Summary Safety Review - Bacitracin for Injection Products - Assessing the Potential Risks of Nephrotoxicity and Anaphylactic Reactions

Product: Bacitracin for injection products

Potential Safety Issue: Kidney injury (nephrotoxicity) and sudden, severe, potentially life-threatening allergic (anaphylactic) reactions

Key Messages

- **Bacitracin for injection products are drugs authorized for sale in Canada to treat:**
  - **Infants with pneumonia and accumulation of pus in the chest (empyema) caused by staphylococcus, a type of bacteria.**
  - **Infected wounds, ulcers, large painful skin sores, other surface skin infections and eye infections.**
  - **Upper and lower respiratory tract infections.**
- **Health Canada reviewed the potential risks of kidney injury (nephrotoxicity) and sudden, severe, potentially life-threatening allergic reactions (anaphylactic reactions) with the use of bacitracin for injection products. This safety review was triggered by a United States Food and Drug Administration (U.S. FDA) Drug Safety Communication.**
- **Health Canada's review concluded that there may be a link between bacitracin for injection products and the risks of nephrotoxicity and anaphylactic reactions.**
- **The indication for bacitracin for injection products in Canada differs from that of the US. Further, a review of additional information by Health Canada on utilization of these products, and physician awareness of these risks in Canada, is necessary.**
- **At this time, to minimize risks in Canada, Health Canada:**
  - **has requested the manufacturers of bacitracin for injection products update the Canadian product safety information and add a Serious Warnings and Precautions Box to further strengthen the information about nephrotoxicity and to include information about anaphylactic reactions;**
  - **has recommended the issuance of a Health Product Risk Communication to inform healthcare professionals about these potential risks;**
- **Health Canada will work with the manufacturers to collect additional information on utilization of these products and their risks in Canada to determine if further measures are needed to mitigate the risks.**

Overview

Health Canada reviewed the potential risks of nephrotoxicity and anaphylactic reactions with the use of bacitracin for injection products further to the U.S. FDA issued Drug Safety Communication dated January 31, 2020. In that communication, the FDA requested all current U.S. manufacturers of bacitracin for injection to voluntarily withdraw their product from the U.S. market. The FDA review determined that U.S. healthcare professionals no longer use bacitracin for injection for the only approved indication of treating infants with pneumonia and empyema caused by staphylococcus. The FDA also considered the availability of other approved, effective treatments that do not have the same serious risks, including nephrotoxicity and anaphylactic reactions.

Health Canada's review did not include non-prescription bacitracin-containing products marketed as ointments, since no safety concerns for these products were identified in the U.S. FDA's Drug Safety Communication.

Use in Canada

- Bacitracin for injection products are drugs authorized for sale in Canada to treat:
    - Infants with pneumonia and accumulation of pus in the chest (empyema) caused by staphylococci, a type of bacteria, when administered by injection into the muscle.
    - Infected wounds, ulcers, large painful skin sores, and other surface skin and eye infections, when applied locally in the form of compresses or drops.
    - Upper and lower respiratory tract infections, when applied as nasal drops or administered by aerosol inhalation.
- Health Canada is aware that bacitracin for injection products are also being used off-label as irrigation solutions for prevention of infections during surgeries. Although Health Canada does not endorse or regulate off-label use of drugs, healthcare professionals may decide to use and prescribe drugs for uses that have not been reviewed and authorized by Health Canada.
- Bacitracin for injection has been on the Canadian market since 1951 and is available under the brand names Bacitracin USP and BaciJect. Bacitracin for injection products are available as 50,000 IU of bacitracin sterile powder for reconstitution per vial.
- There were about 125,000 vials of bacitracin for injection sold per year from 2015 to 2019.

Safety Review Findings

- Health Canada reviewed the available information from searches of the Canada Vigilance database[a], international databases, and published scientific and medical literature.
- Health Canada's assessment of the use of bacitracin for injection and nephrotoxicity focused on 10 published international studies, which included more than 280 patient cases. 8 of these studies supported a link between bacitracin and nephrotoxicity, 1 study had incomplete information on kidney function, and 1 did not identify a link between bacitracin and nephrotoxicity. At the time of the review, Health Canada had not received any Canadian reports of nephrotoxicity linked to the use of bacitracin for injection products. The safety review also looked at 7 international case reports of kidney toxicity related to the use of bacitracin for injection products. These reports could not be assessed further for causality because of the limited information in the reports, errors in the route of administration, and the use of other medications that may have contributed to nephrotoxicity.
- Overall, the review found that treatment with bacitracin for injection is often associated with changes in kidney function, which can return to normal if treatment is stopped early, but can progress to kidney damage or failure if continued. There were no case reports of nephrotoxicity linked to the use of bacitracin for injection in Canada.
- Health Canada's assessment of the use of bacitracin for injection and anaphylactic reactions focused on 14 articles published in the scientific literature. These publications reported evidence supporting a link between bacitracin use and the risk of anaphylactic reactions. Health Canada also assessed 18 case reports, 3 received from the Canada Vigilance

database and 15 from one manufacturer. These 18 case reports included 12 published case reports from the literature articles. There was a link between bacitracin for injection products and anaphylactic reactions in 17 of the 18 cases. Of the 3 case reports from the Canada Vigilance database (1 Canadian and 2 international), a link between the use of bacitracin for injection and anaphylactic reactions was found to be probable in 1 report and possible in the other 2 reports (1 Canadian). Of the 15 international case reports from the manufacturer, 14 cases showed a link between bacitracin use and anaphylactic reactions.

- Overall, the review found that anaphylactic reactions with bacitracin for injection can occur minutes after starting treatment. Many cases required resuscitation with medication. The review also found that bacitracin for injection was used despite previous allergic reactions to bacitracin. There was a single case report of anaphylactic reaction in Canada that was found to be possibly linked to the use of bacitracin for injection. However, the patient was taking other medications at the same time that could have contributed to the anaphylactic reaction.

Conclusions and Actions

- Health Canada's review found a possible link between bacitracin for injection products and the risks of nephrotoxicity and anaphylactic reactions.
- Health Canada has requested that the manufacturers of bacitracin for injection products update the Canadian product safety information and add a Serious Warnings and Precautions Box to further strengthen the information about nephrotoxicity and to include information about anaphylactic reactions.
- Health Canada has recommended the issuance of a Health Product Risk Communication to inform healthcare professionals about these potential risks.
- A review by Health Canada of information on utilization of these products and physician awareness of these risks in Canada is necessary to determine if further measures are needed to mitigate the risks. Health Canada will work with the manufacturers to collect this information.
- Health Canada encourages consumers and healthcare professionals to report any side effects related to the use of bacitracin for injection products and other health products to the Canada Vigilance program.
- Health Canada will continue to monitor safety information involving bacitracin for injection products, 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 should new health risks be identified.

Additional Information

The analysis that contributed to this safety review included scientific and medical literature, Canadian and international information, and what is known about the use of bacitracin for injection products both in Canada and internationally.

For additional information, contact the Marketed Health Products Directorate

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a) Canadian reports can be accessed through the Canada Vigilance Online Database.