Package leaflet: Information for the patient

Ribavirine ratiopharm 200 mg, filmomhulde tabletten
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

1. What [Product name] is and what it is used for

[Product name] contains the active substance ribavirin. This medicine stops the multiplication of hepatitis C virus. [Product name] 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 other medicines. 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 [Product name] and other medicines is used to treat adult patients who have chronic hepatitis C (HCV).

[Product name] 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.

For paediatric patients (children and adolescents) weighing less than 47 kg a solution formulation may be available.

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

2. What you need to know before you take [Product name]

Do not take [Product name]
Do not take [Product name] if any of the following apply to you or the child you are caring for.

Talk to your doctor or **pharmacist** before taking [Product name] 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 “Pregnancy and breast-feeding”)**.**
- are **breast-feeding**.
- had a serious **heart** problem during the past 6 months.
- have any **blood disorders**, 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
Talk to your doctor, pharmacist or nurse before taking [Product name]
There are several serious adverse reactions associated with the combination therapy of ribavirin with (peg)interferon alfa-2b. 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 ribavirin 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

<u>Paediatric population</u>
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 ribavirin:
Haemolysis: [Product name] can cause a break down in red blood cells causing anaemia which may impair your heart function or worsen symptoms of heart disease.
Pancytopenia: [Product name] 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 tablets 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 breastfeeding").
- 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-2b 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 [Product name] before you begin combination treatment.

Use in children and adolescents
If the child is weighing less than 47 kg or unable to swallow tablets, an oral solution of ribavirin may be available.

Other medicines and [Product name]
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 ribavirin 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 [Product name] 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 [Product name] 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 this medicine and for 6 months after stopping treatment. This should be discussed with your doctor (see section "Do not take [Product name]").

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 [Product name] 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.

[Product name] contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

3. How to take [Product name]

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.

Adults
The recommended dose and duration of [Product name] depends on how much the patient weighs and the medicines that are used in combination.

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 [Product name] combined with interferon alfa-2b or peginterferon alfa-2b, is shown in the below table.

[Product name] dose based on body weight when used in combination with interferon alfa-2b or peginterferon alfa-2b in children above 3 years of age and adolescents		
If the **child/adolescent** weighs (kg)	Usual daily [Product name] dose	Number of 200 mg film-coated tablets
47 – 49	600 mg	1 film-coated tablet in the morning and 2 film-coated tablets in the evening
50 – 65	800 mg	2 film-coated tablets in the morning and 2 film-coated tablets in the evening
> 65	See adult dose	

Take your prescribed dose by mouth with water and during your meal. Do not chew the film-coated tablets.
For children or adolescents who cannot swallow a film-coated tablet, an oral solution of ribavirin may be available.

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 [Product name].

If you take more [Product name] than you should
Tell your doctor or pharmacist as soon as possible.

If you forget to take [Product name]

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.

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

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.

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.

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.

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

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),
- 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, hair loss, 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, 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 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 (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.

Side effects in 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, inflamed gums,
- 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.

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), 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.

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 (combined anti-retroviral therapy (cART)) 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 cART, the following other side effects have occurred with the combination of ribavirin and peginterferon alfa-2b (not listed above in adults side effects):
- appetite decreased,
- back pain,
- CD4 lymphocytes decreased,
- defective metabolism of fat,
- hepatitis,
- limb pain,
- oral candidiasis (oral thrush),
- various laboratory blood values abnormalities.

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 national reporting system listed in Appendix V. By reporting side effects you can also help provide more information on the safety of this medicine.

5. How to store [Product name]

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 outer carton and blister or label after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Tablet container
The shelf life of the tablets after first opening is 8 weeks.

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 [Product name] contains
- The active substance is ribavirin. Each film-coated tablet contains 200 mg ribavirin.
- The other ingredients are: Microcrystalline cellulose, croscarmellose sodium, pregelatinised maize starch, colloidal anhydrous silicia, talc, magnesium stearate, hypromellose, macrogol 6000, titanium dioxide, iron oxide yellow.

What [Product name] looks like and contents of the pack
[Product name] are oval, biconvex, ivory film-coated tablets.

[Product name] is available in different pack sizes containing 28, 30, 42, 56, 84, 90, 112, 140, 168 and 180 film-coated tablets in blister or 28, 42, 84, 112 and 168 film-coated tablets in tablet container.

Not all pack sizes may be marketed.

Houder van de vergunning voor het in de handel brengen en fabrikant
Houder van de vergunning voor het in de handel brengen
Ratiopharm GmbH
Graf-Arco-Strasse 3
89079 Ulm
Duitsland

Fabrikant
Merckle GmbH
Ludwig-Merckle-Strasse 3
89143 Blaubeuren
Duitsland

HBM Pharma s.r.o.
Sklabinská 30
03680 Martin
Slowakije

In het register ingeschreven onder
RVG 108116

Dit geneesmiddel is geregistreerd in lidstaten van de EEA onder de volgende namen:
Duitsland: Ribavirin-ratiopharm 200 mg Filmtabletten
Nederland: Ribavirine ratiopharm 200 mg, filmomhulde tabletten

Deze bijsluiter is voor het laatst goedgekeurd in september 2021