported improvement or recovery.

Table 8: Predisposing Factors for Peripheral Neuropathy Reported with Fluoroquinolone use, received by FDA from (January 1, 2003 - August 1, 2012) (N=83)	
Predisposing Factors for Peripheral Neuropathy (n=20)	Diabetes/hyperglycemia: 8 Fibromyalgia: 4 Chemotherapy (past or present): 3 Medications: 3 [amiodarone+HCTZ (1), Flagyl (1), thalidomide (1)] Lyme disease: 3 Post-herpetic neuropathic pain: 1 Discomfort in hands predating FQ administration: 1 Eosinophilia-myalgia syndrome: 1 Previously diagnosed with demyelinating peripheral neuropathy of big toes: 1
Number of Predisposing Factors per Person (n=20)	One: 13 (65%) Two: 6 (30%) Three: 1 (5%)
Multiple courses of FQ documented	N=25 (30%)

Predisposing risk factors for peripheral neuropathy were identified in 24% of patients (n=20). The most common risk factor was diabetes or hyperglycemia, which was reported in 8 patients. Overall, these patients were older, with 22% being 65 years of age or older and only 10% being 40 years of age or younger. Seven patients (35%) had 2 or more risk factors, and multiple lifetime courses of fluoroquinolone therapy were documented in 30% of the cases. There were no documented cases of renal dysfunction.

Table 9: Documented Diagnostic Testing for Peripheral Neuropathy Reported with Fluoroquinolone Use (n=34)	
EMG/NCS/ nerve biopsy	N=18 Positive results: 8 Negative results: 5 Not reported: 5
Other testing (i.e., MRI, not specified)	N=16 Positive results: 11 Negative results: 4 Not reported: 1

Diagnostic testing was also described in 41% of the cases. Approximately half of those with testing reported electrodiagnostic testing, such as electromyography (EMG) or nerve conduction studies, or had received a nerve biopsy. Positive results were seen in 56%, negative results in 26%, and not reported in 17%.

3.2 CASE FOLLOW-UP INFORMATION

Follow-up emails were sent to 13 consumers who provided their email address in the report. Three responses were received, all of whom reported the onset of their peripheral neuropathy in 2011. The first patient was a 41-year old male physician who developed neuropathy and tendonitis; he stated that the neuropathy got better over a period of a year, but he still occasionally experienced mild tendonitis. The second patient was a 29-year old male consumer who still had ongoing peripheral neuropathy and tendonitis 22 months after starting levofloxacin. The last patient was a 64-year old female consumer who, 20 months later, had ongoing peripheral neuropathy in her feet and legs, but had some improvement in her arms and hands.

3.3 LITERATURE SEARCH

3.3.1 Case Reports of Peripheral Neuropathy

The goal of the literature search and the review was to identify compelling case reports describing prolonged disabling peripheral neuropathy in association with the use of a fluoroquinolone. The PubMed search (see Table 4) undertaken on November 12, 2012 identified 37 published articles; after review of titles and abstracts 16 of these were deemed relevant and reviewed in their entirety. Of these 16 articles, 8 provided adequate case descriptions. Citations provided in these 8 articles identified 2 additional useful articles, and an additional publication was identified through an incidental finding from another search. These 11 published articles were the basis of this review.

The table in Appendix 8.5 summarizes the 11 articles. The final column of the table comments on the quality of the evidence provided in each article. A total of 91 cases are described in the literature; after excluding the 45 cases (of dubious quality) reported by Cohen (1), 46 cases remain. Of these, 20 case reports describe both a good temporal relationship and a positive de-challenge. Many cases are confounded but the association with a fluoroquinolone remains plausible. In at least one case, the neuropathy (carpal tunnel syndrome) was a result of tendonitis, a known complication of fluoroquinolones (2). Most of the cases described in the literature report resolution of symptoms (see Appendix 8.5). Of the 46 cases forming the core of this analysis, there is only 1 report (Hedenmalm and Spigset) where symptoms lasted "somewhat more than 1 year."

Based upon this literature review, there appears to be good evidence for an association between use of a fluoroquinolone and development of peripheral neuropathy. Though one person developed symptoms of a neuropathy after 5 months of treatment for osteomyelitis, most other patients developed symptoms of neuropathy within a few days after initiation of the drug (3). Over 20 cases describe resolution of symptoms after discontinuation of the drug. There is one credible report of symptoms extending beyond a year.

3.3.2 Possible Mechanism of Action: Mitochondrial Toxicity

Fluoroquinolones act by inhibiting DNA gyrase and bacterial topoisomerase IV, both of which belong to the topoisomerase type IIA subfamily. Fluoroquinolones have been found to affect

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mammalian topoisomerase II, especially in mitochondria (4). In vitro studies in drug-treated mammalian cells found that nalidixic acid and ciprofloxacin caused a loss of mitochondrial DNA (mtDNA), resulting in a decrease of mitochondrial respiration and an arrest in cell growth (5).

Mitochondrial conditions that are due to an insufficiency of ATP, especially in organs that rely on mitochondria for their energy source, include developmental disorders of the brain, optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, and lactic acidosis (6). Neurodegenerative diseases, like Parkinson's, Alzheimer's, and amyotrophic lateral sclerosis (ALS) have been associated with the loss of neurons due to oxidative stress (4,7).

Nucleoside Reverse Transcriptase Inhibitor (NRTI)-associated peripheral neuropathy has also been associated with inhibition of mtDNA, although the mechanism is different. Pharmacogenetics has been found to be associated with the risk of developing peripheral neuropathy with NRTIs (8); this could also apply to fluoroquinolone, although studies have not yet been done. A more extensive discussion of mitochondrial toxicity can be found in Appendix 8.6.

4 DISCUSSION

Peripheral neuropathy is an identified risk with the fluoroquinolones. It was added to the Warnings or Warnings and Precautions sections of all of the fluoroquinolone labels in 2004. Initial, broad searches of the Adverse Event Reporting System (AERS) database identified over 1000 reports (see Appendix Table 8.7). In order to find serious cases of prolonged, disabling neuropathy, much narrower search criteria were used, including an outcome of disability.

Presumably, these disability cases are among the most severe of all the reported cases. In this case series, 80% of the patients had not recovered from their peripheral neuropathy and the symptoms were still on going at the time the report was submitted. Only 10% reported improvement or recovery. In addition, the duration of peripheral neuropathy ranged from 1 day to 7 years, with 40% having symptoms for a year or longer, again, depending on when the report was submitted.

It may be hard to determine at what point an adverse event is considered permanent, but since the outcome for these reports was given as disability, it is reasonable that the reporter considered it to be a permanent condition. Some narratives described circumstances where a healthy, young, athletic patient took a fluoroquinolone for sinusitis or a urinary tract infection and subsequently was unable to run or ambulate without use of a cane. In a few cases, disability was so severe that continued employment was not possible.

Overall, this review did not identify any predictable risk factors for peripheral neuropathy. The rapid onset of peripheral neuropathy after beginning a fluoroquinolone is an important finding in this review. Symptom onset seemed to be unrelated to the duration of therapy. The median onset was 4 days and 62% had a symptom onset within 5 days; some patients had symptoms after 1 dose. Duration of drug therapy also did not appear to be a factor (34% were on the drug for 5 days or less and only 16% for more than 14 days). Only 24% of patients had

documented risk factors, none had renal dysfunction, and, age was not a significant factor (32% were 40 years of age or less, 14% were 65 years of age or older).

Seven patients stated that when they reported peripheral neuropathy to their physician, they were told to continue taking the fluoroquinolone. Some of these patients were told that this class of drugs could not cause peripheral neuropathy. When the reporting year was examined, 3 occurred before peripheral neuropathy was added to the Warnings and Precautions section of the labels (July 2004), and 4 were after that time. The agency still receives reports for this adverse event.

The findings in this review are very similar to those found in the 2003 review. That review did not limit the search to an outcome of disability, but it also found that most patients were relatively young, healthy, and had no conditions predisposing them to peripheral neuropathy. In addition, the onset was rapid (within a few days), there was rapid progression, and the neuropathy could be irreversible. None of those 108 cases (from the 2003 review) reported a complete recovery.

5 CONCLUSION

In conclusion, FDA continues to receive reports of fluoroquinolones and peripheral neuropathy, an identified risk of fluoroquinolone antibiotic use. The peripheral neuropathy in many cases appears to be unresolved with 40% having symptoms for a year or longer. The onset of peripheral neuropathy after starting fluoroquinolone therapy is rapid. This review did not identify a relationship between peripheral neuropathy and the duration of therapy, dose of the drug, or the age of the patient, and no specific risk factors were identified.

The current fluoroquinolone labels are inconsistent in the details regarding the risk of peripheral neuropathy and do not describe the possible permanence of peripheral neuropathy, rapid onset, nor the need to consider discontinuation of drug with first symptoms.

6 RECOMMENDATIONS

Based on this review, DPV recommends the following:

- Update the information in the Warnings and Precautions section:
    - Replace language suggesting that discontinuation of the drug may prevent an irreversible condition with language reflecting the rapid onset and possible permanence of peripheral neuropathy
    - Add language to discontinue the fluoroquinolone immediately with the first symptoms of peripheral neuropathy, unless the benefit of continued treatment with a fluoroquinolone outweighs the risk
- Make labeling consistent for all fluoroquinolones
- Update the patient education section of the label to reflect this information
- Consider a Drug Safety Communication (DSC) or other forums to communicate to health care professionals and patients that peripheral neuropathy may occur rapidly and

potentially be permanent. If clinically appropriate, the drug should be discontinued immediately.

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8 APPENDICES

8.1 SYSTEMIC FLUOROQUINOLONE APPROVAL DATES AND INDICATIONS

Product Name	Approval Date	Indications
Noroxin® (norfloxacin)	October 31, 1986	Gonorrhea Prostatitis UTI
Cipro® (ciprofloxacin)	October 22, 1987	Acute bacterial exacerbation of chronic bronchitis Acute bacterial sinusitis Acute pyelonephritis Chronic bacterial prostatitis Inhalational anthrax Plague Pneumonia Skin/skin structure infections Superficial ocular infections involving conjunctiva or cornea UTI
Floxin® (ofloxacin)	December 28, 1990	Acute bacterial exacerbation of chronic bronchitis Acute pelvic inflammatory disease Acute uncomplicated gonorrhea Gonococcal infections Mixed infections of the urethra and cervix Nongonococcal urethritis and cervicitis Pneumonia Prostatitis Skin/skin structure infections Uncomplicated cystitis UTI
Levaquin® (levofloxacin)	December 20, 1996	Acute bacterial exacerbation of chronic bronchitis Acute bacterial sinusitis Acute pyelonephritis Chronic bacterial prostatitis Inhalational anthrax Plague Pneumonia Skin/skin structure infections UTI
Avelox® (moxifloxacin)	December 10, 1999	Acute bacterial exacerbation of chronic bronchitis Intra-abdominal infections Pneumonia Skin/skin-structure infections
Factive® (gemifloxacin)	April 4, 2003	Acute bacterial exacerbation of chronic bronchitis Pneumonia

8.2 FDA Approved Peripheral Neuropathy Safety Information for Oral and Parenteral Fluoroquinolones

Fluoroquinolone	Label Version	Peripheral Neuropathy Safety Information
Levofloxacin	April 2012	**Section 5 Warnings and Precautions** *5.8 Peripheral Neuropathy* Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones, including LEVAQUIN®. LEVAQUIN® should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation in order to prevent the development of an irreversible condition. **Section 6 Adverse Reactions** *6.1 Serious and Otherwise Important Adverse Reactions* Peripheral Neuropathy *6.3 Postmarketing Experience* Nervous System Disorders-peripheral neuropathy **Section 17 Patient Counseling Information** *17.3 Serious and Potentially Serious Adverse Reactions* Peripheral Neuropathies: If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, patients should discontinue treatment and contact their physician. *17.6 FDA-Approved Medication Guide* Changes in sensation and possible nerve damage (peripheral neuropathy). Damage to the nerves in arms, hands, legs, or feet can happen in people taking fluoroquinolones, including LEVAQUIN. Talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs or feet: pain, burning, tingling, numbness, weakness. LEVAQUIN may need to be stopped to prevent permanent nerve damage.
Ciprofloxacin	November 2011	**Warnings** *Peripheral Neuropathy* Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation and/or motor strength in order to prevent the development of an irreversible condition. **Precautions** *Information for Patients* That peripheral neuropathies have been associated with ciprofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, they should discontinue treatment and contact their physicians. **Adverse Reactions** *Post-Marketing Adverse Event Reports* Peripheral neuropathy is included in a list of events. **FDA-Approved Medication Guide** Changes in sensation and possible nerve damage (peripheral neuropathy).

Fluoroquinolone	Label Version	Peripheral Neuropathy Safety Information
		Damage to the nerves in arms, hands, legs, or feet can happen in people who take fluoroquinolones, including CIPRO. Talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs or feet: pain, burning, tingling, numbness, weakness. CIPRO may need to be stopped to prevent permanent nerve damage.
Ofloxacin	January 2011	**Warnings** *Peripheral Neuropathy* Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including ofloxacin. Ofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense and vibratory sensation in order to prevent the development of an irreversible condition. **Precautions** *Information for Patients* That peripheral neuropathies have been associated with ofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, they should discontinue treatment and contact their physicians. **Adverse Reactions** *Post-Marketing Adverse Event Reports* Peripheral neuropathy is included in a list of events.
Moxifloxacin	October 2011	**Section 5 Warnings and Precautions** *5.8 Peripheral Neuropathy* Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones. **Section 6 Adverse Reactions** *6.1 Serious and Otherwise Important Adverse Reactions* Peripheral Neuropathy **Section 17 Patient Counseling Information** *17.3 Serious and Potentially Serious Adverse Reactions* Peripheral Neuropathies: If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, patients should discontinue AVELOX and contact their physician. **FDA-Approved Medication Guide** Changes in sensation and possible nerve damage (peripheral neuropathy). Damage to the nerves in arms, hands, legs, or feet can happen in people taking fluoroquinolones, including AVELOX. Talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs or feet: pain, burning, tingling, numbness, weakness. AVELOX may need to be stopped to prevent permanent nerve damage.
Gemifloxacin	October 2011	**Warnings** *Peripheral Neuropathy* Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones. **FDA-Approved Medication Guide** Changes in sensation and possible nerve damage (peripheral neuropathy). Damage to the nerves in arms, hands, legs, or feet can happen in people taking fluoroquinolones, including FACTIVE. Talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy

Fluoroquinolone	Label Version	Peripheral Neuropathy Safety Information
		in your arms, hands, legs or feet: pain, burning, tingling, numbness, weakness. AVELOX may need to be stopped to prevent permanent nerve damage.
Norfloxacin	June 2012	**Warnings** *Peripheral Neuropathy* Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including norfloxacin. Norfloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, an/or motor strength in order to prevent the development of an irreversible condition. **Precautions** *Information for Patients* That peripheral neuropathies have been associated with norfloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, they should discontinue treatment and contact their physicians. **Adverse Reactions** *Post-Marketing Adverse Event Reports* Peripheral neuropathy is included in a list of events. **FDA-Approved Medication Guide** Changes in sensation and possible nerve damage (peripheral neuropathy). Damage to the nerves in arms, hands, legs, or feet can happen in people taking fluoroquinolones, including NOROXIN. Talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs or feet: pain, burning, tingling, numbness, weakness. NOROXIN may need to be stopped to prevent permanent nerve damage.

8.3 APPENDIX- ADVERSE EVENT REPORTING SYSTEM (AERS)

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do 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 all adverse event reports that occur 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, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

8.4 APPENDIX- PT TERMS FOUND IN THE HLGT PERIPHERAL NEUROPATHIES

Acrodynia, Acute polyneuropathy, Anterior interosseous syndrome, Autoimmune neuropathy, axillary nerve injury, Axonal neuropathy, Brachial plexopathy, Brachial plexus injury, Carpal tunnel syndrome, Cervical plexus lesion, Chronic inflammatory demyelinating polyradiculoneuropathy, Congenital neuropathy, Critical illness polyneuropathy, Cubital tunnel syndrome, Demyelinating polyneuropathy, Diabetic amyotrophy, Diabetic foot, Diabetic foot infection, Diabetic mononeuropathy, Diabetic neuropathic ulcer, Diabetic neuropathy, Erb's palsy, Femoral nerve injury, Femoral nerve palsy, Gaucher's disease, Guillain-Barre syndrome, HIV peripheral neuropathy, Indeterminate leprosy, Ischaemic neuropathy, Klumpke's palsy, Lepromatous leprosy, Lewis-Sumner syndrome, Long thoracic nerve palsy, Lumbosacral plexus injury, Lumbosacral plexus lesion, Median nerve injury, Meralgia paraesthetica, Miller Fisher syndrome, Mononeuritis, Mononeuropathy, Mononeuropathy multiplex, Multifocal motor neuropathy, Musculocutaneous nerve injury, Nerve compression, Neuralgic amyotrophy, Neuritis, Neuronal neuropathy, Neuropathic arthropathy, Neuropathic ulcer, Neuropathy peripheral, Neuropathy vitamin B6 deficiency, Obturator neuropathy, POEMS syndrome, Pancoast's syndrome, Peripheral motor neuropathy, Peripheral nerve infection, Peripheral nerve injury, Peripheral nerve lesion, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Peroneal nerve injury, Peroneal nerve palsy, Peroneal nerve palsy postoperative, Phrenic nerve paralysis, Piriformis syndrome, Polyneuropathy, Polyneuropathy alcoholic, Polyneuropathy chronic, Polyneuropathy idiopathic progressive, Polyneuropathy in malignant disease, Posterior interosseous syndrome, Posterior tibial nerve injury, Pudendal canal syndrome, Radial nerve compression, Radial nerve injury, Radial nerve palsy, Radiation neuropathy, Sciatic nerve injury, Sciatic nerve neuropathy, Sciatic nerve palsy, Sensory neuropathy hereditary, Slipping rib syndrome, Sympathetic nerve injury, Tarsal tunnel syndrome, Thoracic outlet syndrome, Toxic neuropathy, Toxic oil syndrome, Tuberculoid leprosy, Type 1 lepra reaction, Ulnar nerve injury, Ulnar nerve palsy, Ulnar neurapraxia, Ulnar neuritis, Ulnar tunnel syndrome, Uraemic neuropathy)

8.5 LITERATURE REVIEW: FLUOROQUINOLONES AND PERIPHERAL NEUROPATHY

Author, Title, Journal, Year	FQ	Findings/Results	Quality of Evidence
1. Panas, M. Hereditary neuropathy unmasked by Levofloxacin. The Annals of Pharmacotherapy. 2011.	Levofloxacin (LQ)	56 YO male develops neuropathy after 3 days of LQ. Genetic analysis: Charcot-Marie-Tooth. Previously asymptomatic. Father & brother (presumed to have same condition) remained asymptomatic. Patients symptoms continued after D/C of drug	N= 1. Credible temporal relationship. Neg dechallenge. Plausible.
2. Liang, V. et al. Carpal tunnel syndrome after Ciprofloxacin-induced tendonitis. Letter to Editor. Journal of Clin Neuromuscular Dis. 2010.	Ciprofloxacin (Cipro)	77 YO female develops bilateral flexor tendonitis after 3 days of Cipro. Though improvement after Cipro was DC'd, there was persistence of some (? new) symptoms (left worse than right) 4 wks later and she saw a neurologist. Electrodiagnostic testing: Carpal Tunnel Syndrome. Surgical intervention (3 + mo later) resulted in resolution.	N= 1. Plausible that it caused the tendonitis which then precipitated the CTS.
3. Murray, C. et al. Trovafloxacin-induced weakness due to a demyelinating polyneuropathy. Southern Med Jn. 2000	Trovafloxacin (Trova)	Six days after initiating trova for pneumonia (complicated) this 50 YO male developed weakness and inability to rise from a seated position related to proximal muscle weakness. Nerve conduction studies showed a demyelinating polyneuropathy. Trova was discontinued and he regained strength over 72 hours. In 6 weeks his walking was almost baseline. Pt had diabetes and this may be a predisposing factor (see Hedenmalm.)	N = 1. Credible temporal relationship and positive de-challenge. Strong case.
4. Hedenmalm, K. & Spigset, O. Peripheral Sensory Disturbances related to Treatment with Fluoroquinolones. J of Antimicrobial Chemotherapy. 1996.	Norfloxacin (Norflox) -- 31. Cipro -- 5. Temafloxacin -- 1.	Paresthesia (n = 30, 81%); Numbness (n=19, 51%); Pain (n=10, 27%), muscle weakness (n = 4,11%). Six cases unilateral. Highest incidence during first weeks of treatment. Pts with DM may have a lower threshold for drug induced PN. A total of 20 patients (71% of those reporting duration) recovered within 2 weeks. One person had symptoms beyond a year; a second person had symptoms for less than 10 months.	N = 37. Based on Swedish register for ADRs. From information provided in tabular form, at least 20 cases seemed (to this reviewer) to be relatively strong with both a good temporal relationship and a positive dechallenge. 4

Author, Title, Journal, Year	FQ	Findings/Results	Quality of Evidence
			of 5 Cipro cases confounded by other drugs; one strong.
5. Schmidt, S. et al. Guillain-Barre syndrome during treatment with ofloxacin. Letter to Editor. J Neurol. 1993.	Ofloxacin (Oflox)	61 YO male develops Guillain-Barre (demyelinating-axonal polyneuritis) after 3 days of treatment with Oflox for UTI. Disease ceased to progress within 24 h after drug DCd and showed a shorter time to plateau than usual.	N = 1. Credible temporal relationship. Time course of disease suggests a positive de-challenge. Though UTI's not known to cause GBS, other infections may do so. History of infection may be confounder. Plausible case.
6. Rollof, J. & Vinge, E. Neurologic adverse effects during concomitant treatment with ciprofloxacin, NSAIDS, and chloroquine: possible drug interaction. Ann Pharmacother. 1993.	Cipro	68 YO female treated chronically with NSAIDS and chloroquine (CQ) developed dizziness and tremors when Cipro was begun for osteitis. Symptoms ceased when NSAIDs and CQ DCd. Symptoms of a PN began when a new NSAID was reintroduced. Symptoms of PN partially resolved when Cipro discontinued. This suggests possible interaction between Cipro and antirheumatic drugs.	N = 1. Suggestive of positive dechallenge and rechallenge. Plausible for drug interaction.
7. Aoun, M. et al. Peripheral neuropathy associated with fluoroquinolones. Letter to Editor. Lancet. 1992	Pefloxacin (Peflox), Oflox, Cipro	37 YO male with osteomyelitis treated with Peflox. After 5 mos of treatment, he developed paresthesia and weakness; EMG positive. Dramatic improvement 10 days after DC of Peflox. Recurrence of osteomyelitis 6 mos later prompted treatment with ofloxacin; within 15 days, his PN returned and ceased within 7 days after stopping ofloxacin. Rechallenge with Peflox and subsequently Cipro brought about relapse of the PN. Patient had remote history of radiochemotherapy including treatment with vincristine.	N= 1. Numerous positive de-challenges and rechallenges. Though he had history of radiochemotherapy, he was asymptomatic without the addition of a FQ. Strong case.

Author, Title, Journal, Year	FQ	Findings/Results	Quality of Evidence
8. Chan, PC et al. Clinical experience with pefloxacin in patients with urinary tract infections. Br J clin Pract. 1990.	Peflox	Authors review 27 patients treated with Peflox for UTI. One patient developed a peripheral neuropathy that resolved 4 wks after DC of Peflox.	N = 1. Positive dechallenge. Plausible case.
9. Cohen, JS. Peripheral neuropathy associated with fluoroquinolones. Annals of Pharmacotherapy. 2001.	Cipro (N=11), LQ (N=33), Oflox (N= 6), others (N=2)[#]	Via the internet, author solicited reports of PNS events associated with fluoroquinolones. 45 cases met criteria. For 33%, event onset was within 24 hours of beginning a FQ; for 84% onset was within 7 days. 47% of cases reported sensory and motor symptoms of PN. 44% reported only sensory symptoms and 9% reported only motor abnormalities. CNS symptoms were reported in 78% of cases; 93% experienced symptoms outside the PNS. Symptoms lasted longer than 1 month in 91% of cases, longer than 3 months in 71% of cases , and 27% have exceeded two years duration.	N=45. Numerous cases are strong in that they describe a credible temporal relationship and a positive dechallenge. Additional cases are plausible. Major caveats about this article are related to the use of the internet to solicit case reports (which lack confirmation of information) and also to the qualifications of the author (a board certified psychiatrist) who provides expert testimony on cases related to fluoroquinolones.
10. Jumma, O. Ciprofloxacin Induced Acute Small Fibre Neuropathy. Le Journal Canadian des Sciences Neurologiques. 2013.		A 49 YO male (s/p intravesical botox injection) developed fever and dysuria; initially treated with another antibiotic, this was changed to Cipro. Within 24 hours he developed burning in his feet. .NCS and EMG inconclusive. "Small fibre assessment with thermal sensation threshold study showed small fibre impairment...." Cipro discontinued after 5 days; his neuropathic pain resolved after three weeks.	N = 1. Credible temporal association and positive dechallenge. Testing consistent with small fibre neuropathy. Strong case.

Author, Title, Journal, Year	FQ	Findings/Results	Quality of Evidence
11. Shields, R. Levofloxacin induced small fiber neuropathy. Muscle & Nerve. 2009.	LQ	After 12 days of LQ for prostatitis, a 52 YO male developed symptoms of a small fiber neuropathy (numbness, tingling, hot and cold sensations, hypersensitivity and bluish color of feet). Electromyography, blood tests and an MRI of the brian and spine were normal. A sudomotor axon reflex test showed reduced responses in left forearm and foot. Symptoms improved after 2 months but symptoms persisted at 4 months.	N = 1. Plausible due to the credible temporal association.
# some patients received more than one type of fluoroquinolone			

8.6 Possible Mechanism of Action: Mitochondrial Toxicity

Fluoroquinolones act by inhibiting DNA gyrase and bacterial topoisomerase IV, both of which belong to the topoisomerase type IIA subfamily. These enzymes act by separating both strands of the DNA double helix for cellular replication, transcription, chromosome condensation, genetic recombination, and repair (9,10). Mammalian cells also contain topoisomerase IIA (11).

Ciprofloxacin has been found to affect mammalian topoisomerase II, especially in mitochondria (4). In vitro studies in drug-treated mammalian cells found that nalidixic acid and ciprofloxacin caused a loss of mitochondrial DNA (mtDNA), resulting in a decrease of mitochondrial respiration and an arrest in cell growth (5). Further analysis found protein-linked double-stranded DNA breaks in the mtDNA from ciprofloxacin-treated cells, suggesting that ciprofloxacin was targeting topoisomerase II activity in the mitochondria (5).

An oxidative phosphorylation (OXPHOS) system is found on the inner membrane of the mitochondrion and it provides approximately 95% of the energy (ATP) requirements of the cell (12). The mitochondrial respiratory chain is a major producer of oxidative stress (13), which occurs when there is a greater production of reactive oxygen species (ROS) than antioxidative processes (4). Approximately 1-4% of oxygen reacting with the respiratory chain is incompletely reduced to the superoxide radical ion, hydrogen peroxide, lipid peroxides, and other free radicals (4,13,14,15). Under normal circumstances, there is a mechanism to remove or prevent the generation of ROS to avoid cellular damage such as lipid peroxidation, mtDNA mutations, and DNA strand breaks (4,12); if this does not happen, it can then lead to even more oxidative damage (14).

Mitochondrial conditions that are due to an insufficiency of ATP, especially in organs that rely on mitochondria for their energy source, include developmental disorders of the brain, optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, and lactic acidosis (6). Neurodegenerative diseases, like Parkinson's, Alzheimer's, and amyotrophic lateral

sclerosis (ALS) have been associated with the loss of neurons due to oxidative stress generated by ROS (4,7). Trovafloxacin was withdrawn from the market in 2001 due to cases of liver failure. Studies in cultured hepatocytes identified the mitochondria as the source of trovafloxacin's hepatotoxicity. In addition, the phototoxic effects of fluoroquinolones were found to be due to the mitochondrial formation of a singlet oxygen ($^1O_2$) and superoxide anion (O_2^-) (4).

A human, prospective study was done to evaluate oxidative stress in patients taking different doses of ciprofloxacin, levofloxacin, and gatifloxacin for 5 days for complicated UTI (16). Superoxide dismutase (SOD), an endogenous antioxidant enzyme that removes free radicals, glutathione, another major antioxidant, plasma antioxidant status and lipid peroxides were evaluated in the 52 patients. Results showed that ciprofloxacin had a significant increase in lipid peroxide levels from the first to the fifth day, almost doubling. There was also a significant decrease (from 73% to 32%) in SOD, as well as glutathione. The results were similar for levofloxacin, although to a lesser degree, but these results were not seen with gatifloxacin. This study showed how increase in lipid peroxides can quickly overwhelm what is left of the plasma antioxidants, leading to impairment of cell integrity and cell death.

Gatifloxacin was withdrawn from the market in 2006 because of severe glucose disturbances. Hyperglycemia has also been associated with peripheral neuropathy. An in vitro study found that high glucose resulted in excessive ROS and mitochondrial dysfunction, which resulted in a high frequency of Schwann cell apoptosis (17). Intermittent high glucose also produced a significantly higher percentage of oxidative stress and apoptosis in Schwann cells than constant high glucose (18). A study done in type 2 diabetic mice saw that with an increase in extracellular glucose, there was excessive mitochondrial fission; this was thought to result in dorsal root ganglia (DRG) neuron oxidative stress and neuronal injury, or activation of the caspase cascade, leading to programmed cell death (19). Another study saw damaged mitochondria within 1-2 hours of exposure to elevated glucose (20).

Like fluoroquinolones, NRTI-associated peripheral neuropathy has been associated with inhibition of mtDNA, although the mechanism is different. Pharmacogenetics may play a role in who develops different adverse events. A study done in 526 white HIV-infected patients identified that those who belonged to the mitochondrial haplogroup T were at increased risk of developing peripheral neuropathy, especially if they had been randomized to take didanosine plus stavudine (8).

8.7 Initial Search Criteria and Crude AERS Report Counts (run on May 2, 2012)

Drugs	MedDRA Restrictions	Other Restrictions	Crude AERS Report Count
All FQ	Peripheral Neuropathy (SMQ narrow)	None	1060
All FQ	Peripheral Neuropathy (SMQ narrow)	Serious, US	604
Currently Marketed	HLGT Peripheral	Serious, US, Date-January 1,	472

Systemic FQs	Neuropathies	2003 through June 1, 2012	
Currently Marketed Systemic FQs	HLGT Peripheral Neuropathies	Disability, US, Date-January 1, 2003 through June 1, 2012	125

8.8 Appendix- AERS Case Numbers, AERS ISR Numbers and Manufacturer Control Numbers

Case # ISR # MFR #
4163523 4394764-3 200418301BWH
6735783 5855952-X US-Bayer- 2004 18301NA
8311074 8180008-3 US-Bayer- 20110104758
6329473 5351027-7 US-Bayer-2007 11702BWH
8708389 8553661-x CTU 482535
6985757 7056876-5 US-JNJFOC-2009 0406804
6570197 5727099-4 US-JNJFOC-2008 0206892
6514835 5526528-9 US-JNJFOC-2007 0500164
6528901 5546748-7 US-JNJFOC- 2006 1206771
4217195 4454721-5 CTU 227578
7902497 7396314-5 CTU 449296
7420798 6765151-5

Case # ISR # MFR #
CTU 420852
5947148 5264932-7 US-JNJFOC-2005 0800106
5736243 4575370-4 CTU 238657
3959500 4127633-4 CTU 195638
7989209 7574223-7 US-Bayer-2011- 048327
3810155 4258230-8 200215779BWH
7047386 6720920-2 US-JNJFOC-2008 0600250
6672101 5778378-6 US-Bayer-2008 25404NA
8101755 7685961-x CTU 461100
8311097 8155883-9 US-Bayer-2011- 121728
5881552 4771507-2 CTU 258148
5985044 4906097-4 CTU 268854
8505658 8274079-3 CTU 473089
8133410 7732854-5 CTU 402161
7328963

Case # ISR # MFR #
6647377-4 US-Bayer- 2010 6890NA
6571148 5699871-0 US-Bayer- 2008 15032NA
6725794 5835866-8 CTU 345654
5688537 4515149-2 CTU 233195
5717373 4551553-4 CTU 236018
5660325 4491821-8 CTU 230725
3999816 4183519-0 CTU 201412
3965449 4138139-0 CTU 196846
6763788 5943082-8 US-Bayer-2008 33563NA
7920685 7279714-4 CTU 443247
8578803 8378900-x CTU 475954
8603239 8401067-6 CTU 476712
6708161 5809948-4 CTU 343322
6131928 5100014-2 CTU 284383
5945854 4854143-9

Case # ISR # MFR #
US-JNJFOC-2005 0500789
5850383 4726909-7 CTU 254177
5840679 4626789-4 CTU 245082
5758192 4599386-7 CTU 241895
3987422 4169051-9 CTU 200040
3955140 4397715-0 NSADSS 2003 024330
8730995 7632142-1 US-FDA-7632142
8591353 8403577-4 US-JNJFOC- 2012 519569
8318361 8018058-x US-JNJFOC-2011 1212355
6660017 5762280-x US-JNJFOC-2008 0600537
5699807 5237293-7 US-JNJFOC-2004 1000343
7669041 7963751-8 US-Bayer-2010 40515NA
8733133 7635483-7 US-FDA-7635483
3792485 4652269-6

Reference ID: 3294875

Case # ISR # MFR #
200211737BWH 6707623 5819527-0 US-Bayer-2002 11737BWH
6588484 5736290-2 US-JNJFOC-2008 0303419
7281280 6585340-2 US-JNJFOC-2009 1001662
5828206 4696453-4 FACT0500386 5792819 4650881-1 CTU 247379
8639901 8457703-7 CTU 478820
8519084 8287849-2 CTU 473538
8556581 8346727-0 CTU 474854 8568361 8363773-1 CTU 475476
7876051 7357039-6

Case # ISR # MFR #
CTU 446939
5809678 4915017-4 2005 10990BWH
3913860 4065994-5 CTU 187761 3965164 4138153-5 CTU 196886
3885161 4036947-8 CTU 183915
7960850 7481160-5 CTU 453343
6029112 4971017-3 CTU 273693
6094635 5060902-2 CTU 281181
5781162 4638833-9 CTU 246448
4067135 4373364-5 NSADSS 2002 020499
4142184 4391492-5 US-JNJFOC-2004 0500436
4139050 4354701-4

Case # ISR # MFR #
US-JNJFOC- 2004 0301215
3946714 4110914-8 CTU 192712
7552153 6939172-3 US-Pfizer Inc- 2010 101893
5793394 4780401-2 US-JNJFOC-2005 0500822
8655201 8484008-5 CTU 479789
6131913 5099831-7 CTU 284433
3427804 5402261-9 J&J 980702- 107054556
5686351 4508870-3 CTU 232646
7123532 6361176-2 CTU 392015
5820183 4688772-2 CTU 250801
5801731 4662580-0 CTU 248439
4191723

Case # ISR # MFR #
4422062-8 CTU 224490
8615111 8436844-9 US-Bayer-2012- 058330
8523420 8301009-8 US-Bayer-2012- 037428
6620284 5726166-9 US-Bayer-2008 19763NA
7295186 6600752-6 CTU 409182
5992203 4918834-3 CTU 270231
5804380 4666186-9 CTU 248943
4126904 4337500-9 CTU 216445

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/s/

DEBRA E BOXWELL
04/17/2013

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ALLEN D BRINKER
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MIN CHU CHEN
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