Update on Nitrosamine Impurity found in Latent TB Drug Rifapentine

Update to York Region health care providers as of March 31, 2021

In August 2020, notice was sent that a nitrosamine impurity was detected in Priftin®, a rifapentine drug manufactured by Sanofi. At that time, health care professionals treating patients with latent tuberculosis infections were advised not to begin new patients on Priftin® until further notice.

Since then, the Public Health Agency of Canada conducted a benefit-risk assessment and issued new recommendations for use of Priftin®.

Health Canada has advised Sanofi that it will not object to the release of lots of Priftin® on the Canadian market with an interim limit of ≤20 ppm at release and ≤25 ppm at the end of shelf life. This is a temporary measure until Sanofi can reduce or eliminate the impurity. At 25 ppm, the potential increased excess cancer risk is estimated at 1 additional cancer case for every 34,000 patients exposed to this impurity.

Until the impurity is eliminated by Sanofi, the use of existing lots of Priftin® can be resumed for treatment of LTBI **only in situations where there is a high risk of non-adherence or non-completion of treatment, or where other treatment alternatives are not feasible or suitable.** Please ensure a complete course of treatment is available before initiating patients on Priftin® for LTBI.

For more information, please see the following documents shared by the Ministry of Health.

Contact York Region Public Health

If you have any questions about rifapentine or tuberculosis, call our tuberculosis team at **1-877-464-9675 ext. 76000** or visit york.ca/TB

Notice Update: Nitrosamine impurity found in Priftin® (rifapentine)

The following information is an update to the notice sent to Canada's Chief Medical Officers of Health, effective August 10, 2020, regarding a nitrosamine impurity, 1-cyclopentyl-4-nitrosopiperazine (CPNP), detected in Priftin® 150mg tablets manufactured by Sanofi. In that notice, health care professionals treating patients with latent tuberculosis infection (LTBI) were advised not to start new patients on Priftin until further notice and that patients already taking Priftin for LTBI could complete their course of treatment.

Background

In light of the impurity issue, Sanofi had paused the release of Priftin from its manufacturing site. CPNP is mutagenic, indicating that its presence in rifapentine may be associated with a potential increased excess cancer risk in humans. Priftin is not authorized for sale in Canada but is imported from the U.S. into Canada through the Access to Drugs in Exceptional Circumstances regulatory pathway. In the U.S., Priftin has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of both active TB disease and LTBI. The Public Health Agency of Canada (PHAC) and the First Nations and Inuit Health Branch (FNIHB) at Indigenous Services Canada (ISC) provided the notifications that enabled the drug to be imported into Canada through the pathway for use in all jurisdictions for the treatment of LTBI only.

What has occurred since August 10, 2020

In collaboration with Health Canada and ISC, and with input from leading TB experts, PHAC conducted a Benefit-Risk Assessment (BRA) to help inform decisions concerning access to Priftin. Dr. Theresa Tam and Dr. Tom Wong, the Public Health Officers who submitted the notifications, agreed that the benefits of the 3-month once-weekly regimen of rifapentine and isoniazid (INH) (commonly referred to as 3HP) outweighed the potential health risks posed by the impurity detected in Priftin. They recommended, however, that Priftin be used only in situations where there is a high risk of non-adherence or non-completion of treatment, or where other treatment alternatives are not feasible or suitable. As a result, the decision was made to retain Priftin on the List of Drugs for an Urgent Public Health Need.

Based on the BRA, Health Canada has advised Sanofi that it will not object to the release of lots of Priftin on the Canadian market with an interim limit of ≤20 ppm at release and ≤ 25 ppm at the end of shelf life. This is a temporary measure until which time Sanofi can reduce or eliminate the impurity. At 25 ppm, the potential increased excess cancer risk is estimated at 1 additional cancer case for every 34,000 patients exposed to CPNP.

Current recommendations for the use of Priftin in Canada

Lots of Priftin currently on the Canadian market contain the CPNP impurity at levels ranging from 12 ppm to 25 ppm. These levels exceed the acceptable concentration limit of 0.11 ppm. At Health Canada's request, Sanofi has committed to test lots prior to release and to further test lots currently on the market. The interim limit of ≤20 ppm at release, and ≤ 25 ppm at the end of shelf life, is in effect until Sanofi can reduce CPNP in Priftin to within the acceptable limit of

≤ 0.11 ppm. Health Canada is monitoring progress closely and expects Sanofi to make every necessary effort to reduce the level of the impurity to at, or below, the acceptable concentration limit of 0.11 ppm as soon as possible.

In the meantime, the use of existing lots of Priftin on the Canadian market can be resumed for the treatment of LTBI under the recommended conditions – that is, **only in situations where there is a high risk of non-adherence or non-completion of treatment, or where other treatment alternatives are not feasible or suitable.** Health care professionals are advised to ensure a complete course of treatment is available before initiating patients on Priftin for LTBI.

Benefits of 3HP for the treatment of LTBI

A patient-centred approach to LTBI treatment is an essential component of TB prevention and control and an important step towards TB elimination. Evidence of the effectiveness of preventive therapy in high-risk individuals is abundant, and proof of the population-level effect of preventive therapy exists in many settings across the globe. Preventive therapy yields significant health and cost benefits both in the short and long term.

In recent years, a key breakthrough in the prevention of active TB disease has been the introduction of 3HP as an acceptable alternative treatment for LTBI. 3HP has been shown to be as effective as the standard treatment of 9 months of INH monotherapy while demonstrating higher treatment completion rates. This preventive treatment constitutes a major advance in treating persons with LTBI and in contributing to the control of active TB disease, particularly in high-income, low-incidence countries like Canada. ISC recognizes that 3HP has become a preferred treatment for LTBI in many communities facing recurrent outbreaks of active TB disease resulting from ongoing community transmission. Canadian TB experts have warned that any erosion of the gains made in implementing 3HP in northern communities with historically high TB incidence could lead to a major setback in efforts to prevent and control active TB disease in those communities.

Pharmacists and physicians interested in acquiring Priftin through the Access to Drugs in Exceptional Circumstances regulatory pathway should follow normal ordering procedures applicable in their province or territory. A patient information sheet accompanies this update. Patients who have concerns about their health, or want information about available LTBI treatment options, should speak directly with their health care providers.

Additional Resources

- Access to Drugs in Exceptional Circumstances regulatory pathway
- List of Drugs for an Urgent Public Health Need
- U.S. FDA Updates and Press Announcements on Nitrosamines in Rifampin and Rifapentine
- Nitrosamine impurities in medications

Priftin® (Rifapentine)**:**

What you need to know about current rifapentine treatment for latent tuberculosis infection

What is latent tuberculosis (TB) infection?

Tuberculosis is caused by germs that are called bacteria. Latent TB is when the TB bacteria are "asleep" in your body. Latent TB cannot spread to others.

If TB bacteria wake up (and become active TB), they can spread to others and make you and those around you very sick.

If you have latent TB infection, there is a 5% chance that it will become active TB.

- Active TB can spread to others, particularly to those living in the same house as you.
- Active TB is a potentially deadly disease.

What is Rifapentine?

Rifapentine (pronounced: RIF·a·PEN·teen) is an antibiotic. It is taken by mouth with another antibiotic called isoniazid to treat latent TB. This treatment is taken once a week for 12 weeks and is known as "3HP." 3HP treatment is a much shorter treatment compared to other latent TB treatment options. Other treatments can last up to 9 months. Treating latent TB with antibiotics is much safer than not treating the infection because it helps to prevent it from progressing to active TB.

Rifapentine currently has a nitrosamine impurity

What is a nitrosamine impurity?

Sometimes, unwanted molecules are formed in the process of making a drug. These are called impurities. A nitrosamine (ni·tro·sa·mine) impurity has been found in the rifapentine currently in Canada.

Did you know? Everyone is exposed to low levels of nitrosamines. They are found in tobacco products, air pollution and in foods such as processed meats, and dairy products. Nitrosamines are also naturally found in water and vegetables.

What is the health risk of a nitrosamine impurity?

Some nitrosamines are probable carcinogens in humans. This means that long-term exposure to a level above what is considered safe could increase the risk of cancer. We are all exposed to low levels of nitrosamine impurities in some foods (such as meats, dairy products and vegetables) and in drinking water. These impurities are not expected to cause harm when ingested at very low levels.

What is the risk of taking rifapentine that is currently available?

Rifapentine that is currently on the market has higher levels of a nitrosamine impurity than what is normally considered acceptable. This specific nitrosamine impurity has not been shown to develop cancer in animals or humans. However, it has been shown to cause gene mutations in an in vitro study, and it is structurally similar to other nitrosamines that have been shown to develop cancer in humans.

There is a certain level of risk related to impurities in medications that is considered acceptable by scientific bodies around the world: no more than 1 additional cancer case for every 100,000 people exposed to a specific impurity in a medication over a lifetime. Drawing from animal data and data from a different nitrosamine, Health Canada has estimated that up to 1 person out of 34,000 patients exposed to this nitrosamine may develop cancer. On average, everyone already has nearly a 1 in 2 chance of developing cancer in their lifetime.

Canadian TB experts carefully looked at the absence of human cancer evidence, weighing the potential nitrosamine risks against the known benefits of this short weekly treatment for 3 months. They decided to recommend rifapentine to remain available as a treatment option to Canadians. For many people the benefits of taking rifapentine with the nitrosamine impurity will outweigh the risks of leaving their latent TB infection untreated.

Health Canada is working with the manufacturer of Priftin (rifapentine) to ensure this issue is resolved as quickly as possible.

Is rifapentine right for you?

Rifapentine (3HP treatment) may be the right option for you if you have contraindications to other latent TB treatments or if taking treatments for longer than 3 months is not feasible.

Talk to your health care provider to get more information on latent tuberculosis treatment options and to help you make the decision for your health.

You can also visit this link for more information on nitrosamines: https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/nitrosamine-impurities.html

*Please verify with your health care provider if the information on this information sheet is still valid.

Date: March 2021