

Summary Safety Review - Diuretics, Including Acetazolamide - Assessing the Potential Risk of Certain Eye Disorders

Product: Diuretics, including acetazolamide-containing products

Potential Safety Issue: Eye disorders: Choroidal effusion (fluid build up in the back of the eye), acute myopia (sudden nearsightedness) and acute angle-closure glaucoma (sudden increased pressure in the eye)

Key Messages

- **Diuretics (water pills) are authorized for sale in Canada to treat various medical conditions, but are mainly used to reduce swelling caused by a build up of body fluids (edema) and to lower high blood pressure. Acetazolamide, which has diuretic properties, is authorized for sale in Canada to treat increased pressure in the eye (glaucoma), certain types of seizures, overdose from acetylsalicylic acid (ASA) and edema.**
- **Health Canada reviewed the risks of choroidal effusion (CE), acute myopia (AM) and acute angle-closure glaucoma (AACG) with the use of diuretics, including acetazolamide-containing products. This safety review was triggered by updates made to the product safety information for certain diuretics by the European Medicines Agency.**
- **At the time of the review, the Canadian product safety information for some diuretics included information related to one or all of these eye disorders. The purpose of this review was to assess if additional actions were required for diuretics marketed in Canada.**
- **Health Canada's review of the available information showed a link between the use of certain diuretics, namely products containing hydrochlorothiazide, chlorthalidone, indapamide and acetazolamide, and the risks of CE with AM or with AACG or with both AM and AACG. Health Canada's review also concluded that there might be a link between the diuretic Zaroxolyn (metolazone) and the risk of these eye disorders.**
- **Health Canada will work with manufacturers of affected products to update the Canadian product safety information to add a warning about the risks of CE with AM or with AACG or with both AM and AACG. Health Canada will also inform healthcare professionals about these updates through a Health Product InfoWatch communication.**

Overview

Health Canada reviewed the potential risks of choroidal effusion (CE), acute myopia (AM) and acute angle-closure glaucoma (AACG) with the use of diuretics, including acetazolamide. The safety review was triggered by updates made by the European Medicines Agency to include these risks in the product safety information for certain diuretics.

At the time of the review, the Canadian product safety information for some diuretics included information related to one or all of these eye disorders. The purpose of this review was to assess if additional actions were required for diuretics marketed in Canada.

Use in Canada

- Diuretics are prescription drugs authorized for sale in Canada to treat various medical conditions, but are mainly used to reduce swelling caused by a build up of body fluids (edema) and to lower high blood pressure. Acetazolamide is authorized for sale in Canada to treat increased pressure in the eye (glaucoma), certain types of seizures and overdose from acetylsalicylic acid (ASA). Acetazolamide for Injection is also authorized to treat edema.
- Diuretics, including acetazolamide, have been marketed in Canada since 1968 under different brand names. Single ingredient and combination products are available. Generic versions of diuretics are also available.
- Diuretics, including acetazolamide, are widely used in Canada. There were over 31 million prescriptions for these drugs filled in 2019.

Safety Review Findings

- Health Canada reviewed the available information from searches of the Canada Vigilance database^a, international databases and published literature.
- Health Canada reviewed 49 cases (1 Canadian, 48 foreign) of choroidal effusion, acute myopia or acute angle-closure glaucoma with the use of diuretics, including acetazolamide. The 48 foreign cases included 7 reported to the Canada Vigilance database and 41 that were only available through the scientific literature.
- Health Canada's review found a link between the use of certain diuretics and the risks of CE with AM or with AACG or with both AM and AACG. For hydrochlorothiazide, 7 cases (1 Canadian) showed a possible link and 1 case was not likely to be linked. For chlorthalidone, 4 cases were considered possibly linked and 1 case could not be assessed due to insufficient information in the report. For indapamide, 7 cases were found to be possibly linked and 1 case was unlikely to be linked. For furosemide, 1 case was found to be possibly linked, 2 cases were not likely to be linked and 1 case did not have enough information to be assessed. Of the 19 acetazolamide cases reviewed, 1 case was found to be probably linked, 12 cases were possibly linked, 1 case was unlikely to be linked and 5 cases could not be assessed. The remaining 5 cases were considered unlikely to have a link (spironolactone, triamterene, methylothiazide^b, azosemide^b) or did not have enough information to be assessed (xipamide^b).
- At the time of the review, no information was found to support a link between Zaroxolyn and the risk of eye disorders. However, given the similar chemical structure of Zaroxolyn to chlorthalidone and indapamide, the risks of CE, AM or AACG with Zaroxolyn use could not be excluded.
- While the published literature supported a link between the risks of CE, AM or AACG with certain diuretics, including acetazolamide, it did not identify a clear biological mechanism to explain how diuretics, including acetazolamide, could lead to these eye disorders.

Conclusions and Actions

- Health Canada's review of the available information showed a link between the use of certain diuretics, namely products containing hydrochlorothiazide, chlorthalidone, indapamide and acetazolamide, and the risks of CE with AM or with AACG or with both AM and AACG. In addition, Health Canada's review concluded that there might be a link between Zaroxolyn and the risk of these eye disorders.
- Health Canada will work with manufacturers to update the Canadian product safety information for products containing hydrochlorothiazide, chlorthalidone, indapamide and acetazolamide as well as Zaroxolyn to add a warning about the risks of CE with AM or with AACG or with both AM and AACG. Health Canada will also inform healthcare professionals about these updates through a Health Product InfoWatch communication.
- Health Canada encourages consumers and healthcare professionals to [report](#) any side effects related to the use of diuretics, including acetazolamide, and other health products to the Canada Vigilance Program.
- Health Canada will continue to monitor safety information involving diuretics, including acetazolamide-containing 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 adverse reaction reports, and what is known about the use of diuretics, including acetazolamide-containing 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](#).
 - b. These drug products are not currently marketed in Canada.