Package leaflet: Information for the user

Rebetol® 40 mg/mL oral solution
ribavirin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

This Package Leaflet contains information for the paediatric patient (child or adolescent, 3 through 17 years of age), or for his or her parent or caregiver.

1. What Rebetol is and what it is used for

Rebetol contains the active substance ribavirin. This medicine stops the multiplication of hepatitis C virus. Rebetol must not be used alone.

The combination of Rebetol and other medicines is used to treat patients who have chronic hepatitis C (HCV).
Rebetol may be used in paediatric patients (children 3 years of age and older and adolescents), who are not previously treated and without severe liver disease.

2. What you need to know before you use Rebetol

Do not take Rebetol
Do not take Rebetol if any of the following apply to you or the child you are caring for.

If you are not sure, **talk to your doctor** or **pharmacist** before taking Rebetol.
- 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 “Pregnancy and breast-feeding”).
- are **breast-feeding**.
- had a serious **heart** problem during the past 6 months.
- have any **blood disorder**s, such as anaemia (low blood count), thalassemia, sickle-cell anaemia.

Reminder: Please read the “Do not take” section of the Package Leaflet for the other medicines used in combination with this medicine.

Warnings and precautions
There are several serious adverse reactions associated with the combination therapy of ribavirin with (peg)interferon alfa. These include:

- Psychiatric and central nervous system effects (such as depression, suicidal thoughts, attempted suicide and aggressive behaviour, etc.). 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
- Severe eye disorders
- Dental and periodontal disorders: Dental and gum disorders have been reported in patients receiving Rebetol in combination with (peg)interferon alfa-2b. 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
- Inability to achieve full adult height may occur in some children and adolescents
- Increased hormone related to your thyroid (TSH) in children and adolescents

Paediatric population
If you are caring for a child and your doctor decides not to defer combination treatment with peginterferon alfa-2b or interferon alfa-2b until adulthood, it is important to understand that this combination therapy induces a growth inhibition that may be irreversible in some patients.

In addition these events have occurred in patients taking Rebetol:
Haemolysis: Rebetol can cause a break down in red blood cells causing anaemia which may impair your heart function or worsen symptoms of heart disease.
Pancytopenia: Rebetol can cause a decrease in your platelet and red and white blood cell count when used in combination with peginterferon.

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 or the child you are caring for take, prescribe a different pack size of this medicine, 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.

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.

Talk to your doctor if you or the child you are caring for:

- are a woman of **childbearing** age (see section "Pregnancy and breast-feeding").
- are a **male** and your female partner is of childbearing age (see section "Pregnancy and breast-feeding").
- had a previous **heart** condition or have heart disease.
- have another **liver** problem in addition to hepatitis C infection.
- have problems with your **kidneys**.
- have **HIV** (human immunodeficiency virus) or have ever had any other problems with your immune system.

Please refer to the Package Leaflet of (peg)interferon alfa for more detailed information on these safety issues.

Reminder: Please read the "Warnings and precautions" section of the Package Leaflet for the other medicines used in combination with Rebetol before you begin combination treatment.

Other medicines with Rebetol
Tell your doctor or pharmacist if you or the child you are caring for are taking, have recently taken or might take:

- azathioprine is a medicine that suppresses your immune system, using this medicine in combination with Rebetol may increase your risk of developing severe blood disorders.
- anti-Human Immunodeficiency Virus (HIV) medicines - [nucleoside reverse transcriptase inhibitor (**NRTI**), and/or combined anti-retroviral therapy (**cART**)]:
  - Taking this medicine in combination with an alpha interferon and an anti-HIV medicine 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 alpha 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 alpha 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 cART may be at increased risk of worsening liver function. Adding treatment with an alpha interferon alone or in combination with ribavirin may increase the risk in this patient subset.

Reminder: Please read the "Other medicines" section of the Package Leaflet for the other medicines used in combination with Rebetol before you begin combination treatment with this medicine.

Pregnancy and breast-feeding
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:

- **Girl** or **woman** of childbearing age:
  You must have a negative pregnancy test before treatment, each month during treatment, and for the 9 months after treatment is stopped. You must use effective contraception during your treatment and for 9 months after the last dose. 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 6 months after treatment has stopped.
  You or your female partner must use an effective contraceptive during the time you are taking Rebetol and for 6 months after stopping treatment. This should be discussed with your doctor (see section "Do not take Rebetol").

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

Driving and using machines
This medicine does not affect your ability to drive or use machines; however, other medicines used in combination with Rebetol 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.

Rebetol contains benzyl alcohol (E 1519)

This medicine contains 0.5 mg of benzyl alcohol per mL.
Benzyl alcohol may cause allergic reactions.
Ask your doctor or pharmacist for advice if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

Rebetol contains propylene glycol (E 1520)
This medicine contains 100.3 mg propylene glycol in each mL.

Rebetol contains sodium
This medicine contains up to 23.8 mg sodium (main component of cooking / table salt) in each daily dose. This is equivalent to 1.19 % of the recommended maximum daily dietary intake of sodium for an adult.

Rebetol contains sodium benzoate (E 211)
This medicine contains 1 mg sodium benzoate per mL.

Rebetol contains sorbitol (E 420)
This medicine contains 142 mg sorbitol in each mL. Sorbitol is a source of fructose. If your doctor has told you that you (or your child) have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.

Rebetol contains sucrose
If you have been told by your doctor that you have **an intolerance to some sugars**, contact your doctor before taking this medicine. Sucrose may be harmful to the teeth.

3. How to use Rebetol

General information about taking this medicine:

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 or the child you are caring for weighs.

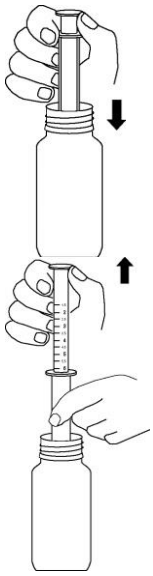
Use in children and adolescents
Dosing for children above 3 years of age and adolescents depends on how much the person weighs and the medicines that are used in combination. The recommended dose of Rebetol combined with interferon alfa-2b or peginterferon alfa-2b, is shown in the below table.

Rebetol oral solution - Usual dosage to be used with interferon alfa-2b or peginterferon alfa-2b in children above 3 years of age and adolescents		
If the patient weighs this many kg	Measure and give this dose	
	Morning Dose	Evening Dose
10-12	2 mL	2 mL
13-14	3 mL	2 mL
15-17	3 mL	3 mL
18-20	4 mL	3 mL
21-22	4 mL	4 mL
23-25	5 mL	4 mL
26-28	5 mL	5 mL
29-31	6 mL	5 mL
32-33	6 mL	6 mL

Rebetol oral solution - Usual dosage to be used with interferon alfa-2b or peginterferon alfa-2b in children above 3 years of age and adolescents		
If the patient weighs this many kg	Measure and give this dose	
	Morning Dose	Evening Dose
34-36	7 mL	6 mL
37-39	7 mL	7 mL
40-41	8 mL	7 mL
42-44	8 mL	8 mL
45-47	9 mL	8 mL

1. Measure:
You can measure the dose with the oral dosing syringe provided.

The plastic oral dosing syringe consists of two parts, an opaque barrel, and a white plunger rod that fits into the barrel.
The rod is marked with 0.5 mL markings starting at 1.5 mL (at the very top of the rod) and ending at 10 mL.



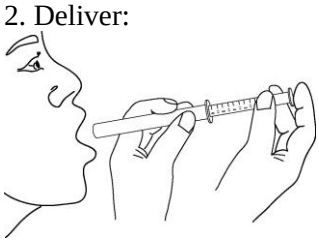
A. Insert the assembled dosing syringe into the bottle of Rebetol oral solution.

B. While keeping the tip in the liquid, pull the rod out. As the solution fills the syringe, you will see the numbers on the rod go up, such as 1.5 mL, 2.0 mL, 2.5 mL, etc.
Reminder: Your doctor may have changed the amount based on recent test results.

C. Pull the rod out until you can read the correct number of mL for the dose you are measuring.

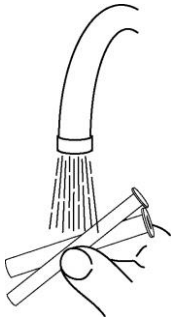
D. Take the oral syringe out of the bottle and check to see that the correct amount appears in the bottom of the syringe. If you have too much or too little, try again until you have the correct amount.

2. Deliver:



Try <u>not</u> to let the oral syringe touch the inside of the mouth.
Hold the syringe to your mouth and release the dose into your mouth (or the mouth of the patient you are caring for) by pushing in the rod.
Swallow the dose.

3. Rinse:



If the syringe has touched the inside of the mouth, rinse it with water before inserting it in the bottle again.
The syringe should be rinsed with water after each use to avoid stickiness.

4. Taking all your medicine:
Take or give the prescribed dose by mouth in the morning and evening, with a meal.

Reminder: This medicine is used in combination with other medicines for hepatitis C virus infection. For complete information be sure to read the "How to use" section of the Package Leaflet for the other medicines used in combination with Rebetol.

If you take more Rebetol than you should
Tell your doctor or pharmacist as soon as possible.

If you forget to take Rebetol
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.

4. Possible side effects

Like all medicines, this medicine used in combination with other medicines can cause side effects, although not everybody gets them. Although not all of these unwanted effects may occur, they may need medical attention if they do occur.

The side effects listed in this section were observed primarily when ribavirin was used in combination with interferon-containing products.

Refer also to the package leaflets of the other medicines that are used in combination with ribavirin for information on the side effects for those products.

Contact your doctor immediately if you notice any of the following side effects occurring during combination treatment with other medicines:
- 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.

Children and adolescents
The following side effects have been reported with the combination of this medicine and an interferon alfa-2b product **in children and adolescents**:

Very commonly reported side effects (may affect more than 1 in 10 people):
- 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),
- decrease in thyroid gland activity (which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms),
- feeling depressed or irritable, feeling sick to stomach, feeling unwell, mood swings, tired feeling, trouble falling asleep or staying asleep, virus infection, weakness,
- diarrhoea, dizziness, fever, flu-like symptoms, headache, loss of or increase in appetite, loss of weight, decrease in the rate of growth (height and weight), pain on right side of ribs, pharyngitis (sore throat), shaking chills, stomach pain, vomiting,
- dry skin, hair loss, irritation, itching, muscle pain, muscle aches, pain in joints and muscles, rash.

Commonly reported 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 triglycerides in the blood, excess of uric acid (as in gout) in the blood, increase in thyroid gland activity (which may cause nervousness, heat intolerance and excessive sweating, weight loss, palpitation, tremors),
- agitation, anger, aggressive behaviour, behaviour disorder, difficulty concentrating, emotional instability, fainting, feeling anxious or nervous, feeling cold, feeling confused, feeling of restlessness, feeling sleepy, lack of interest or attention, mood changes, pain, poor quality sleep, sleepwalking, suicide attempt, trouble sleeping, unusual dreams, wanting to harm yourself,
- bacterial infections, common cold, fungal infections, abnormal vision, dry or teary eyes, ear infection, eye irritation or pain or infection, change in taste, changes in your voice, cold sores, coughing, inflamed gums, nose bleed, nose irritation, oral pain, pharyngitis (sore throat), rapid breathing, respiratory infections, scaling lips and clefts in the corners of the mouth, shortness of breath, sinusitis, sneezing, sores in mouth, sore tongue, stuffy or runny nose, throat pain, toothache, tooth abscess, tooth disorder, vertigo (spinning feeling), weakness,
- chest pain, flushing, palpitations (pounding heart beat), rapid heart rate,
- abnormal liver function,
- acid reflux, back pain, bedwetting, constipation, gastroesophageal or rectal disorder, incontinence, increased appetite, inflammation of the membrane of the stomach and intestine, stomach upset, loose stools,
- urination disorders, urinary tract infection,
- difficult, irregular, or no menstrual period, abnormally heavy and prolonged menstrual periods, disorder of vagina, inflammation of the vagina, testis pain, development of male body traits,
- acne, bruising, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), increased or decreased sensitivity to touch, increased sweating, increase in muscle movement, tense muscle, limb pain, nail disorder, numbness or tingling feeling, pale skin, rash with raised spotted lesions, shaky hands, redness of skin or skin disorder, skin discolouration, skin sensitive to sunlight, skin wound, swelling due to a build-up of excess water, swollen glands (swollen lymph nodes), tremor, tumour (unspecified).

Uncommonly reported side effects (may affect up to 1 in 100 people):
- abnormal behaviour, emotional disorder, fear, nightmare,
- bleeding of the mucous membrane that lines the inner surface of the eyelids, blurred vision, drowsiness, intolerance to light, itchy eyes, facial pain,
- chest discomfort, difficult breathing, lung infection, nasal discomfort, pneumonia, wheezing,
- low blood pressure,
- enlarged liver,
- painful menstruation,
- itchy anal area (pinworms or ascarids), blistering rash (shingles), decreased sensitivity to touch, muscle twitching, pain in skin, paleness, peeling of skin, redness, swelling.

Adults

Rebetol when used in combination with direct antiviral agents:

When this medicine was used in combination with other medicines to treat hepatitis C (also called direct antiviral agents) in adult clinical studies, the most frequently reported side-effects associated with this medicine were anaemia (low red cell count), nausea, vomiting, tiredness, fatigue, insomnia (difficulty to sleep), cough, shortness of breath, itching and rash.

The additional following *side effects* have occurred with the combination of this medicine and an alpha interferon product **in adults but not in children**:

Commonly reported side effects (may affect up to 1 in 10 people):
- decrease in certain white blood cells called leukocytes that help fight infection, excess of sugar in the blood, low calcium level in the blood,
- amnesia, crying, bleeding gums, feeling faint, anger, memory impaired, mental disorder,

- cardiac murmur (abnormal heart beat sounds), difficult breathing, low or high blood pressure,
- blurred vision, changes in your hearing, ringing in ears, earache, bloating, burning sensation on tongue, change in taste, taste loss, dry mouth, migraine, nonproductive cough, thirst,
- abnormal urine, passing more urine than usual,
- irritated colon, irritation of prostate gland, intestinal gas (flatus),
- jaundice (yellow skin),
- disorder of ovary, breast pain, lack of interest in sex or inability to perform, erectile problem,
- abnormal hair texture, arthritis, psoriasis, muscle spasm, puffy or swollen hands and ankles, swollen face, unsteady when walking, water impairment.

Uncommonly reported side effects (may affect up to 1 in 100 people):
- hearing or seeing images that are not present,
- heart attack, panic attack,
- hypersensitivity reaction to the medication,
- inflammation of pancreas, pain in bone, diabetes mellitus,
- muscle weakness.

Rarely reported side effects (may affect up to 1 in 1,000 people):
- 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 (may affect up to 1 in 10,000 people):
- suicide,
- stroke (cerebrovascular events).

Not known side effects (frequency cannot be estimated from the available data):
- 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 self-harm 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), and 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, 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.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store . By reporting side effects, you can also help provide more information on the safety of this medicine.

5. How to store Rebetol

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month. Once the bottle has been opened, the oral solution can be used for 1 month.

Do not store above 30ºC.

Do not use this medicine without advice of your doctor or pharmacist if you notice any change in the appearance of the solution.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rebetol contains

- The active substance is ribavirin 40 mg/mL.
- The other ingredients are: sodium citrate, citric acid, anhydrous, sodium benzoate (E 211), glycerol, sucrose, sorbitol liquid (crystallising) (E 420), propylene glycol (E 1520), purified water, natural and artificial bubble gum flavouring containing benzyl alcohol (E 1519) and propylene glycol.

What Rebetol looks like and contents of the pack

This solution is packaged in 118 mL size amber glass bottles containing 100 mL of oral solution. A 10 mL oral dosing syringe is provided to measure the dose.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder in Great Britain: Merck Sharp & Dohme (UK) Limited, 120 Moorgate, London, EC2M 6UR, UK.

Marketing Authorisation Holder in UK (Northern Ireland): Merck Sharp & Dohme B.V., Waarderweg 39, 2031 BN Haarlem, The Netherlands.

Manufacturer: Cenexi HSC, 2, rue Louis Pasteur, 14200 Hérouville-Saint-Clair, France

For any information about this medicine, please contact:

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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