PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS REGULATIONS (PREPARATIONS) 1986

This medicine can be sold under doctor's prescription only

PEGINTRON® PRE-FILLED PEN
80 mcg, 100 mcg, 120 mcg, 150 mcg
Powder and solvent for solution for S.C. injection

Each pre-filled pen contains:
Peginterferon alfa-2b 80 mcg per 0.5 mL, 100 mcg per 0.5 mL, 120 mcg per 0.5 mL, 150 mcg per 0.5 mL.
Peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol).

For a list of inactive ingredients see section 6.1 "**What PegIntron contains**".
See also section 2.6 "**Important information about some of the ingredients of PegIntron**".

Read all of this leaflet carefully before you start using this medicine.
If you receive combination therapy with ribavirin capsules, carefully read the ribavirin package insert as well.

- Keep this leaflet. You may need to read it again.
- This leaflet contains concise information about **PegIntron**. If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their medical condition seems similar to yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- The medicine **PegIntron** is not intended for patients under 18 years of age.
- Eye disorders may occur (such as: blurred vision, hypersensitivity to light) which might disturb driving. If such eye disorders develops, driving should be avoided.

1. WHAT PEGINTRON IS USED FOR?

The active substance in this medicine is a protein called peginterferon alfa-2b, which belongs to the class of medicines called interferons. Interferons are made by your body’s immune system to help fight infections and severe diseases. This medicine is injected into your body to work with your immune system. This medicine is used for the treatment of chronic hepatitis C, a viral infection of the liver.

The combination of this medicine, ribavirin and boceprevir is recommended for use for some types of chronic hepatitis C virus infection (also called HCV infection) in adults 18 years of age and older. It may be used in adults who have not been previously treated for HCV infection or who have previously used medicines called interferons and pegylated interferons.
The combination of this medicine and ribavirin is recommended for adults 18 years of age and older who have not previously been treated with these medicines. This includes adults also infected with clinically stable HIV (Human Immunodeficiency Virus). The combination can also be used to treat adults who have already failed treatment with an interferon alpha or peginterferon alpha in combination with ribavirin or interferon alpha alone. If you have a medical condition making use of ribavirin dangerous or if you already have had a problem taking it, your doctor will likely prescribe this medicine alone.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

Therapeutic group: Interferons.

2. BEFORE YOU USE PEGINTRON

2.1 Do not use PegIntron:

You should tell your doctor before starting treatment if you:

- are allergic to peginterferon alfa-2b or any of the other ingredients of this medicine (listed in section 6).
- are allergic to any interferon.
- have had severe heart problems.
- have heart disease that has not been well controlled during the past 6 months.
- have severe medical conditions that leave you very weak.
- have autoimmune hepatitis or any other problem with your immune system.
- are taking medicine that suppresses (weakens) your immune system.
- have advanced, uncontrolled liver disease (other than hepatitis C).
- have thyroid disease that is not well controlled with medicines.
- have epilepsy, a condition that causes convulsions (seizures, or “fits”).
- are being treated with telbivudine (see section "2.3 Taking other medicines").

You must not use **PegIntron** if any of the conditions above should apply to you.

Reminder: Please also read the "Do not take" section of the Package Leaflet for ribavirin and boceprevir before using them in combination with this medicine.

2.2 Special warnings and precautions concerning use of PegIntron

Seek medical help immediately in case of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives).

Talk to your doctor before taking this medicine if you:

- have had a severe **nervous or mental disorder**, or have a **history of substance abuse** (e.g. alcohol or drugs).
- are being treated for a **mental illness** or had treatment in the past for any other nervous or mental disorder, including **depression** (such as feelings of sadness, dejection) or **suicidal or homicidal behavior** (see section 4 “**Side effects**”).
- have ever had a **heart attack** or a **heart problem**.
- have **kidney disease**, your doctor may prescribe a lower than usual dose and monitor your kidney blood values regularly during treatment. If this medicine is used in combination with ribavirin, your doctor should monitor you more carefully for a decrease in red blood cell count.
- have **cirrhosis** or other **liver problems** (other than hepatitis C).
- develop symptoms associated with a **cold** or other respiratory infection, such as **fever**, **cough**, or any **difficulty in breathing**.
- are **diabetic** or have **high blood pressure**, your doctor may ask you to have an eye examination.
- have had any serious **illness affecting breathing** or **blood**.
- have the skin disorders, **psoriasis** or **sarcoidosis**, which may become worse while you are using this medicine.
- are planning to become **pregnant**, discuss this with your doctor before starting to use this medicine.
- have received an **organ transplant**, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.
- are also being treated for **HIV** (see section 2.3 "**Taking other medicines**").

Reminder: Please read the “Warnings and precautions” section of the Package Leaflet for ribavirin and boceprevir before using it in combination with this medicine.

Teeth and mouth problems have been reported in patients receiving this medicine in combination with ribavirin. You may develop **gum disease**, which could lead to loss of teeth. You may develop a **dry mouth** or **vomiting**, both of which can damage your teeth. It is important to brush your teeth thoroughly twice a day, rinse your mouth out if you vomit, and have regular dental check-ups.

During treatment, some patients may experience **eye problems**, or loss of vision in rare instances.
Your doctor should carry out an eye examination before starting your treatment. In case of any changes in vision, you must tell your doctor and have a prompt and complete eye examination. If you have a medical condition that may lead to future eye problems (e.g. diabetes or high blood pressure), you should receive regular eye exams during therapy. If your eye disorder becomes more severe or if you develop new eye disorders, your treatment will be discontinued.

While being treated with **PegIntron**, your doctor may advise to drink extra fluids to help prevent low blood pressure.

Your doctor will test your blood before you begin therapy and throughout the treatment to make sure that the therapy you are getting is safe and effective.

2.3 Taking other medicines
If you are taking or have recently taken other medicines including medicines obtained without a prescription and nutritional supplements, inform the doctor of pharmacist. Especially tell your doctor or pharmacist if you:

- are infected with both **Human Immunodeficiency Virus** (HIV-positive) and **Hepatitis C Virus** (HCV) and are being treated with an anti-HIV medicine(s) – [nucleoside reverse transcriptase inhibitor (**NRTI**), and/or highly active anti-retroviral therapy (**HAART**)]. Your doctor will monitor you for signs and symptoms of these conditions.
    - are taking this medicine in combination with ribavirin and an anti-HIV medicine(s), this may increase the risk of lactic acidosis, liver failure, and blood abnormalities: reduction in number of red blood cells, white blood cells and blood clotting cells called platelets. Patients with advanced liver disease receiving HAART may be at increased risk of worsening liver function, therefore adding treatment with this medicine alone or in combination with ribavirin may increase their risk.
    - With **zidovudine** or **stavudin**e, it is not certain if ribavirin will change the way these medicines work. Therefore, blood tests will be performed routinely to be sure that the HIV infection is not getting worse. If it gets worse, your doctor will decide whether or not your ribavirin treatment needs to be changed. Additionally, patients treated with this medicine and ribavirin combination therapy and **zidovudine** could be at increased risk of developing anaemia (low number of red blood cells). Therefore the use of zidovudine with this medicine and ribavirin combination therapy is not recommended.

  Reminder: Please read the "**Taking other medicines**" section of the Package Leaflet for **ribavirin** before using it in combination with this medicine.
- are taking **telbivudine**. If you take **telbivudine** with this medicine or any other type of injectable interferon, your risk of developing peripheral neuropathy (numbness, tingling and/or burning sensations in the arms and/or legs) is higher. These events may also be more severe. Therefore, you must not take this medicine at the same time as telbivudine.

2.4 Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

<u>Pregnancy</u>
In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect of this medicine on human pregnancy is not known. Girls or women of childbearing potential need to use effective birth control during the treatment with this medicine.
Ribavirin can be very damaging to an unborn baby. Therefore, you and your partner must take **special precautions** in sexual activity if there is any chance for pregnancy to occur:

- if you are a **woman** of childbearing age who is taking ribavirin:

you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You must use an effective birth control during the time you are taking ribavirin and for 4 months after stopping treatment. This should be discussed with your doctor.

- if you are a **man** who is taking ribavirin:

do not have sex with a pregnant woman unless you **use a condom**. If your female partner is not pregnant but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. You or your partner must use an effective birth control during the time you are taking ribavirin and for 7 months after stopping treatment. This should be discussed with your doctor.

Breast-feeding

It is not known whether this medicine is present in human milk. Therefore, you should not **breast-feed** an infant if you are taking this medicine. Ask your doctor for advice.

Reminder: Please read the “Pregnancy and breast-feeding” section of the Package Leaflet for **ribavirin** before using it in combination with this medicine.

2.5 Driving and using machines

Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking this medicine.

2.6 Important information about some of the ingredients of PegIntron

This medicine contains sucrose. If you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

3. HOW TO USE PEGINTRON?

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

General information about taking this medicine

Your doctor has determined the correct dose of this medicine based on how much you weigh. If necessary, the dose may be changed during treatment.

This medicine is intended for subcutaneous use. This means that it is injected through a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. **Detailed instructions for subcutaneous administration are provided in the Addendum to the patient leaflet "How to use the PegIntron pre-filled pen"**.

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the solution you prepared before you use it. The solution should be clear and colourless. Do not use the solution if it is discoloured (changed its colour from the original) or if there are bits of particles in the solution. Discard the **PegIntron** pre-filled pen with any solution that is left in it after you give yourself the injection. For disposal instructions, see section 5 "**How to store PegIntron**".

Inject this medicine once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Always use this medicine exactly as your doctor has told you. Do not exceed the recommended dosage, and take it for as long as prescribed.

If your doctor prescribes this medicine with ribavirin or with ribavirin and boceprevir, please read the Package Leaflets of ribavirin and boceprevir before you begin combination treatment.

PegIntron in combination treatment

This medicine, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram per kilogram of body weight once a week. If you have kidney disease, your dose may be lower, depending upon your kidney function.

PegIntron alone
This medicine, when given alone, is usually given at a dose of 0.5 or 1.0 microgram per kilogram of body weight once a week, for 6 months to 1 year. If you have kidney disease, your dose may be lower, depending upon your kidney function. Your doctor will determine the correct dose for you.

All patients
If you are injecting this medicine yourself, please be sure that the dose that has been prescribed is clearly provided on the package of medicine you receive.

If you use more PegIntron than you should
Tell your doctor or healthcare professional as soon as possible.
If you have taken an overdose, or if a child has accidentally swallowed the medicine, proceed immediately to a hospital emergency room and bring the package of the medicine with you.

If you forget to take PegIntron
Take/administer the dose of this medicine as soon as you remember, but only if within 1-2 days after the forgotten dose. If it is very close to your next injection, do not double the dose to make up for the forgotten dose, but continue your treatment as usual.
If you are uncertain, contact your doctor or pharmacist.

Complete the full course of treatment as instructed by the doctor.
Even if there is an improvement in your health, do not discontinue use of this medicine before consulting your doctor.

How can you contribute to the success of the treatment?
Do not take medicines in the dark! Check the label and the dose each time you take your medicine. Wear glasses if you need them.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. SIDE EFFECTS

Like all medicines, the use of **PegIntron** can cause side effects in some of the users. Do not be alarmed by reading these side effects, you may not suffer from any of them.
When this medicine is used alone, some of these effects are less likely to occur, and some have not occurred at all.

Psychiatric side effects and central nervous system effects:
Some people get depressed when taking this medicine alone or in combination treatment with ribavirin, and in some cases people have had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. Ask a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Contact your doctor immediately if you notice any of the following serious side effects occurring during treatment:

Very common side effects (may affect more than 1 in 10 people):
- breathing problems (including shortness of breath),

- feeling depressed,
- trouble sleeping, thinking or concentrating, dizziness,
- severe stomach pain or cramps,
- fever, or chills beginning after a few weeks of treatment,
- painful or inflamed muscles (sometimes severe),

Common side effects (may affect up to 1 in 10 people):
- chest pain, changes in the way your heart beats,
- confusion,
- difficulty remaining alert, numbness or tingling feeling,
- pain in your lower back or side, difficulty or inability to pass urine,
- problems with your eyes or your eyesight or hearing,
- severe or painful reddening of your skin or mucous membrane,
- severe bleeding from your nose, gums or any other part of your body,

Uncommon side effects (may affect up to 1 in 100 people):
- wanting to harm yourself,
- hallucinations,

Rare side effects (may affect up to 1 in 1,000 people):
- convulsion ("fit"),
- blood or clots in stool (or black, tarry stool),

Unknown frequency side effects (frequency cannot be estimated from the available data):
- Wanting to harm others.

Other side effects that have been reported **in adults** include:

Very common side effects (may affect more than 1 in 10 people):
- feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings,
- headache, dizziness, tired feeling, shaking chills, fever, flu-like symptoms, virus infection, weakness,
- difficult breathing, pharyngitis (sore throat), coughing,
- stomach pain, vomiting, nausea, diarrhea, loss of appetite, loss of weight, dry mouth,
- hair loss, itching, dry skin, rash, irritation or redness (and rarely, skin damage) at the site of injection,
- decreases in the number of red blood cells (that may cause fatigue, shortness of breath, dizziness), decrease in certain white blood cells (that makes you more susceptible to different infections),
- pain in joints and muscles, muscle and bone pain.

Common side effects (may affect up to 1 in 10 people):
- decrease in blood clotting cells called platelets, that may result in easy bruising and spontaneous bleeding, excess of uric acid (as in gout) in the blood, low calcium level in the blood,
- decrease in thyroid gland activity (which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms), increase in thyroid gland activity (which may cause nervousness, heat intolerance and excessive sweating, weight loss, palpitation, tremors), swollen glands (swollen lymph nodes), thirst,
- changed behaviour or aggressive behaviour (sometimes directed against others), agitation, nervousness, feeling sleepy, trouble sleeping, unusual dreams, lack of interest in activities, lack of interest in sex, erectile problem, increased appetite, confusion, shaky hands, poor coordination, vertigo (spinning feeling), numbness, pain or tingling feeling, increased or decreased sensitivity to touch, tense muscles, limb pain, arthritis, migraine, increased sweating,
- eye pain or infection, blurred vision, dry or teary eyes, changes in hearing/loss of hearing, ringing in ears,

- sinusitis, respiratory infections, stuffy or runny nose, difficulty in speaking, nosebleed, cold sores (herpes simplex), fungal or bacterial infections, ear infection/earache,
- indigestion (stomach upset), heartburn, redness or sores in mouth, burning sensation on tongue, red or bleeding gums, constipation, intestinal gas (flatus), bloating, hemorrhoids, sore tongue, change in taste, tooth problem, excessive loss of body water, enlarged liver,
- psoriasis, sensitivity to sunlight, rash with raised spotted lesions, redness of skin or skin disorders, puffy face, puffy hands or feet, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), acne, hives, abnormal hair texture, nail disorder, pain at the site of injection,
- difficult, irregular or no menstrual period, abnormally heavy and prolonged menstrual period, problem affecting ovary or vagina, pain in breast, sexual problem, irritation of prostate gland, increased need to pass urine,
- chest pain, pain on the right side around your ribs, feeling unwell, low or high blood pressure, feeling faint, flushing, palpitations (pounding heart beat), rapid heart rate.

Uncommon side effects (may affect up to 1 in 100 people):
- suicide, attempted suicide, thoughts about threatening the life of yourself, panic attack, delusions, hallucination,
- hypersensitivity reaction to the medication, heart attack, inflammation of the pancreas, pain in bone and diabetes mellitus,
- cotton wool spots (white deposits on the retina).

Rare side effects (may affect up to 1 in 1,000 people):
- diabetic ketoacidosis (medical emergency due to build-up of ketone bodies in the blood as a result of out-of-control diabetes),
- seizures (convulsions) and bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement),
- eye problems including changes in vision, damage to the retina, obstruction of the retinal artery, inflammation of the optic nerve, swelling of the eye,
- congestive heart failure, abnormal heart rhythm, pericarditis (inflammation of the lining of the heart), inflammation and degeneration of muscle tissue and peripheral nerves, kidney problems,
- sarcoidosis (a disease characterized by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands).

Very rare side effects (may affect up to 1 in 10,000 people):
- aplastic anaemia, stroke (cerebrovascular events), toxic epidermal necrolysis/Stevens Johnson Syndrome/erythema multiforme (a spectrum of rashes with varying degree of severity including death which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes and sloughing of the affected area of the skin).
- loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses.

Side effects of unknown frequency (frequency cannot be estimated from the available data):
- pure red cell aplasia (a condition where the body stopped or reduced the production of red blood cells). This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.
- facial palsy (weakness and slumping on one side to the face), severe allergic reactions such as angioedema (an allergic skin disease characterized by patches of swelling involving the skin and its subcutaneous layers, the mucous membranes, and sometimes the internal organs), mania (excessive or unreasonable enthusiasm), pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself), Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), change in colour of the tongue.
- thoughts about threatening the life of others.

- pulmonary fibrosis (scarring of the lungs).
- pulmonary arterial hypertension – a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. This may occur in particular in patients with risk factors such as HIV infection or severe liver problems (cirrhosis). The side effect may develop at various time points during treatment, typically several months after starting treatment with **PegIntron**.

If you suffer from **HCV/HIV co-infection and you are receiving HAART**, adding this medicine to existing treatment may increase your risk of lactic acidosis, liver failure, and development of blood abnormalities (reduction in number of red blood cells which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).

The following other side effects (not listed above) have occurred with the combination of this medicine and ribavirin capsules in HCV/HIV co-infected patients receiving HAART:
- oral candidiasis (oral thrush),
- defective metabolism of fat,
- CD4 lymphocytes decreased,
- appetite decreased,
- back pain,
- hepatitis,
- limb pain,
- and various laboratory blood values abnormalities.

If any of the side effects gets serious or if you suffer from a side effect not mentioned in this leaflet, consult your doctor.

Reminder to patients prescribed combination therapy of this medicine, boceprevir and ribavirin:
Please read the "Possible side effects" section of these Package Leaflets.

Side effects can be reported to the Ministry of Health by using the online form for adverse events reporting which is on the Ministry of Health Homepage: **www.health.gov.il**
or by following the link:
https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

5. HOW TO STORE PEGINTRON?

- Avoid Poisoning! This medicine, as all other medicines, must be stored in a safe place out of the reach and sight of children and/or infants, in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by a doctor!
- Do not use **PegIntron** after the expiry date (exp. date) which is stated on the pack. The expiry date refers to the last day of the indicated month.
- Store in the refrigerator at a temperature of 2°C-8°C. Do not freeze.
- After reconstitution, use the reconstituted solution immediately or within 24 hours if stored in a refrigerator at a temperature of 2°C-8°C.
- Do not use this medicine if you notice discolouration of the powder, which should be white. The reconstituted solution should be clear and colourless. Do not use if it is discoloured or if bits of particles are present. After administering the dose, discard the **PegIntron** pre-filled pen and any unused solution contained in it.
- Do not throw away medicines via wastewater or household waste. Dispose of the used pre-filled pen safely in a closed container. Ask your healthcare provider or pharmacist for an appropriate container. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. FURTHER INFORMATION

6.1 What PegIntron contains

- The active substance is peginterferon alfa-2b.
- Each pre-filled pen contains: Peginterferon alfa-2b 80 mcg per 0.5 mL, 100 mcg per 0.5 mL, 120 mcg per 0.5 mL, 150 mcg per 0.5 mL.
- The other ingredients are:
  Powder: Sodium phosphate dibasic anhydrous, sodium phosphate monobasic dihydrate, sucrose, polysorbate 80.
  Solvent: Water for injection

6.2 What PegIntron looks like and contents of the pack

This medicine is a powder and solvent (liquid) for solution for injection in a pre-filled pen (REDIPEN).
The white powder and the clear and colourless solvent are both contained in a two-chamber glass cartridge assembled into a single use pre-filled pen.

Contents of pack: 1 pre-filled pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs.

6.3 Marketing authorization holder

Merck, Sharp & Dohme (Israel-1996) Company Ltd., P.O.Box 7121, Petah-Tikva 49170.

6.4 Manufacturer

Schering-Plough Labo N.V., Heist-op-den-Berg, Belgium.

This Leaflet was checked and approved by the Ministry of Health on March 2016.

Drug registration no. listed in the official registry of the Ministry of Health:

PegIntron pre-filled pen 80 mcg 130.34.30856.00
PegIntron pre-filled pen 100 mcg 130.35.30857.00
PegIntron pre-filled pen 120 mcg 130.36.30858.00
PegIntron pre-filled pen 150 mcg 130.37.30859.00