PART III: CONSUMER INFORMATION

PrZEVALIN®
Ibritumomab tiuxetan

This leaflet is part III of a three-part Product Monograph for ZEVALIN and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about ZEVALIN. Contact your doctor if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ZEVALIN is used to treat certain types of B-cell non-Hodgkin's lymphoma (NHL). This is a cancer of certain white blood cells called B lymphocytes (B-cells). ZEVALIN is used if an earlier treatment has not worked, or has stopped working.

What it does:
ZEVALIN is a type of targeted cancer therapy called radioimmunotherapy. ***Radioimmunotherapy*** refers to a treatment that combines a source of radiation, such as a radioisotope, with a component of the immune system, such as an antibody.

Antibodies are part of the body's natural defence system, the immune system. Antibodies circulate in the blood stream and are able to recognize and attach themselves to foreign substances that enter the body, such as bacteria. This alerts other parts of the immune system to help destroy and remove the foreign substance from the body. Scientists can now make antibodies that recognize and attach to specific targets. The antibody used in ZEVALIN is designed to recognize and attach to B-cells, including the cancerous B-cells in patients with B-cell NHL.

A ***radioisotope*** is an atom that gives off energy in the form of radiation. When ZEVALIN is combined with a radioisotope, it is said to be radiolabeled. For therapeutic purposes, ZEVALIN is combined with yttrium-90 (^{90}Y), which produces a type of radiation called beta emission.

As ZEVALIN enters the bloodstream, the antibody portion recognizes and attaches to a B-cell, allowing the energy emitted from the yttrium-90 to penetrate and damage or kill the cancerous B-cell. In what is called a "cross-fire" effect, the emitted energy can also reach and destroy neighbouring cancer cells.

When it should not be used:
You must not be given ZEVALIN:

- If you have an allergy (if you are hypersensitive) to the active ingredient (ibritumomab tiuxetan), to yttrium chloride, to rituximab, to mouse proteins or to any of the other ingredients in ZEVALIN (see below).
- If you are pregnant or nursing

What the medicinal ingredient is:
The medicinal ingredient is ibritumomab tiuxetan. Ibritumomab is a man-made antibody that can recognize and attach to B-cells.

What the important nonmedicinal ingredients are:
The other ingredients are human serum albumin, hydrochloric acid, pentetic acid, potassium chloride, potassium phosphate monobasic, sodium acetate trihydrate, sodium chloride, sodium hydroxide, sodium phosphate dibasic dodecahydrate and water for injection.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Because ZEVALIN is a radiopharmaceutical, it can only be given by doctors and other health professionals who are specially trained and experienced in the safe use and handling of radioisotopes.**
- **Deaths have occurred within 24 hours of receiving infusion with rituximab, an essential part of the ZEVALIN therapeutic regimen. Approximately 80% of fatal infusion reactions occurred in association with the first rituximab infusion. Patients who develop severe infusion reactions should have rituximab and ^{90}Y-ZEVALIN infusions stopped immediately and receive medical treatment (see WARNINGS AND PRECAUTIONS - Severe infusion reactions).**
- **Treatment with ZEVALIN can result in very low blood cell counts for a prolonged period of time (see SIDE EFFECTS AND WHAT TO DO ABOUT THEM).**
- **To ensure safe administration, the dose of ZEVALIN that you receive should not exceed the maximum allowable dose of 32 mCi (1200 MBq).**

BEFORE you receive the ZEVALIN therapeutic regimen, talk to your doctor if:

- You have an allergy to ibritumomab tiuxetan, yttrium chloride, rituximab, mouse proteins or to any of the other ingredients in ZEVALIN (see **ABOUT THIS MEDICATION: What the important nonmedicinal ingredients are**).
- You are pregnant or could be pregnant. You should not receive ZEVALIN if you are pregnant.

- You are breastfeeding. You must not receive ZEVALIN if you are breastfeeding.

Your doctor will need to think carefully whether to give you ZEVALIN in some cases:

- If a quarter or more of your bone marrow contains malignant abnormal cells.
- If you have a marked reduction in bone marrow cells.
- If the number of your platelets is less than 100,000/mm^3 or if the number of one type of white blood cells (called neutrophils) is less than 1,500/mm^3.
- If you have had a failed stem cell collection.

If you have had certain other types of antibody treatment before starting ZEVALIN, you may be more likely to have an allergic reaction (hypersensitivity). You may therefore need to be tested for special antibodies. Your doctor will tell you if this applies to you.

After treatment with ZEVALIN, and if your doctor plans to treat you with some other antibody, please tell your doctor about your treatment with ZEVALIN. This will help avoid a possible allergic reaction (hypersensitivity).

Severe infusion reactions:
Rituximab, a key part of the ZEVALIN therapeutic regimen, has been known to cause a severe allergic reaction in some patients. This severe allergic reaction does not occur often. When it does occur, it is usually during the first infusion of rituximab. In some patients, this severe allergic reaction has led to death within 24 hours of receiving rituximab. Symptoms of this severe allergic reaction include low blood oxygen levels, fluid in the lungs, severe difficulty in breathing, disturbances in heart rhythms, heart attack and disruption in bodily functions related to a sudden decline in heart function. Patients who develop symptoms of this severe type of allergic reaction should have their rituximab or ZEVALIN infusions stopped and receive medical treatment.

Prolonged low blood cell counts:
Treatment with ZEVALIN can result in very low blood cell counts for a prolonged period of time (see **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**). The ZEVALIN therapeutic regimen should not be given to patients with 25% or more of their bone marrow cells affected by lymphoma and/or patients whose bone marrow may have difficulty recovering from therapy.

Skin and mucous membrane reactions:
If you notice a skin or mucous membrane reaction during or after ZEVALIN or rituximab treatment, inform your doctor immediately, because in rare instances such reactions have been reported to develop into severe cases, even with the possibility of death.

Secondary cancers:
Following treatment with the ZEVALIN therapeutic regimen, development of a second type of cancer involving blood cells has occurred in a small percentage of cancer patients (less than 2 in 100) participating in ZEVALIN studies. The risk of these secondary cancers occurring after certain cancer drugs called alkylating agents is already known to doctors. Previous treatment with alkylating agents is, however, widespread prior to ZEVALIN treatment. Therefore it is difficult to know whether ZEVALIN itself contributes to this risk of developing a secondary cancerous disease.

Immunization:
The safety of immunization with any vaccine, particularly live viral vaccines, following therapy with ZEVALIN has not been studied. The ability of the body to respond to any vaccine following ZEVALIN treatment has also not been studied.

Driving and using machines:
It is possible that ZEVALIN will affect your ability to drive and to operate any tools or machines as dizziness is a common side effect. Please take care, and do not try to drive or operate machines until you are sure you are not affected.

Children and adolescents:
The safety and effectiveness of ZEVALIN in children and adolescents have not yet been established.

Precautions to be taken <u>after</u> receiving ZEVALIN:
The amount of radiation that your body will be exposed to during the ZEVALIN therapeutic regimen is smaller than it would be during radiotherapy. With the type of radioactivity from ZEVALIN (pure beta emission) there is no direct effect of radiation outside the body. You are not exposing other people to radiation. The effects of ZEVALIN stay mainly within your body and bodily fluids, such as urine and blood. A small part of the radioactivity will leave your body through your urine. The remainder will break down within the body, leaving no radioactive remains.

Typically, there is no need to stay in the hospital or to avoid contact with family, friends or co-workers after treatment with ZEVALIN. However, it is advisable to observe some safety precautions for the week following treatment with the therapeutic dose of ZEVALIN, to minimize any potential radiation exposure to other people. If you have any questions concerning the precautions listed below or about participation in a particular activity, be sure to discuss them with your doctor.

Safety precautions to be followed for 7 days

- Wash your hands thoroughly after using the bathroom.
- Use a condom during sexual intercourse to avoid transfer of bodily fluids.

Pregnancy precautions

- **If you could get pregnant,** use reliable contraception. Pregnancy should be ruled out before you start treatment and must be avoided during treatment and for **one year** after treatment.
- **Men who have been given ZEVALIN** and who could become fathers must use reliable contraception during and for **one year** after treatment.

Breastfeeding

- **Talk to your doctor before starting breast-feeding** after the end of treatment as it is not known whether ZEVALIN is excreted in human milk. Some antibodies are excreted in human milk. Women must not breastfeed during and for **one year** after treatment.

After receiving ZEVALIN, follow your doctor's instructions and the guidelines included in this leaflet regarding going home and back to work.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor if you are taking or have recently taken any other medicines, even those you bought without a prescription.

If you take blood thinners or other medications that interfere with blood clotting, such as warfarin (Coumadin®), ASA (ASPIRIN®), nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen (Motrin®, Advil®) and naproxen (Naprosyn®), or COX-2 inhibitors like celecoxib (Celebrex®), your doctor will need to monitor your blood and platelet counts carefully during and after receiving ZEVALIN.

PROPER USE OF THIS MEDICATION

ZEVALIN will be given to you under the supervision of a health professional who is specially trained and experienced in the safe use of radiopharmaceuticals.

Do I need to make special preparations before beginning treatment with ZEVALIN?
In general, you do not need to make any special preparations before you begin treatment with the ZEVALIN therapeutic regimen. You can continue with your normal activities and your regular diet. You may also wear your regular clothes to receive your treatments. Your doctor or nurse may have some specific suggestions or recommendations for you to follow.

How is the ZEVALIN therapeutic regimen given?
The ZEVALIN therapeutic regimen is intended as a single course of treatment, consisting of two hospital visits, approximately one week apart.

On your first visit (day 1), you will receive treatment with rituximab, an antibody similar to the one used in ZEVALIN. Rituximab is given before ZEVALIN to allow ZEVALIN to better target the lymphoma cells within your body. Rituximab is administered by intravenous infusion, which means that the medicine is given by a drip into the vein. The infusion may take several hours to complete.

On your second visit (day 7, 8 or 9), you will receive a second rituximab infusion. Within four hours after receiving this second rituximab infusion, you will receive your ZEVALIN treatment. Radiolabeled ZEVALIN is administered by intravenous infusion over 10 minutes.

Important: You must receive rituximab before you can be given ZEVALIN. Please ask your doctor for the rituximab patient brochure for important information on this product.

How much ZEVALIN is given?
The doctor will calculate your individual dose. This depends on your body weight and the number of your blood platelets.

What kind of follow-up is needed after completing ZEVALIN treatment?
Your doctor will want to obtain complete blood cell counts and platelet counts weekly for at least 12 weeks following completion of the ZEVALIN therapeutic regimen. Some patients may need more frequent monitoring. Speak to your doctor concerning all details of your follow-up treatment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, ZEVALIN can have side effects and most people receiving it are likely to get some of these. Because many side effects resemble the effects of the illness, it is not always clear if a reaction seen in clinical trials was due to ZEVALIN or not.

During treatment with the ZEVALIN therapeutic regimen:
The most common side effects during treatment included

weakness, nausea, infection, chills and fever, abdominal or general pain, shortness of breath, headache, vomiting, sore throat, cough and dizziness. If you experience any of these side effects, or any effects not mentioned here, tell a healthcare professional immediately.

Treatment with the ZEVALIN therapeutic regimen may cause a severe and potentially fatal allergic reaction. This severe reaction typically occurs with the first administration of rituximab. Ask your doctor for the rituximab patient information for important information on side effects with rituximab.

Following treatment with the ZEVALIN therapeutic regimen:
Following treatment with ZEVALIN, you will likely experience a period of decreased blood cell counts. For some patients, blood cell counts may become very low. Low white blood cell counts can decrease your ability to fight infections. Low red blood cell counts can cause fatigue. Low platelet counts can cause difficulty in forming blood clots, leading to increased bruising or bleeding. Low blood cell counts can occur up to two months following completion of the ZEVALIN therapeutic regimen and counts may remain low for a few weeks. Your body is usually able to recover normal blood counts within a few weeks after this period of decreased blood cell counts.

Very low blood counts may lead to serious or life-threatening complications, such as infections. Some patients have needed transfusions or have been given medications to help their blood counts recover faster. Your doctor may provide you with special instructions if your blood counts become very low.

Other side effects related to ZEVALIN treatment may occur, but are generally mild in severity. These may include nausea, vomiting, abdominal pain, diarrhea, increased cough, shortness of breath, dizziness, tiredness, loss of appetite, nervousness and bruising.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor	
		Only if severe	In all cases
Common (occurring between 1 and 10 of every 100 patients)	Allergic reactions		✓
	Black tarry stools		✓
	High fever		✓
	Infections		✓
	Prolonged pauses in breathing during sleep		✓
Uncommon (occurring between 1 and 10 of every 1000 patients)	Difficulty breathing		✓
	Hives or swelling beneath the skin		✓
	Rapid heart rate		✓
	Unusual vaginal bleeding (hemorrhage)		✓
	Vomiting of blood		✓
Rare (occurring between 1 and 10 of every 10,000 patients)	Skin or mucous membrane reactions		✓

This is not a complete list of side effects. If you have any unexpected effects after receiving ZEVALIN, contact your doctor.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online:	www.healthcanada.gc.ca/medeffect
Call toll-free at:	1-866-234-2345
Complete a Canada Vigilance Reporting Form and:	
Fax toll-free to:	1-866-678-6789, or
Mail to:	Canada Vigilance Program Health Canada Postal Locator 0701C Ottawa ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada website at: www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Servier Canada Inc. at: 1-800-363-6093

This leaflet was prepared by Servier Canada Inc.

SERVIER CANADA INC.
235, Boulevard Armand Frappier
Laval, Québec
H7V 4A7

Last revised: March 05, 2020