**APPROVED**
**The Order of Ministry of Health of Ukraine**
**11.01.2019 № 81**
**Registration certificate**
**№ UA/9527/91/01**

**AMENDED**
**The Order of Ministry of Health of Ukraine**
**18.10.2023 № 1808**

# INSTRUCTION
## for medical use

## VIRORIB®

***Composition:***
*active substance:* ribavirin;
1 capsule contains ribavirin 200 mg;
*excipients:* lactose monohydrate, croscarmellose sodium, povidone, magnesium stearate, colloidal silicon dioxide anhydrous;
hard gelatin capsule: gelatin, purified water, Patent blue V (E131), carmoisine (E 122), titanium dioxide (E 171), Ponceau 4R (E 124), Sunset Yellow FCF (E 110).

**Pharmaceutical form.** Capsules.
*Basic physico-chemical properties:* capsules with a pink body and a violet cap that contain white powder.

**Pharmacotherapeutic group.**
Direct-acting antivirals. Nucleosides and nucleotides, excluding reverse transcriptase inhibitors. ATC Code J05A B04.

***Pharmacological properties.***
*Pharmacodynamics*.
Ribavirin is a synthetic nucleoside analogue with *in vitro* activity against some RNA and DNA viruses. The mechanism by which ribavirin in combination with peginterferon α-2b or interferon α-2b exerts its effects against hepatitis C virus is unknown. Ribavirin monotherapy of chronic hepatitis C has no effect on eliminating the virus (Hepatitis C virus RNA) or improving hepatic histology after 6–12 months of therapy and 6 months of follow-up. However, the combination of ribavirin with peginterferon α-2b or interferon α-2b in clinical trials led to high levels of response to treatment compared to monotherapy with peginterferon α-2b or interferon α-2b.
*Pharmacokinetics*.
Ribavirin is absorbed easily following oral administration of a single dose ($T_{max}$ = 1.5 hours) and is rapidly distributed in the body. The elimination phase is prolonged. The half-lives of absorption, distribution and elimination of a single dose are 0.05; 3.73; and 79 hours, respectively. Ribavirin is intensively absorbed; only 10% of the radiolabelled dose is excreted in the feces. However, absolute bioavailability is approximately 45–65% which appears to be due to the first-pass metabolism. There is a linear dependence between the dose and the bioavailability index ($AUC_{tf}$) when administering single

doses of 200 mg to 1200 mg of ribavirin. The volume of distribution is approximately 5000 L. Ribavirin does not bind to plasma proteins.
The transfer of ribavirin via the non-plasma route has been most extensively studied in erythrocytes; it has been shown that, in general, transport occurs via an $e_s$-type equilibrative nucleoside transporter. This type of transporter is present in virtually all cell types and can be a factor that accounts for a large volume of ribavirin distribution. The ratio of whole blood: plasma ribavirin concentrations is approximately 60:1; the excess of ribavirin in whole blood exists in the form of ribavirin nucleotides isolated in erythrocytes.
Ribavirin is metabolized in two ways: a reversible phosphorylation and a degradative transformation involving deribosylation and amide hydrolysis to form a triazole carboxyacid metabolite. Both ribavirin itself and its metabolites – triazol carboxamide and triazole carboxylic acid are excreted from the body in the urine.
For ribavirin, following single oral administration, high pharmacokinetic variability was demonstrated in both one patient and between different patients (the variability of AUC and $C_{max}$ in one patient is approximately 30 %), which may be due to extensive first pass metabolism and significant transfer within and beyond the blood compartment.
Upon multiple dosing, ribavirin accumulates extensively in plasma; the ratio of multiple-dose to single-dose bioavailability ($AUC_{12h}$) is 6. Upon oral dosing (600 mg 2 times a day), steady-state ribavirin concentration was reached by the end of the 4th week; while it was about 2.2 ng/ml. After discontinuation of dosing the half-life was approximately 298 hours, which probably reflects slow elimination from non-plasma compartments.
Ability to penetrate into seminal fluid. The ability of ribavirin to penetrate into seminal fluid has been studied. Ribavirin concentrations in seminal fluid is approximately 2-fold higher compared to serum. However, ribavirin systemic exposure in women after sexual intercourse with a man who receives treatment remains extremely limited compared to therapeutic plasma concentrations of ribavirin.
*Food effect.* The bioavailability of a single oral dose of ribavirin is increased upon co-administration of a high fat meal ($AUCt_f$ and $C_{max}$ both increased by 70 %). It is possible that the increased bioavailability is due to delayed transit or modified pH.
*Renal function*. In patients with renal insufficiency, the pharmacokinetics of ribavirin in single-dose administration varies ($AUCt_f$ and $C_{max}$ are increased) compared with control subjects (creatinine clearance > 90 ml/min). This change appears to be due to reduction of apparent clearance in these patients. Ribavirin concentrations are essentially unchanged by hemodialysis.
*Hepatic function.* The pharmacokinetics of ribavirin upon single-dose administration in patients with mild, moderate or severe hepatic insufficiency (type A, B or C according to the Child-Pugh classification) is similar to the pharmacokinetics of ribavirin in healthy volunteers in the control group.
Elderly patients (≥ 65 years of age). Specific pharmacokinetic analyses for elderly subjects have not been performed. However, in the conducted studies, age was not a key factor affecting the kinetics of ribavirin; renal function is the determining factor.
Children.
The pharmacokinetics of ribavirin in combination with peginterferon α-2b or with interferon α-2b (dose-normalized) did not differ in adults and children aged 5 to 16 years.

**Clinical characteristics.**
***Indications.***
*Triple-drug therapy.*
Virorib® in combination with boceprevir and peginterferon α-2b is indicated for the treatment of chronic hepatitis C (genotype 1) in adult patients (aged 18 years and more) with compensated liver disease, who have not previously received treatment, or if previous treatment had proved ineffective.
It is recommended to read the instruction for use of peginterferon α-2b and boceprevir if the drug Virorib® is used in combination with such drugs.
*Dual-drug therapy.*
Virorib® is indicated for the treatment of chronic hepatitis C in adults, adolescents and children aged 3 years and more; the drug should be used only in combination with peginterferon α-2b or interferon α-

2b. The drug Virorib® must not be used as monotherapy.
It is recommended to read the instruction for use of peginterferon α-2b or interferon α-2b if the drug Virorib® is used in combination with such drugs.
There is no information regarding the safety or efficacy of using the drug Virorib® with other forms of interferon (i.e., besides α-2b).
Treatment-naïve patients.
*Adults (aged 18 years and older).*
Virorib ® is indicated:
- in a triple-drug treatment regimen: in combination with peginterferon α-2b and boceprevir for the treatment of chronic hepatitis C (genotype 1) in adult patients with compensated liver disease;
- in a dual-drug treatment regimen: in combination with interferon α-2b or peginterferon α-2b for the treatment of chronic hepatitis C in naive adult patients (in the absence of decompensation of liver function, increased ALT level and positive test for hepatitis C virus RNA (HCV RNA);
- in a dual-drug treatment regimen: in combination with peginterferon α-2b for the treatment of chronic hepatitis C in patients with compensated cirrhosis and/or clinically stable HIV co-infection.
*Dual-drug therapy.*
*Children aged 3 years and more, adolescents.*
Virorib® is indicated, in combination with peginterferon α-2b or interferon α-2b for the treatment of chronic hepatitis C in children aged 3 years and more, as well as adolescents, who have not been treated before, in the absence of liver decompensation and in the presence of hepatitis C virus RNA.
When deciding on whether to defer treatment until adulthood, it is important to consider that this combination therapy induces growth inhibition that may be irreversible in some patients. The decision regarding the treatment should be made individually for each patient.
Previously treated patients.
*Adults.*
Virorib® is indicated:
- in a triple-drug treatment regimen: in combination with peginterferon α-2b and boceprevir for the treatment of chronic hepatitis C (genotype 1) in adult patients with compensated liver disease;
- in a dual-drug treatment regimen: in combination with peginterferon α-2b for the treatment of chronic hepatitis C in case if the previous treatment with α-interferon (pegylated or non-pegylated) only or its combination with ribavirin was ineffective;
- in a dual-drug treatment regimen: in combination with interferon α-2b for the treatment of chronic hepatitis C in case previous monotherapy with α-interferon was initially effective (normalization of ALT by the end of the treatment course), but later a relapse occurred.

***Contraindications.***
Hypersensitivity to ribavirin or to any of the drug components.
Pregnancy. Therapy must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.
Men whose female partners are pregnant.
Breast-feeding period.
Severe cardiac diseases, including unstable and uncontrolled forms that are observed within 6 months prior to the initiation of treatment.
Severe, debilitating diseases.
Chronic renal failure or creatinine clearance < 50 ml/min and/or conditions that require hemodialysis.
Severe hepatic dysfunction (B or C degree according to the Child-Pugh Classification) or decompensated liver cirrhosis.
Hemoglobinopathies (e.g., thalassemia, sickle-cell anemia).
Prescription of peginterferon α-2b is contraindicated in patients coinfected with the hepatitis C/HIV virus with liver cirrhosis and liver dysfunction corresponding to the Child-Pugh Score of ≥ 6 points.
Anamnestic or clinical data on severe psychiatric disorder, in particular severe depression, suicidal ideations or attempted suicide in children and adolescents.

History of autoimmune hepatitis or other autoimmune diseases (due to combination with peginterferon α-2b or interferon α-2b).

***Interaction with other medicinal products and other forms of interaction.***
Interactions studies have only been performed in adult patients.
According to the results of *in vitro* studies using human liver microsome preparations, cytochrome P450 enzymes do not take part in metabolic transformations of ribavirin. Ribavirin does not inhibit cytochrome P450 enzymes. There is no evidence from toxicity studies that ribavirin stimulates the enzymatic activity of the liver. Therefore, there is a minimal probability for interactions with cytochrome P450.
By inhibiting inosine monophosphate dehydrogenase, ribavirin may affect azathioprine metabolism with further accumulation of 6-methylthioinosine monophosphate, which is associated with myelotoxicity in patients receiving azathioprine treatment. It is recommended to avoid using pegylated α-interferon and ribavirin concomitantly with azathioprine. In individual cases where the benefit of administering ribavirin concomitantly with azathioprine outweighs the potential risk, it is recommended that frequent hematologic monitoring be performed during concomitant azathioprine use to identify signs of myelotoxicity, and if they are present, these medicinal products should be discontinued.
No interaction studies have been conducted with ribavirin and other medicinal products, except for peginterferon α-2b, interferon α-2b and antacids.
Interferon α-2b. No pharmacokinetic interactions were noted between ribavirin and peginterferon α -2b or interferon α -2b in a multiple-dose pharmacokinetic study.
Antacids. The bioavailability of ribavirin 600 mg was decreased by co-administration with an antacid drug containing magnesium and aluminium compounds or simethicone; $AUC_{tf}$ decreased by 14 %. It is possible that the decreased bioavailability in this study was due to delayed transit of ribavirin or modified pH. This interaction is not considered to be clinically relevant.
Nucleoside analogues. Use of nucleoside analogues, alone or in combination with other nucleosides, may lead to lactic acidosis. Ribavirin *in vitro* increases phosphorylated metabolites of purine nucleosides. This effect may potentiate the risk of lactic acidosis induced by purine nucleoside analogues (e.g., didanosine or abacavir). Co-administration of ribavirin and didanosine is not recommended. Cases of mitochondrial toxicity (lactic acidosis and pancreatitis), of which some fatal, have been registered.
There have been reports of exacerbation of anemia caused by ribavirin, when zidovudine was used as part of a HIV treatment regimen, although the exact mechanism has not yet been studied. Because of the increased risk of anemia ribavirin is not recommended for use in combination with zidovudine. The regimen of co-administration of zidovudine and ribavirin in combination with highly active antiretroviral therapy (HAART) should be reviewed in case of anemia. This is especially important for patients with a known history of zidovudine-induced anemia.
The possibility of interaction with ribavirin may persist for up to 2 months (5 half-lives for ribavirin) after cessation of ribavirin therapy due to the long half-life.
No interaction has been observed between ribavirin and non-nucleoside reverse transcriptase inhibitors or protease inhibitors.
Controversial data have been published regarding co-administration of abacavir and ribavirin. Some data suggest a risk of a lower response to treatment with pegylated interferon/ribavirin in patients with hepatitis C and HIV co-infection receiving abacavir-containing antiretroviral therapy. Precautions should be taken when using these drugs concomitantly.

***Administration details.***
Psychiatric and Central Nervous System (CNS) effects. Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during ribavirin combination therapy with peginterferon α-2b or interferon α-2b, and even during the 6-months follow-up period after discontinuation of such treatment. Among children and adolescents who have been treated with ribavirin in combination with interferon α-2b, suicidal ideations or suicide attempts during the treatment and the 6-month follow-up period after treatment were observed more frequently than

among adults (2.4 % versus 1 %). As in adult patients, children and adolescents experienced other psychiatric effects (for example, depression, emotional lability, and somnolence). When using α-interferons, other CNS disorders have been observed, including aggressive behavior (sometimes directed against others such as thoughts of murder), bipolar disorder, mania, confusion, and disturbance of mental status.

Patients should be closely monitored to identify any signs or symptoms of psychiatric disorders. In case of such symptoms, the prescribing physician has to evaluate the potential severity of such adverse effects and the need for appropriate treatment. If psychiatric symptoms persist or worsen, as well as if suicidal ideations or thoughts of murder appear, it is recommended to discontinue treatment with the drug Virorib® in combination with peginterferon α-2b or interferon α-2b and, if necessary, provide appropriate psychiatric care to the patient.

*Patients with a history or clinical signs of severe psychiatric conditions*. If combined therapy with the drug Virorib® and peginterferon α-2b or interferon α-2b is judged to be necessary in adult patients with clinical or anamnestic data on severe psychiatric conditions, it should only be initiated after appropriate individualized diagnostic and therapeutic management of the psychiatric condition.

The use of the drug Virorib® and peginterferon α-2b or interferon α-2b for the treatment of children and adolescents with clinical or anamnestic data on severe psychiatric conditions is contraindicated.

*Patients who use/abuse psychoactive substances*. Patients with viral hepatitis C who simultaneously use psychoactive substances (alcohol, cannabis) have a high risk of psychiatric disorders or exacerbation of the existing psychiatric disorder during treatment with α-interferon. If treatment with α-interferon is necessary in such patients, the presence of concomitant psychiatric disorders and potential for use of other substances should be carefully evaluated, and appropriate measures should be taken before starting the therapy. If necessary (for assessment of treatment and follow-up), applying an interdisciplinary approach should be considered, including consulting a psychologist or a narcologist. The patient's condition should be carefully monitored during the treatment and after its discontinuation. Early intervention is recommended in case of reappearance or development of psychiatric disorders and use of psychoactive substances.

Hemolysis. There are clinical data regarding the decrease in hemoglobin levels in adult patients (< 10 g/dl), as well as in children and adolescents treated with a combination of ribavirin and peginterferon α-2b or interferon α-2b. Although ribavirin has no direct effect on the cardiovascular system, anemia associated with ribavirin may affect the cardiac function and/or exacerbate the symptoms of coronary disease. Therefore, Virorib® should be prescribed with caution in patients with cardiac diseases. Cardiac status must be assessed before the initiation of treatment and monitored during the therapy. If any signs of deterioration of the cardiovascular system occur, therapy should be stopped.

Cardiovascular system. Adult patients who have or had congestive heart failure, myocardial infarction and/or arrhythmia, should be under constant medical supervision. It is recommended that patients with cardiac diseases have electrocardiograms taken prior to and during the course of treatment. Arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of therapy. There are no data regarding the use of combined therapy in children and adolescents with a history of cardiovascular diseases.

Immediate hypersensitivity. In case of acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchospasm, anaphylaxis), the drug Virorib® should be discontinued immediately, and appropriate treatment should be prescribed. Transient rashes do not necessitate the interruption of treatment.

Ophthalmological changes. Ribavirin should be used in combination with α-interferons. In rare cases, during the combination treatment with α-interferons, cases of retinopathy have been reported, including retinal bleeding, retinal exudates, papilledema, optic neuropathy and retinal artery or vein occlusion which may cause vision loss. All patients should undergo ophthalmological examination before starting the treatment. Immediate full ophthalmological examination should be conducted for patients who have signs of eye disease or deterioration of vision. Periodic ophthalmological examination should be conducted in patients with existing ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) during combination treatment with α-interferons. Combined treatment with α-interferons should be discontinued in patients with new or exacerbated existing ophthalmic diseases.

Liver function. All patients who have shown signs of significant deterioration of liver function during the treatment should be closely monitored. Therapy should be discontinued in patients, who have shown increased coagulation, which may indicate liver decompensation.
Potential for increased immunosuppression. A report has been published on pancytopenia and bone marrow suppression that occurred within 3–7 weeks after the administration of peginterferon and ribavirin concomitantly with azathioprine. Such myelotoxicity disappeared within 4–6 weeks after withdrawal of hepatitis C antiviral therapy and concomitant azathioprine, and did not reappear after reintroduction of the individual use of any of the drugs.
HIV and hepatitis C virus co-infection.
*Mitochondrial toxicity and lactic acidosis*. Caution should be taken in patients with HIV-infection and concomitant hepatitis C virus infection receiving treatment with nucleoside reverse transcriptase inhibitors (especially didanosine and stavudine) together with a combination of ribavirin and interferon α-2b. In HIV-positive patients receiving nucleoside reverse transcriptase inhibitors, physicians should carefully monitor markers of mitochondrial toxicity and lactic acidosis when ribavirin is administered. In particular, ribavirin is not recommended for use together with didanosine and stavudine due to the risk of mitochondrial toxicity and to limit the risk of overlapping mitochondrial toxicity, respectively.
*Decompensation of the liver function in patients with HIV and hepatitis C virus co-infection and advanced cirrhosis*. Patients with concomitant HIV infection and advanced cirrhosis receiving HAART may have an increased risk of liver function decompensation and fatal outcome. Additional use of α-interferons separately or in combination with ribavirin increases the above risk in this category of patients. Other baseline factors in co-infected patients that may increase the risk of decompensated liver function include treatment with didanosine and elevated bilirubin serum concentrations. The condition of co-infected patients receiving both antiretroviral therapy and anti-hepatitis treatment should be closely monitored and the degree of liver dysfunction should be assessed according to the Child-Pugh classification. In case of liver decompensation, anti-hepatitis treatment should be immediately discontinued and the antiretroviral treatment regimen re-evaluated.
*Hematological disorders in patients with HIV and hepatitis C virus co-infection*. Patients with HIV co-infection receiving HAART and ribavirin treatment in combination with peginterferon α-2b may have an increased risk of hematologic disorders (e.g., neutropenia, thrombocytopenia and anemia) compared with patients with hepatitis C virus. Most of these disorders disappear upon dose reduction, however, it is necessary to closely monitor the hematological parameters in such patients. Patients treated with ribavirin and zidovudine have an increased risk of anemia, therefore, concomitant use of ribavirin with zidovudine is not recommended.
*Patients with low CD4 cell counts*. Data on the efficacy and safety of treatment of patients with HIV-infection and hepatitis C virus with CD4 cell count < 200/μl are limited. Treatment of patients with low CD4 cell counts should be conducted carefully.
Instructions should be followed for the medical use of the respective antiretroviral medicinal products that are used together concomitantly with drugs to treat hepatitis C (to obtain information about the toxicity of each drug and possible increased toxicity with the combined use of ribavirin and peginterferon α-2b).
Dental and periodontal disorders. There are reports on the development of dental and periodontal disorders (which may lead to tooth loss) in patients receiving combination therapy of ribavirin and peginterferon α-2b or interferon α-2b. In addition, dry mouth can have a negative effect on the teeth and the oral mucosa during long-term combination therapy of ribavirin and peginterferon α-2b or interferon α-2b. Patients should be advised to thoroughly brush the teeth 2 times a day and undergo regular dental examinations. Moreover, some patients may experience vomiting, after which they must rinse the mouth thoroughly.
Laboratory tests. Complete blood count (full blood count with the white blood differential) and blood chemistry test (electrolytes, serum creatinine, liver function tests, uric acid) should be conducted in all patients prior to initiating therapy. Acceptable baseline blood values prior to initiation of combination therapy are as follows:

- hemoglobin adults: ≥ 120 g/l (female) and ≥ 130 g/l (male);
  children and adolescents: ≥ 110 g/l (girls) and ≥ 120 g/l (boys);

- platelets $\geq 100 \times 10^9$/l;
- neutrophil count $\geq 1{,}5 \times 10^9$/l.

Laboratory tests should be performed on the 2nd and 4th week of treatment, periodically thereafter as clinically appropriate. HCV-RNA should be measured periodically during treatment.
*Females of reproductive age.* Women undergoing treatment as well as women whose male sexual partners are undergoing treatment should perform monthly pregnancy tests throughout the entire period of treatment and for 4 months and 7 months, respectively, after completion of treatment, as ribavirin must not be used during pregnancy.
Uric acid concentrations may increase with ribavirin due to hemolysis, therefore, the potential signs of the development of gout must be carefully monitored in pre-disposed patients.

*Excipients.*
The drug contains lactose. Patients with intolerance to some sugars should consult their physician before taking the medicinal product.
The product contains Ponceau 4R (E 124), Sunset Yellow FCF (E 110), carmoisine (E 122), which may cause allergic reactions.

*Use during pregnancy or breastfeeding.*
*Pregnancy.* The use of Virorib® is contraindicated during pregnancy.
*Breastfeeding*. It is not known whether ribavirin is excreted in human milk. Because of the potential for adverse reactions in breast-fed infants, breast-feeding must be discontinued prior to initiation of treatment.
Women of reproductive age/male and female contraception.
*Women (female patients)*. Virorib® must not be used during pregnancy. Female patients should use effective contraception to prevent pregnancy. Therapy must not be initiated until a negative pregnancy test result is obtained. Women of reproductive age and their sexual partners must use effective contraceptives during treatment and for 9 months after treatment has been concluded; routine monthly pregnancy tests must be performed during this time. If a woman becomes pregnant during treatment or within 9 months after treatment, she must be advised of the significant teratogenic risk of ribavirin to the fetus.
*Men (male patients) and their female partners.* Effective contraception must be used to prevent pregnancy in female partners of male patients treated with the drug Virorib®. Ribavirin accumulates intracellularly and is cleared from the body very slowly. It remains unknown whether ribavirin contained in sperm can exert its potential teratogenic or genotoxic effects on the embryo/fetus. Although data on approximately 300 prospectively followed pregnancies with paternal exposure to ribavirin have not shown an increased risk of congenital malformation compared to the general population, nor any specific pattern of malformation, men (male patients) and their female partners of reproductive age must each use an effective contraceptive during treatment with ribavirin and for 6 months after treatment is concluded. Routine monthly pregnancy tests must be performed during this time. Men whose partners are pregnant must be instructed to use a condom to minimize delivery of ribavirin to the female partner.

*Effect on reaction rate when driving motor transport or using other mechanisms.*
Ribavirin has no or negligible influence on the ability to drive motor transport or use other mechanisms, however, when combined with peginterferon α-2b or interferon α-2b, there is some possible influence. Therefore, patients who develop fatigue, somnolence or confusion during treatment should avoid driving or operating other mechanisms.

***Dosage and administration.***
Therapy should be conducted by a physician experienced in the management of chronic hepatitis C.
Virorib® should be used in combination with peginterferon α-2b or interferon α-2b (dual-drug regimen), or – in adults with chronic hepatitis C (genotype 1) – in combination with boceprevir and peginterferon α-2b (triple-drug scheme).

When administering combination therapy, instructions for the medical use of boceprevir, peginterferon α-2b or interferon α-2b should also be followed.

Dosage.

The dose of the drug Virorib® depends on the patient's body weight. Virorib®, capsules, should be taken orally, with food, daily, in 2 divided doses (in the morning and evening).

*Adult patients.*

The dose of the drug Virorib® depends on the patient's body weight (see table 1).

Virorib® should be used in combination with either peginterferon α-2b (1.5 μg/kg/week) or interferon α-2b (3 million IU 3 times a week). The regimen of combined therapy is determined by the physician individually, taking into account the expected effectiveness and safety of the selected combination.

Table 1. The dose of the drug Virorib® (depending on patient's body weight) for patients with Hepatitis C virus monoinfection or hepatitis C virus and HIV co-infection, as well as regardless of genotype.

| Body weight (kg) | Virorib® daily dose | Number of 200 mg capsules |
|---|---|---|
| < 65 | 800 mg | 4 (2 morning, 2 evening) |
| 65–80 | 1000 mg | 5 (2 morning, 3 evening) |
| 81–105 | 1200 mg | 6 (3 morning, 3 evening) |
| > 105 | 1400 mg | 7 (3 morning, 4 evening) |

*Duration of therapy in treatment-naive patients.*

*Triple-drug treatment scheme.*

Read the instructions for medical use of boceprevir and peginterferon α-2b.

*Dual-drug treatment scheme (with peginterferon α-2b).*

*Predictability of sustained virological response.* In patients infected with the hepatitis C virus genotype 1 who failed to achieve a reduction in HCV-RNA to below the lower limit of detection, or those who did not achieve an adequate virological response after 4 or 12 weeks of treatment, the probability of developing a stable virological response is very low, so such patients are advised to discontinue this treatment.

Genotype 1.

In patients who exhibit negative hepatitis C virus RNA after 12 weeks of treatment, therapy should be continued for the next 9 months (48 weeks total).

For patients who after 12 weeks of treatment exhibit the level of HCV-RNA decreased by ≥ 2 log compared to the initial period, re-evaluation should be performed at week 24 of treatment and, if the level of HCV-RNA is lower than the limit of detection, a full course of treatment is required (that is, a total of 48 weeks). However, if after 24 weeks of treatment, HCV-RNA levels still exceed the limit of detection, treatment should be discontinued.

For the subgroup of patients with a genotype 1 infection and a low viral load (<600000 IU/ml), in whom after 4 weeks of treatment HCV-RNA is not detected and after 24 weeks of treatment HCV-RNA remains negative, treatment can be either discontinued after these 24 weeks, or continued for an additional 24 weeks (i.e., the overall duration of treatment is 48 weeks). However, the 24-week treatment may be associated with a higher risk of relapse compared with the 48-week treatment.

Genotype 2 or 3. The recommended duration of treatment is 24 weeks for all patients except for patients with HIV co-infection whose treatment should last 48 weeks.

Genotype 4. Patients infected with genotype 4 are considered more difficult to treat; however, limited clinical data (n = 66) have revealed similarities in the treatment of these patients and patients with genotype 1.

*Duration of therapy in treatment-naive patients co-infected with hepatitis C and HIV.*

*Dual-drug treatment scheme.* For patients co-infected with HIV the recommended duration of Virorib® treatment in doses based on body weight (see table 1) is 48 weeks, regardless of the genotype.

*Predictability of the development or lack of virologic response in treatment-naive patients with Hepatitis C virus and HIV co-infection.*

Early virologic response by week 12 of treatment (at least 2-log viral load decrease or HCV-RNA levels below the detection limit) is a prognostic factor for the development of a sustained virologic response. In the negative prediction group (patients who have not demonstrated an early virologic response) 99 % of patients (67 of 68 patients) did not achieve a sustained virologic response when using ribavirin combination therapy with peginterferon α-2b. In the positive prediction group (patients who demonstrated an early virologic response) 50 % of patients (52 of 104 patients) achieved a sustained virologic response when using the combination therapy.

*Duration of treatment upon retreatment.*

*Triple-drug treatment scheme.* Read the instructions for medical use of boceprevir and peginterferon α-2b.

*Dual-drug treatment scheme (with peginterferon α-2b).*

*Predictability of sustained virologic response.* All patients, regardless of viral genotype, who after 12 weeks of treatment demonstrated HCV-RNA levels decreased below the detection limit, require a 48-week course of treatment. When re-treating patients, who after 12 weeks of treatment demonstrated no virologic response (i.e., the HCV-RNA value is not reduced to below the detection limit), the probability of achieving a sustained virologic response after 48 weeks of treatment is very low.

For patients with genotype 1 virus who have no reaction to treatment, the appropriateness of re-treatment with a duration of over 48 weeks has not been studied upon combination therapy of pegylated interferon using α-2b and ribavirin.

Use of Virorib® capsules in combination with interferon α-2b (only in the dual-drug treatment scheme).

*Duration of therapy with the use of interferon α-2b.*

Based on clinical studies the recommended duration of treatment is at least 6 months. During clinical studies in which the treatment lasted for 1 year, patients who have not achieved a virologic response after 6 months of treatment (hepatitis C virus RNA below the detection limit) had a very low probability of achieving a sustained virologic response (hepatitis C virus RNA below the detection limit within 6 months after completing the therapy).

Genotype 1. For patients with the HCV-RNA undetectable after 6 months of treatment, it is necessary to continue the treatment for the next 6 months (i.e., for a total of 1 year).

Any other genotype. For patients with the HCV-RNA undetectable after 6 months of treatment, the decision to continue treatment for up to 1 year is based on other prognostic factors (e.g., patient age > 40 years, male sex, bridging fibrosis).

*Children (dual-drug treatment scheme).*

The drug Virorib® can be used in children with a body weight of at least 47 kg and who can swallow capsules.

The dose of the drug Virorib® for children and adolescents should be determined based on the body weight, and the dose of peginterferon α-2b and interferon α-2b should be determined by the body surface area.

*Pediatric dose in combination treatment with peginterferon α-2b.*

Virorib® at a dose of 15 mg/kg per day is recommended for use in combination with peginterferon α-2b for subcutaneous administration at a dose of 60 mcg/$m^2$ per week (table 2).

*Pediatric dose in combination treatment with interferon α-2b.*

In clinical studies conducted for this patient group, ribavirin and interferon α-2b were used at doses of 5 mg/kg per day and 3 million IU/$m^2$, respectively, 3 times a week (table 2).

Table 2. The dose of the drug Virorib® for children and adolescents based on body weight when used in combination with interferon α-2b or peginterferon α-2b

| Body weight (kg) | Virorib® daily dose | Number of 200 mg capsules |
|---|---|---|
| 47–49 | 600 mg | 3 (1 morning, 2 evening) |
| 50–65 | 800 mg | 4 (2 morning, 2 evening) |
| > 65 | Corresponds to the adult dosage (table 1) | |

*Duration of treatment for children and adolescents.*

Genotype 1. The recommended duration of treatment is 1 year. It is recommended to discontinue the treatment in children and adolescents treated with interferon α-2b (pegylated or non-pegylated) in combination with the drug Virorib® if, after 12 weeks of treatment, the levels of hepatitis C virus RNA decreased by < 2 $\log_{10}$ compared with the baseline, or if in 24 weeks of the treatment the HCV-RNA is still detectable.
Genotype 2 or 3. The recommended duration of treatment is 24 weeks.
Genotype 4. The recommended duration of treatment is 1 year. It is recommended to discontinue the treatment in children and adolescents treated with peginterferon α-2b in combination with the drug Virorib® if, after 12 weeks of treatment, the HCV-RNA levels decreased by < 2 $\log_{10}$ compared with the baseline, or if after 24 weeks of treatment HCV-RNA is still detectable.
*Dose modification for all patients*.
*Combination therapy.*
In case of severe adverse reactions or pathological abnormalities in laboratory findings during combination therapy with Virorib® and peginterferon α-2b or interferon α-2b, or Virorib®, peginterferon α-2b and boceprevir, the dose should be modified (as indicated in table 3) until adverse reactions abate. Dose reduction is not recommended. Since compliance with the treatment regimen can be important for the result of the therapy, the dose should be kept as close to the recommended standard dose as possible. The potential negative effect of ribavirin dose reduction on the efficacy results cannot be excluded.

Table 3. Recommendations on dose adjustments based on laboratory parameters

| Laboratory parameters | Reduction of the daily dose of Virorib® only (see note 1), if: | Reduction of the daily dose of peginterferon α-2b or interferon α-2b only (see note 2), if: | Discontinuation of combined treatment in case of values indicated below: ** |
|---|---|---|---|
| Hemoglobin (adult patients without cardiac disease) | < 100 g/l | - | < 85 g/l |
| Hemoglobin (adult patients with history of stable cardiac disease) | Hemoglobin decreased by ≥ 20 g/l during any 4 week period during treatment (permanent administration of the reduced dose) | | <120 g/l after 4 weeks of treatment following dosage reduction |
| White blood cells | - | < 1,5 × $10^9$/l | < 1,0 × $10^9$/l |
| Neutrophils | - | < 0,75 × $10^9$/l | < 0,5 ×$10^9$/l |
| Platelets | - | < 50 × $10^9$/l (adults)<br>< 70 × $10^9$/l (children and adolescents) | < 25 × $10^9$/l (adults)<br>< 50 × $10^9$/l (children and adolescents) |
| Bilirubin direct | - | - | 2,5 × ULN* |
| Bilirubin indirect | > 5 mg/dl | - | > 4 mg/dl (adults)<br>> 5 mg/dl<br>(more than 4 weeks)<br>(children and adolescents treated with interferon α-2b) or<br>> 4 mg/dl (more than 4 weeks) (children and adolescents treated with peginterferon α-2b) |

| | | | |
|---|---|---|---|
| Creatinine (blood serum) | - | - | > 2,0 mg/dl |
| Creatinine clearance | - | - | Discontinuation of Virorib®, if the creatinine clearance is < 50 ml/min |
| ALT/AST | - | - | 2 × baseline and > 10 × ULN** |

* ULN – upper limit of normal.

** Follow the instructions for medical use of peginterferon α-2b or interferon α-2b for recommendations regarding dose adjustment and discontinuation of interferon α-2b and pegylated interferon α-2b.

Note 1. For adult patients, the Virorib® dose should for the first time be reduced by 200 mg per day (except for patients receiving a 1400 mg dose; for them, the dose should be reduced by 400 mg per day). If necessary, the dose should be further reduced by an additional 200 mg per day. Patients whose Virorib® dose is reduced to 600 mg per day should take 1 capsule of 200 mg in the morning and 2 capsules of 200 mg in the evening.

For children and adolescents treated with Virorib® in combination with peginterferon α-2b, the Virorib® dose should for the first time be reduced to 12 mg/kg per day, and the second time – to 8 mg/kg per day. For children and adolescents treated with Virorib® in combination with interferon α-2b, the Virorib® dose should be reduced to 7.5 mg/kg per day.

Note 2. For adult patients treated with Virorib® in combination with peginterferon α-2b, the peginterferon α-2b dose should for the first time be reduced to 1 mcg/kg per week. If necessary, the peginterferon α-2b dose may be reduced to 0.5 mcg/kg per week.

For children and adolescents treated with Virorib® in combination with peginterferon α-2b, the peginterferon α-2b dose should for the first time be reduced to 40 mcg/$m^2$ per week, and the second time, the peginterferon α-2b dose should be reduced to 20 mcg/$m^2$ per week.

For adults as well as for children and adolescents treated with Virorib® in combination with interferon α-2b, the dose of interferon α-2b should be reduced by half.

*Special patient groups.*

*Use in renal impairment*. Due to the decrease in apparent creatinine clearance in patients with renal impairment, the pharmacokinetics of ribavirin in this patient group varies. Therefore, it is recommended to evaluate renal function in all patients before initiating therapy with Virorib®. Patients with creatinine clearance below 50 ml/min should not be treated with Virorib®. Patients with impaired renal function should be thoroughly monitored with respect to the development of anemia. If the serum creatinine concentrations rise to > 2.0 mg/dl (table 3), Virorib® and peginterferon α-2b or interferon α-2b should be discontinued.

*Use in hepatic impairment.* No pharmacokinetic impact of ribavirin on the hepatic function has been found. Therefore, patients with hepatic impairment do not require Virorib® dose adjustment. The use of ribavirin is contraindicated in severe hepatic dysfunction or decompensated liver cirrhosis.

*Use in the elderly (≥ 65 years of age).* There does not appear to be a significant age-related effect on the pharmacokinetics of ribavirin. However, as in younger patients, renal function must be determined prior to administration of Virorib®.

*Use in patients under the age of 18.* Virorib® in combination with peginterferon α-2b or interferon α-2b may be prescribed in children from the age of 3 and adolescents. The choice of the treatment scheme depends on the individual characteristics of the patient. The safety and efficacy of the drug Virorib® in combination with other forms of interferon (i.e., except α-2b) for this category of patients have not been evaluated.

*Use in patients co-infected with HIV.* Patients taking nucleoside reverse transcriptase inhibitors in association with ribavirin and peginterferon α-2b or interferon α-2b may be at an increased risk of

mitochondrial toxicity, lactic acidosis, and hepatic decompensation. Instructions for medical use of the appropriate antiretroviral drugs should also be followed when prescribing such therapy.

*Children.*
Growth and development (children and adolescents).
During the 48-week course of combined treatment with interferon (standard and pegylated)/ribavirin in patients aged 3 to 17 years weight loss and growth retardation were often observed. The available data from a long-term follow-up regarding treatment with a combination of pegylated interferon/ribavirin confirm a significant slowdown of growth, despite the fact that 5 or more years had passed after discontinuation of treatment.
*Individual assessment of the benefit/risk in children.*
The expected benefits of the treatment should be carefully compared with the safety data obtained in clinical studies involving children and adolescents.

- It is important to consider that the combination therapy induces growth inhibition, leading to reduced growth rate in some patients.
- The risk should be compared with the characteristics of the disease in the child such as signs of disease progression (especially fibrosis), concurrent disease which may negatively affect disease progression (such as HIV co-infection), as well as with prognostic factors with respect to the virologic response (genotype of hepatitis C virus and viral load).

If possible, treatment of the child should be carried out after the pubertal growth spurt to reduce the risk of growth retardation. Although data are limited, no signs of long-term effects on puberty over 5 years of follow-up were observed.
Additional monitoring of thyroid function in children and adolescents.
It has been reported that some children treated with ribavirin and interferon α-2b (pegylated and non-pegylated) demonstrated an increase of TSH and a transient decrease in hormone levels (below the lower limit of normal). The level of TSH should be determined prior to initiation of interferon α-2b administration. If any thyroid abnormality is detected, it should be treated with conventional therapy. If TSH levels can be maintained in the normal range by medication, treatment with interferon α-2b (pegylated and non-pegylated) may be initiated. Thyroid dysfunction during treatment with ribavirin and interferon α-2b, as well as ribavirin and peginterferon α-2b, was observed. If thyroid abnormalities are detected, the thyroid status should be evaluated, and appropriate treatment conducted. Thyroid function should be monitored (in particular the TSH level) every 3 months in children and adolescents.

***Overdose.***
*Triple-drug treatment scheme.* (See the instruction for medical use of boceprevir).
*Dual-drug treatment scheme.* The known maximum overdose of ribavirin was 10 g (50 capsules of 200 mg), together with 39 million IU of interferon α-2b in the form of a solution for injection (13 subcutaneous injections of 3 million IU each). This is the amount taken in one day by a patient in a suicide attempt. The patient was observed for two days in the emergency room; during this time, no adverse reactions related to overdose have been noted.
*Treatment:* withdrawal of the drug, symptomatic treatment.

***Adverse reactions.***
Use of ribavirin in combination with direct antiviral agents.
Based on the review of safety data derived from clinical studies in adults receiving direct antiviral agents in combination with ribavirin, the most frequent adverse reactions identified as associated with ribavirin were anemia, nausea, vomiting, asthenia, fatigue, insomnia, cough, dyspnea, pruritus and rash. The majority of these adverse reactions, except for anemia, were not serious and resolved without discontinuation of treatment.
*Adults.*
*Infections and infestations:* viral infection, influenza, herpes simplex, fungal infection, bacterial infection (including sepsis), respiratory tract infection, lower respiratory tract infection, pharyngitis, bronchitis, pneumonia, rhinitis, sinusitis, otitis media, urinary tract infection.

*Neoplasms benign, malignant and unspecified (including cysts and polyps):* neoplasm unspecified.
*Blood and lymphatic system disorders:* anemia, hemolytic anemia, aplastic anemia, leukopenia, lymphopenia, neutropenia, thrombocytopenia, pure red-cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, lymphadenopathy.
*Immune system disorders:* drug hypersensitivity, acute hypersensitivity reactions including urticaria, angioedema, bronchospasm, anaphylaxis, sarcoidosis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, systemic lupus erythematosus, vasculitis.
*Endocrine system disorders:* hypothyroidism, hyperthyroidism.
*Metabolic disorders:* anorexia, increased appetite, hyperglycemia, diabetes mellitus, hyperuricemia, hypocalcemia, dehydration, hypertriglyceridemia.
*Psychiatric disorders*: depression, apathy, crying, anxiety, emotional lability, aggressive behavior, agitation, anger, mood altered, abnormal behavior, nervousness, panic attack, confusion, insomnia, sleep disturbances, abnormal dreams, suicidal ideation, suicide, homicidal ideation, suicide attempt, psychosis, hallucinations, mania, bipolar disorder, decreased libido, mental status change.
*Nervous system disorders:* headache, migraine, dizziness, dry mouth, taste loss, dysgeusia, dysphonia, impaired concentration, amnesia, memory impairment, ataxia, paresthesia, hypoesthesia, hyperesthesia, somnolence, disturbance of attention, tremor, neuropathy, peripheral neuropathy, seizures, cerebrovascular hemorrhage, cerebrovascular ischemia, encephalopathy, polyneuropathy, facial palsy, mononeuropathy.
*Eye disorders:* visual impairment, blurred vision, disturbance of visual acuity, decreased visual acuity or loss of visual field, conjunctivitis, eye irritation, eye pain, lacrimal gland disorder, dry eye, retinal hemorrhage, retinopathy (including macular edema), retinal artery occlusion, retinal vein occlusion, optic neuritis, papilledema, retinal exudates, serous retinal detachment.
*Ear and labyrinth disorders:* vertigo, hearing impairment/loss, tinnitus, ear pain.
*Cardiovascular disorders:* palpitation, tachycardia, arrhythmia, myocardial infarction, cardiomyopathy, ischemic heart disease, pericardial effusion, pericarditis, hypotension, hypertension, hot flushes, vasculitis, peripheral ischemia.
*Respiratory disorders:* dyspnea, nasal congestion, rhinorrhea, nasal bleeding, respiratory disorder, cough, respiratory tract congestion, sinus congestion, increased upper airway secretion, pharyngolaryngeal pain, pulmonary infiltrates, pneumonitis, interstitial pneumonitis.
*Gastrointestinal disorders:* stomatitis, ulcerative stomatitis, mouth ulceration, oral pain, glossitis, cheilitis, gingivitis, gingival bleeding, tongue pigmentation, dental disorders, periodontal disorders, dental disease, nausea, vomiting, dyspepsia, abdominal pain, upper right quadrant pain, gastroesophageal reflux, abdominal distention, flatulence, colitis, diarrhea, frequent loose stools, constipation, colitis, ischemic colitis, ulcerative colitis, pancreatitis.
*Hepatobiliary disorders:* hepatomegaly, jaundice, hyperbilirubinemia, hepatotoxicity (including fatalities).
*Skin and subcutaneous tissue disorders:* alopecia, abnormal hair structure, nail disorder, pruritus, dry skin, rash, maculopapular rash, erythematous rash, psoriasis, aggravated psoriasis, eczema, photosensitivity reaction, night sweats, excessive sweating (hyperhidrosis), dermatitis, acne, boil, erythema, urticaria, skin disorders, bruise, cutaneous sarcoidosis, Stevens–Johnson syndrome, toxic epidermal necrolysis, erythema multiforme.
*Musculoskeletal disorders:* arthralgia, arthritis, back pain, pain in extremities, bone pain, musculoskeletal pain, myalgia, muscle weakness, rhabdomyolysis, myositis, muscle cramps.
*Urinary system disorders:* frequent urination, polyuria, abnormal discoloration of urine, renal failure, renal impairment, nephrotic syndrome.
*Reproductive system disorders:* <u>females</u>: amenorrhea, menorrhagia, menstrual disorder, dysmenorrhea, breast pain, ovarian disorder, vaginal disorder; <u>males:</u> impotence, prostatitis, erectile dysfunction, sexual dysfunction (not specified).
*General disorders:* fatigue, chills, pyrexia, influenza-like illness, asthenia, irritability, chest pain, chest discomfort, peripheral edema, malaise, feeling abnormal, thirst, face edema.
*Investigation findings:* weight decrease, cardiac murmur.
<u>Patients with HIV co-infection.</u>

In patients with HIV co-infection receiving ribavirin in combination with peginterferon α-2b, other adverse reactions (that were not reported in patients with hepatitis C virus mono-infection) were: oral candidiasis, lipodystrophy acquired, decreased CD4 lymphocytes, decreased appetite, increased gamma glutamyl transferase, back pain, increased blood amylase levels, increased blood lactic acid, cytolytic hepatitis, increased lipase, and pain in the limbs.

*Mitochondrial toxicity.*

Mitochondrial toxicity and lactic acidosis have been reported in HIV-positive patients receiving highly active antiretroviral therapy and complex ribavirin treatment for Hepatitis C virus co-infection.

*Laboratory values in patients with HIV co-infection.*

Patients with HIV co-infection have often demonstrated such signs of hematologic toxicity as neutropenia, thrombocytopenia and anemia, however, in most cases these disorders disappeared following dose modification, and did not require premature discontinuation of treatment. Hematologic disorders were more frequently reported in patients receiving ribavirin in combination with peginterferon α-2b when compared to patients receiving ribavirin in combination with interferon α-2b.

*Decrease of CD4 lymphocytes.*

Treatment with ribavirin in combination with peginterferon α-2b within the first 4 weeks was associated with a decrease in the absolute CD4+ cell count, without a reduction in the CD4 + cells percentage. This decrease in the absolute CD4+ cell count was reversible after dose reduction or discontinuation of therapy. The use of ribavirin in combination with peginterferon α-2b was not associated with a noticeable negative impact on the control of HIV viremia during the treatment period or follow-up. Safety data for patients with HIV co-infection with CD4 < 200 cells/ µl are limited.

Children.

The profile of adverse reactions in children is mostly similar to that in adult patients, although some adverse reactions are child-specific and are related to weight loss and growth retardation, the reversibility of which is unknown. The degree of growth inhibition was the greatest in prepubertal children.

*Infections and invasions:* viral infection, influenza, oral herpes, herpes simplex, shingles, bacterial infection, fungal infection, pulmonary infection, nasopharyngitis, pharyngitis, streptococcal pharyngitis, otitis media, pneumonia, sinusitis, tooth abscess, urinary tract infection, vaginitis, cellulitis, ascariasis, enterobiasis.

*Neoplasms benign, malignant and unspecified (including cysts and polyps):* neoplasm unspecified**.**

*Blood and lymphatic system disorders:* anemia, neutropenia, thrombocytopenia, lymphadenopathy.

*Endocrine disorders:* hypothyroidism, hyperthyroidism, virilism.

*Metabolic disorders:* anorexia, increased appetite, decreased appetite, hypertriglyceridemia, hyperuricemia.

*Psychiatric disorders:* depression, insomnia, emotional lability, suicidal ideations, suicidal thoughts, suicide attempts, aggression, confusion, affect lability, altered behavior, agitation, somnambulism, anxiety, altered mood, restlessness, nervousness, sleep disorder, abnormal dreams, apathy, abnormal behavior, depressed mood, emotional disorder, fear, nightmares, anger.

*Nervous system disorders:* headache, dizziness, hyperkinesia, tremor, dysphonia, paresthesia, hypoesthesia, hyperesthesia, impaired concentration, somnolence, deterioration of attention, poor quality of sleep, neuralgia, lethargy, psychomotor hyperactivity.

*Eye disorders:* conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder, conjunctival hemorrhage, eye pruritus, keratitis, blurred vision, photophobia, serous retinal detachment.

*Ear and labyrinth disorders:* vertigo.

*Cardiovascular system disorders:* tachycardia, palpitation, pallor, hot flushes, hypotension.

*Respiratory system disorders:* dyspnea, tachypnea, nose bleeding, cough, nasal congestion, nasal irritation, rhinorrhea, sneezing, pharyngolaryngeal pain, difficulty breathing, nasal discomfort.

*Gastrointestinal disorders:* abdominal pain, upper abdominal pain, vomiting, diarrhea, nausea, mouth ulceration, ulcerative stomatitis, stomatitis, aphthous stomatitis, dyspepsia, cheilosis, glossitis, gastroesophageal reflux, rectal disorders, gastrointestinal disorders, constipation, frequent loose stools, toothache, dental disorders, stomach discomfort, oral pain, gingivitis, gastroenteritis.

*Hepatobiliary system disorders:* hepatic dysfunction, hepatomegaly.

*Skin disorders:* alopecia, rash, pruritus, photosensitivity reaction, maculopapular rash, eczema, hyperhidrosis, acne, skin disorders, nail disorders, skin discoloration, dry skin, erythema, bruise, pigmentation, atopic dermatitis, skin exfoliation.
*Musculoskeletal disorders:* arthralgia, myalgia, musculoskeletal pain, pain in extremity, back pain, muscle contracture.
*Urinary system disorders:* enuresis, urination disorders, urinary incontinence, proteinuria.
*Reproductive system disorders*: females: amenorrhea, menorrhagia, menstrual disorders, vaginal disorders, dysmenorrhea; males: testicular pain.
*General disorders:* fatigue, increased fatigability, chills, pyrexia, influenza-like illness, asthenia, malaise, irritability, chest pain, edema, feeling cold, chest discomfort, facial pain.

*Investigation findings:* growth rate decrease (height and/or weight decrease for age), increased blood TSH (thyroid stimulating hormone) levels, increased thyroglobulin levels, presence of antithyroid antibodies.
*Injuries, poisoning and procedural complications:* contusion, skin lacerations.

***Shelf life.***
3 years.

**Storage conditions.**
Store at a temperature not more than 25 ºC.
Keep out of reach of children.

**Package.**
10 capsules are in a blister or strip; 10 blisters or strips are in a carton pack № 100 (10 × 10).

**Conditions of supply.**
Prescription only.

**Manufacturer.**
LLC “KUSUM PHARM”.

**Address of manufacturer and manufacturing site.**
40020, Ukraine, Sumy region, Sumy, Skryabina Str., 54.

**Last revision date.**
18.10.2023 № 1808