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

This medicine can be sold under doctor's prescription only

REBETOL®

200 mg
Capsules

Each capsule contains:
Ribavirin 200 mg

For a list of inactive ingredients see section 6.1 "What **Rebetol** contains". See also section 2.7 “Important information about some of the ingredients of **Rebetol".**

Read all of this leaflet carefully before you start taking this medicine.

- This leaflet contains concise information about **Rebetol.** 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.
- This medicine is intended for adult patients. This medicine is not intended for children and adolescents under 18 years of age.

1. WHAT REBETOL IS AND WHAT IT IS USED FOR?

Rebetol capsules contain the active substance ribavirin. This medicine stops the multiplication of many types of viruses, including hepatitis C virus. **Rebetol** capsules are intended to treat patients 18 years of age or older who have chronic hepatitis C.
This medicine must not be used without peginterferon alfa-2b or interferon alfa-2b, i.e. **Rebetol** must not be used alone.

Depending on the genotype of the hepatitis C virus that you have, your doctor may choose to treat you with a combination of this medicine with boceprevir and peginterferon alfa-2b (tritherapy).
Adult patients without genotype 1, can only use peginterferon alfa-2b or interferon alfa-2b and this medicine (bitherapy).
There may be some further treatment limitations if you have or have not been previously treated for chronic hepatitis C infection. Your doctor will recommend the best course of therapy.

The combination of this medicine and peginterferon alfa-2b is used to treat previously untreated adult patients who have chronic hepatitis C (HCV) infection and who are co-infected with clinically stable HIV.

There is no safety or efficacy information on the use of **Rebetol** with other forms of interferon (i.e., not alfa-2b).

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

Therapeutic group: guanosine analog.

2. BEFORE YOU USE REBETOL

This medicine is not intended for use in patients under the age of 18 years.

2.1 Do not take Rebetol if you:

Do not take Rebetol
If any of the following apply to you, **do not take** this medicine, and **tell your doctor** if you:

- are allergic to ribavirin or any of the other ingredients of this medicine (listed in section 6).
- are pregnant or planning to become pregnant (see section 2.5 “Pregnancy, breast-feeding and fertility”).
- are breast-feeding.
- had a problem with your heart during the past 6 months.
- have severe medical conditions that leave you very weak.
- have severe kidney disease and/or are on haemodialysis.
- have a serious problem with your liver other than chronic hepatitis C.
- have any blood disorders, such as anaemia (low blood count), thalassemia, sickle-cell anaemia.
- have autoimmune hepatitis or any other problem with your immune system.
- are taking medicine that suppresses your immune system (that protects you against infection and some diseases).

Reminder: Please read the “Do not take” section of the Package Leaflets for boceprevir, peginterferon alfa-2b or interferon alfa-2b before you begin using them with this medicine.

2.2 Special warnings concerning use of Rebetol

Seek medical help **immediately** if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing or hives) while taking this treatment.

Before starting treatment with Rebetol, tell your doctor if you:

- are an adult who has or had a severe nervous or mental disorder, confusion, unconsciousness, or have had thoughts of suicide or have attempted suicide, or have a history of substance abuse (e.g., alcohol or drugs).
- have ever had depression or develop symptoms associated with depression (e.g. feeling of sadness, dejection, etc.) while on treatment with this medicine (see section 4 “Side effects”).
- are a woman of childbearing age (see section 2.5 “Pregnancy, breast-feeding and fertility”).
- are a male and your female partner is of childbearing age (see section 2.5 “Pregnancy, breastfeeding and fertility”).
- had a previous serious heart condition or have cardiac disease.
- are older than 65 years or if you have problems with your kidneys.
- have or have had any serious illness.
- have thyroid problems.

During treatment with this medicine in combination therapy with an alfa interferon, dental and gum disorders, which may lead to loss of teeth, have been reported. In addition, dry mouth that could have a damaging effect on teeth and membranes of the mouth has been reported during long-term treatment with this medicine in combination therapy with an alfa interferon. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

During treatment with **Rebetol** in combination therapy with an alfa interferon, patients may experience eye problems, or loss of vision in rare instances. If you receive ribavirin in combination with an alfa interferon, you should have a baseline eye examination. Any patient complaining of decrease or loss of vision must have a prompt and complete eye examination. Patients with preexisting

eye disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic eye exams during combination therapy with ribavirin and an alfa interferon. Combination therapy with ribavirin and an alfa interferon should be discontinued in patients who develop new or worsening eye disorders.

Reminder: Please read the “Warnings and precautions” section of the Package Leaflets for boceprevir, peginterferon alfa-2b or interferon alfa-2b before you begin combination treatment.

2.3 Taking other medicines

If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, you should tell the attending doctor or pharmacist.

Especially inform your doctor or pharmacist if you:

- are receiving azathioprine in combination with ribavirin and pegylated alfa interferons and, therefore may be at an increased risk of developing severe blood disorders.
- are infected with both Human Immunodeficiency Virus (HIV-positive) and Hepatitis C Virus (HCV) and are being treated with an anti-HIV medicinal product(s) - [nucleoside reverse transcriptase inhibitor (NRTI), and/or highly active anti-retroviral therapy (HAART)]:
    - Taking this medicine in combination with an alfa interferon and an anti-HIV medicinal product(s) may increase the risk of lactic acidosis, liver failure, and blood abnormalities development (reduction in number of red blood cells which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).
    - With zidovudine or stavudine, it is not certain if this medicine will change the way these medicines work. Therefore, your blood will be checked regularly to be sure that the HIV infection is not getting worse. If it gets worse, your doctor will decide whether or not your **Rebetol** treatment needs to be changed. Additionally, patients receiving zidovudine with ribavirin in combination with alfa interferons could be at increased risk of developing anaemia (low number of red blood cells). Therefore the use of zidovudine and ribavirin in combination with alfa interferons is not recommended.
    - Due to the risk of lactic acidosis (a build-up of lactic acid in the body) and pancreatitis, the use of ribavirin and didanosine is not recommended and the use of ribavirin and stavudine should be avoided.
    - Co-infected patients with advanced liver disease receiving HAART may be at increased risk of worsening liver function. Adding treatment with an alfa interferon alone or in combination with ribavirin may increase the risk in this patient subset.

Reminder: Please read the “Taking other medicines” section of the Package Leaflet for peginterferon alfa-2b, interferon alfa-2b, or boceprevir before you begin combination treatment with this medicine.

2.4 Taking Rebetol with food and drink

Rebetol must be taken with food (see section 3 “How to use **Rebetol**”).

2.5 Pregnancy, breast-feeding and fertility

If you are pregnant, you must not take this medicine. This medicine can be very damaging to your unborn baby (embryo).

Both female and male patients must take **special precautions** in their sexual activity if there is any possibility for pregnancy to occur:

- **Woman of childbearing age:**
  You must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. This should be discussed with your doctor.
- **Men:**
  Do not have sex with a pregnant woman unless you use a condom. This will lessen the possibility for ribavirin to be left in the woman’s body.

If your female partner is not pregnant now 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 female partner must use an effective contraceptive during the time you are taking this medicine and for 7 months after stopping treatment. This should be discussed with your doctor (see section 2.1 “Do not take **Rebetol**”).

If you are a woman who is breast-feeding, you must not take this medicine. Discontinue breastfeeding before starting to take this medicine.

2.6 Driving and using machines
This medicine does not affect your ability to drive or use machines; however, boceprevir, peginterferon alfa-2b or interferon alfa-2b may affect your ability to drive or use machines. Therefore, do not drive or use machines if you become tired, sleepy, or confused from this treatment.

2.7 Important information about some of the ingredients of Rebetol
Each capsule contains a small amount of lactose.
If you have been told by your doctor that you have an intolerance to some sugars, discuss with your doctor before taking this medicinal product. See also section 6.1 "What **Rebetol** contains".

3. HOW TO USE REBETOL?
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
Do not take more than the recommended dosage and take the medicine for as long as prescribed.
Your doctor has determined the correct dose of this medicine based on how much you weighs.

Standard blood tests will be taken to check your blood, kidney and liver function.
- Blood tests will be done regularly to help your doctor to know if this treatment is working.
- Depending upon the results of these tests, your doctor may change/adjust the number of hard capsules you take and/or change the length of time to take this treatment.
- If you have or develop severe kidney or liver problems, this treatment will be stopped.

The recommended dose of this medicine, according to how much the patient weighs, is shown in the table below:
1. Look for the line that shows how much the adult weighs.
2. Read across on the same line to see how many hard capsules to take.
   Reminder: If your doctor’s instructions are different from the amounts in the below table, follow your doctor’s instructions.
3. If you have any questions about the dose, ask your doctor.

Rebetol hard capsule for oral use - dose based on body weight		
If the **adult** weighs (kg)	Usual daily **Rebetol** dose	Number of 200 mg capsules
< 65	800 mg	2 capsules in the morning and 2 capsules in the evening
65 – 80	1,000 mg	2 capsules in the morning and 3 capsules in the evening
81 - 105	1,200 mg	3 capsules in the morning and 3 capsules in the evening
> 105	1,400 mg	3 capsules in the morning and 4 capsules in the evening

Take your prescribed dose by mouth with water and during your meal. Do not chew the hard capsules.

Reminder: This medicine is used in combination with peginterferon alfa-2b, interferon alfa-2b or boceprevir for hepatitis C virus infection. For complete information be sure to read the “How to use” section of the Package Leaflet for peginterferon alfa-2b, interferon alfa-2b or boceprevir.

Interferon medicine that is used in combination with this medicine may cause unusual tiredness; if you are injecting this medicine yourself, use it at bedtime.

This medicine is not intended for children under 18 years old.

Examinations and monitoring
Before starting treatment with **Rebetol** in combination with an alfa interferon, the doctor will refer you to an eye examination (see section 2.2 "Special warnings concerning use of **Rebetol**").
During treatment with **Rebetol** in combination with an alfa interferon, blood tests will be done regularly, you should have regular dental examinations and you may additionally be referred to periodic eye exams (see section 2.2 "Special warnings concerning use of **Rebetol**" and section 3 "How to use **Rebetol**?").

Woman of childbearing age:
You must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped
Men:
If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. (see section 2.5 "Pregnancy, breast-feeding and fertility").

If you take more Rebetol than you should
Tell your doctor or pharmacist 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 Rebetol
If you are self-administering treatment in combination with interferon alfa-2b, peginterferon alfa-2b or boceprevir, take/administer the missed dose as soon as possible during the same day. If an entire day has gone by, check with your doctor. Do not take a double dose to make up for a forgotten dose.

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
Please read the "Side effects" section of the Package Leaflet for boceprevir, peginterferon alfa-2b or interferon alfa-2b.

Like all medicines, **Rebetol** used in combination with an alfa interferon product can cause side effects, in some of the users.

Do not be alarmed by reading the list of side effects, you may not suffer from any of them. Although not all of these unwanted effects may occur, they may need medical attention if they do occur.

Psychiatric and Central Nervous System:
Some people get depressed when taking this medicine in combination treatment with an interferon, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking 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 side effects occurring during combination treatment with an alpha interferon product:

- chest pain or persistent cough; changes in the way your heart beats, fainting,
- confusion, feeling depressed; suicidal thoughts or aggressive behaviour, attempt suicide, thoughts about threatening the life of others,
- feelings of numbness or tingling,
- trouble sleeping, thinking or concentrating,
- severe stomach pain, black or tar-like stools, blood in stool or urine, lower back or side pain,
- painful or difficult urination,
- severe bleeding from your nose,
- fever or chills beginning after a few weeks of treatment,
- problems with your eyesight or hearing**,**
- severe skin rash or redness.

Possible side effects listed below are grouped by frequency of occurrence:
Very common (may affect more than 1 in 10 people)
Common (may affect up to 1 in 10 people)
Uncommon (may affect up to 1 in 100 people)
Rare (may affect up to 1 in 1,000 people)
Very rare (may affect up to 1 in 10,000 people)
Not known (frequency cannot be estimated from the available data)

The following side effects have been reported with the combination of this medicine hard capsules and an alfa interferon product **in adults**:

Very commonly reported side effects:

- decreases in the number of red blood cells (that may cause fatigue, shortness of breath, dizziness), decrease in neutrophils (that make you more susceptible to different infections),
- difficulty concentrating, feeling anxious or nervous, mood swings, feeling depressed or irritable, tired feeling, trouble falling asleep or staying asleep,
- cough, dry mouth, pharyngitis (sore throat),
- diarrhoea, dizziness, fever, flu-like symptoms, headache, nausea, shaking chills, virus infection, vomiting, weakness,
- loss of appetite, loss of weight, stomach pain,
- dry skin, irritation, pain or redness at the site of injection, hair loss, itching, muscle pain, muscle aches, pain in joints and muscles, rash.

Commonly reported side effects:

- decrease in blood clotting cells called platelets that may result in easy bruising and spontaneous bleeding, decrease in certain white blood cells called lymphocytes that help fight infection,

decrease in thyroid gland activity (which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms), excess of sugar or uric acid (as in gout) in the blood, low calcium level in the blood, severe anaemia,

- fungal or bacterial infections, crying, agitation, amnesia, memory impaired, nervousness, abnormal behaviour, aggressive behaviour, anger, feeling confused, lack of interest, mental disorder, mood changes, unusual dreams, wanting to harm yourself, feeling sleepy, trouble sleeping, lack of interest in sex or inability to perform, vertigo (spinning feeling),
- blurred or abnormal vision, eye irritation or pain or infection, dry or teary eyes, changes in your hearing or voice, ringing in ears, ear infection, earache, cold sores (herpes simplex), change in taste, taste loss, bleeding gums or sores in mouth, burning sensation on tongue, sore tongue, inflamed gums, tooth problem, migraine, respiratory infections, sinusitis, nose bleed, nonproductive cough, rapid or difficult breathing, stuffy or runny nose, thirst, tooth disorder,
- cardiac murmur (abnormal heart beat sounds), chest pain or discomfort, feeling faint, feeling unwell, flushing, increased sweating, heat intolerance and excessive sweating, low or high blood pressure, palpitations (pounding heart beat), rapid heart rate,
- bloating, constipation, indigestion, intestinal gas (flatus), increased appetite, irritated colon, irritation of prostate gland, jaundice (yellow skin), loose stools, pain on the right side around your ribs, enlarged liver, stomach upset, frequent need to urinate, passing more urine than usual, urinary tract infection, abnormal urine,
- difficult, irregular, or no menstrual period, abnormally heavy and prolonged menstrual periods, painful menstruation, disorder of ovary or vagina, breast pain, erectile problem,
- abnormal hair texture, acne, arthritis, bruising, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), hives, increased or decreased sensitivity to touch, nail disorder, muscle spasms, numbness or tingling feeling, limb pain, pain at the site of injection, pain in joints, shaky hands, psoriasis, puffy or swollen hands and ankles, sensitivity to sunlight, rash with raised spotted lesions, redness of skin or skin disorder, swollen face, swollen glands (swollen lymph nodes), tense muscles, tumour (unspecified), unsteady when walking, water impairment.

Uncommonly reported side effects:

- hearing or seeing images that are not present (hallucinations),
- heart attack, panic attack,
- hypersensitivity reaction to the medication,
- inflammation of pancreas, pain in bone, diabetes mellitus,
- muscle weakness.

Rarely reported side effects:

- seizure (convulsions)
- pneumonia,
- rheumatoid arthritis, kidney problems,
- dark or bloody stools, intense abdominal pain
- sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands),
- vasculitis.

Very rarely reported side effects:

- suicide,
- stroke (cerebrovascular events).

Not known side effects:

- thoughts about threatening the life of others,
- mania (excessive or unreasonable enthusiasm),
- pericarditis (inflammation of the lining of the heart), pericardial effusion [a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself,

- change in colour of the tongue.

The attempt to harm yourself has also been reported in adults, children, and adolescents.

This medicine in combination with an alpha interferon product may also cause:
- aplastic anaemia, 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,
- delusions,
- upper and lower respiratory tract infection,
- inflammation of the pancreas,
- severe rashes which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes (erythema multiforme, Stevens Johnson syndrome), toxic epidermal necrolysis (blistering and peeling of the top layer of skin).

The following other side effects have also been reported with the combination of this medicine and an alpha interferon product:
- abnormal thoughts, hearing or seeing images that are not present (hallucinations), altered mental status, disorientation,
- angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing),
- Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord),
- bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction), constant cough,
- eye problems including damage to the retina, obstruction of the retinal artery, inflammation of the optic nerve, swelling of the eye and cotton wool spots (white deposits on the retina),
- enlarged abdominal area, heartburn, trouble having bowel movement or painful bowel movement,
- acute hypersensitivity reactions including urticaria (hives), bruises, intense pain in a limb, leg or thigh pain, loss of range of motion, stiffness, sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands).

This medicine in combination with peginterferon alfa-2b or interferon alfa-2b may also cause:
- dark, cloudy or abnormally coloured urine,
- difficulty breathing, changes in the way your heart beats, chest pain, pain down left arm, jaw pain,
- loss of consciousness,
- loss of use, drooping or loss of power of facial muscles, loss of feeling sensation,
- loss of vision.

You or your caregiver should call your doctor immediately if you have any of these side effects.

If you are a HCV/HIV co-infected adult patient receiving anti-HIV treatment, the addition of this medicine and peginterferon alfa-2b may increase your risk of worsening liver function (highly active anti-retroviral therapy (HAART)) and increase your risk of lactic acidosis, liver failure, and blood abnormalities development (reduction in number of red blood cells which carry oxygen, certain white

blood cells that fight infection, and blood clotting cells called platelets) (NRTI).
In HCV/HIV co-infected patients receiving HAART, the following other side effects have occurred with the combination of **Rebetol** hard capsules and peginterferon alfa-2b (not listed above):

- appetite decreased,
- back pain,
- CD4 lymphocytes decreased,
- defective metabolism of fat,
- hepatitis,
- limb pain,
- oral candidiasis (oral thrush),
- various laboratory blood values abnormalities.

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

Reminder to patients prescribed combination therapy of this medicine, boceprevir and peginterferon alpha-2b: Please read also the “side effects” section of the Package Leaflet of boceprevir for side effects that have been reported with tritherapy.

5. HOW TO STORE REBETOL?

- 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 **Rebetol** after the expiry date (exp. date) which is stated on the pack. The expiry date refers to the last day of the indicated month.
- Do not use this medicine without advice of your doctor or pharmacist if you notice any change in the appearance of the hard capsules.
- **Storage conditions**: Store below 25°C.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

6.1 What Rebetol contains

- The active substance is ribavirin.
- Each capsule contains 200 mg of ribavirin**.**
- In addition to the active ingredient the medicine also contains inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate.
  The capsule shell contains gelatin, titanium dioxide and sodium lauryl sulfate (used as a manufacturing aid, at very low levels).
  The capsule shell imprint contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution and colouring agent (FD&C aluminum lake).
- Each capsule contains 40 mg of lactose monohydrate, see also section 2.7 “Important information about some of the ingredients of **Rebetol".**

6.2 What Rebetol looks like and contents of the pack

This medicine is a white, opaque, hard capsule imprinted with blue ink.

This medicine is available in different pack sizes containing 70, 84, 140 or 168 capsules of 200 mg to be swallowed.
Not all pack sizes may be marketed.
Your physician will prescribe the pack size which is best for you.

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 January 2015.

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116-93-29850-01