

## **Summary Safety Review - Fluoroquinolones - Assessing the potential risk of aneurysm (a balloon-like bulge) and dissection (a separation or tear in the layers of the wall) of the aorta (a major blood vessel)**

**Product:** Systemic fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin and norfloxacin)

**Potential Safety Issue:** Aneurysm (a balloon-like bulge) and dissection (a separation or tear in the layers of the wall) of the aorta (the major blood vessel that carries blood from the heart to the body)

### **Key Messages**

- Fluoroquinolones are antibiotic prescription drugs that are authorized for sale in Canada to treat many types of bacterial infections, including urinary tract and respiratory infections.
- Following published studies<sup>1-4</sup> that found an increased risk of aortic aneurysm and aortic dissection in patients treated with fluoroquinolones, Health Canada carried out a safety review.
- Health Canada's review concluded that there may be a link between systemic fluoroquinolone use and the risk of aortic aneurysm and dissection.
- Health Canada is working with the manufacturers to update the product safety information for all systemic fluoroquinolones to include information about this potential risk.

### **Overview**

Health Canada carried out a safety review of the potential risk of aortic aneurysm and aortic dissection with the use of fluoroquinolones. The safety review was triggered by published studies, including one study conducted in Canada<sup>1</sup>.

An aortic dissection is a tear of the inside lining of the aorta, the major blood vessel that carries blood from the heart to the rest of the body. An aortic aneurysm is a balloon-like bulge in the wall of the aorta. A rupture of the aneurysm can cause bleeding and, in the most serious cases, may lead to death. Patients with an aortic aneurysm frequently do not show any symptoms and the aneurysm may not be diagnosed until it ruptures. Both aortic dissection and ruptured aneurysm can cause severe pain and death.

While a tear and bulge can occur in any artery, they are most common in the aorta.

High blood pressure (hypertension) and the build-up of plaques inside arteries (atherosclerosis) are major risk factors for aortic dissections and/or aneurysms.

## Use in Canada

- Fluoroquinolones have been marketed in Canada since 1986. They are available as generics and brand names: Cipro (ciprofloxacin), Avelox (moxifloxacin), levofloxacin, and norfloxacin.
- Fluoroquinolones are prescription drugs authorized for sale in Canada to treat many types of bacterial infections, including urinary and respiratory tract infections. They can be taken by mouth (oral), injection, or inhalation. There are some fluoroquinolones that can be applied to the eyes and ears.
- The review was limited to several oral, injectable, and inhalation fluoroquinolones available in Canada. As products that are applied to the eyes and ears have not been reported to cause aneurysms or dissections of the aorta, Health Canada's review did not assess these products.
- Around 4 million prescriptions are filled every year for fluoroquinolones.

## Safety Review Findings

- At the time of the review, Health Canada received 28 international published reports, and 4 Canadian reports<sup>a</sup> of aortic aneurysms and dissections with the use of fluoroquinolones. Of the Canadian reports, 3 were further assessed as they met the criteria defined for this review. One report showed a possible link between aortic aneurysm and the use of levofloxacin. The other 2 cases could not be assessed due to insufficient information.
- Health Canada also looked at the scientific literature and focussed on 4 published studies. Although there were limitations to these studies, they showed an approximately two-fold increased risk of aortic aneurysm and dissection in patients treated with fluoroquinolones, including one Canadian study<sup>1</sup>.
- The European Medicines Agency (EMA)<sup>b</sup> and the United States Food and Drug Administration (US FDA)<sup>c</sup> are updating the product safety information for fluoroquinolones to include the risk of aortic aneurysm and dissection.

## Conclusions and Actions

- Health Canada's review of the available information has concluded that there may be a link between the use of systemic fluoroquinolones (given by mouth, by injection, or by inhalation) and aortic aneurysm and dissection. Given the frequent use of fluoroquinolones in Canada and the information reviewed, these side effects are considered rare.
- Health Canada recommended that the product safety information for all systemic fluoroquinolone products be updated to include information about this rare but serious adverse effect. In addition, Health Canada will inform Canadians and healthcare professionals of this new safety information in the [Health Product InfoWatch](#).
- Health Canada is working with the manufacturers to update the product safety information of all systemic fluoroquinolone products marketed in Canada.
- Health Canada will continue to monitor safety information involving fluoroquinolones, as it does for all health products on the Canadian market, to identify and assess potential

harms. Health Canada will take appropriate and timely action if and when any new health risks are identified.

### **Additional Information**

The analysis that contributed to this safety review included scientific and medical literature, Canadian and international adverse reaction reports and what is known about the use of these drugs both in Canada and internationally.

For additional information about Health Canada's safety review, please [contact the Marketed Health Products Directorate](#).

If manufacturers or industry associations require more information at this time, they are encouraged to contact the [Therapeutic Products Directorate](#).

1. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. *BMJ Open*. 2015;5(11):e010077
2. Lee C, Gabriel Lee M, Chen Y, Lee S, Chen Y, Chen S, et al. Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. *JAMA Intern Med*. 2015;175(11):1839-47.
3. Pasternak B, Inghammar M, Svanström H. Fluoroquinolone use and risk of aortic aneurysm and dissection: Nationwide cohort study. *BMJ*. 2018;360:k678.
4. Lee C, Lee M-G, Hsieh R, Porta L, Lee W, Lee S, et al. Oral Fluoroquinolone and the Risk of Aortic Dissection. *J Am Coll Cardiol*. 2018;72(12):1369-78.
  - a. Canadian reports can be accessed through the [Canada Vigilance Online Database](#).
  - b. PRAC recommendations on signals adopted at the 3-6 September 2018 PRAC meeting; available at [https://www.ema.europa.eu/documents/prac-recommendation/prac-recommendations-signals-adopted-3-6-september-2018-prac-meeting\\_en-0.pdf](https://www.ema.europa.eu/documents/prac-recommendation/prac-recommendations-signals-adopted-3-6-september-2018-prac-meeting_en-0.pdf)
  - c. The United States Food and Drug Administration (US FDA) drug safety communication issued on December 20<sup>th</sup> 2018; available at: <https://www.fda.gov/Drugs/DrugSafety/ucm511530.htm>; accessed on January 16, 2019