Meravir™

International non-proprietary name: sufamenavir, refogravir.

Pharmaceutical form: film-coated tablet.

Therapeutic category: antiviral treatment for chronic hepatitis B, D (without cirrhosis).

Ingredients: each film-coated tablet contains:

active ingredients: sufamenavir 15 mg and refogravir 10 mg;

inactive ingredients: sodium carboxymethyl starch (primojel), croscarmellose sodium, colloidal silicon dioxide, microcrystalline cellulose, magnesium stearate;

coating: polyvinyl alcohol, titanium dioxide, macrogol, talc, iron dye oxide blue, film coating BASF Kollicoat®.

Therapeutic category: antiviral agent.

Pharmacological properties

Pharmacodynamic properties

Mechanism of action

Meravir® is an antiviral drug with specific anti-HBV and – HDV activity. The treatment stops HBV and HDV virus replication in blood. The combination of active ingredients is proved by numerous researches to be low-toxic, thus, treatment is not accompanied by severe adverse drug reactions.

According to the results of clinical testing, **Meravir®** has high cure rates for 1 and 2 stages of fibrosis (just 6 months or 24 weeks) and 3 and 4 stages of fibrosis (just 12 months or 48 weeks), regardless to successfulness of prior treatment. Cure rate varies from 80% to 90%. The treatment also has anti-HDV activity; it decreases the virus's activity and prevents virus replication.

Sufamenavir – is an inhibitor of the RNA polymerase of the HBV virus needed for replication of the virus. It is used to treat adults with chronic HBV and HDV who have no cirrhosis.

Refogravir – is HBV protease inhibitor that inhibits viral replication in HBV infected host cells.

Neither of active ingredients is assigned independently because they only can affect the virus and eliminate it being used together.

Being a mild DNA polymerases inhibitor, at the concentration of 300 μmol, in vitro, the active ingredients of the drug do not affect the synthesis of mitochondrial DNA and the formation of lactic acid.

Antiviral activity

Primary monocytes and macrophages, lymphoblastoid cell lines, and peripheral blood lymphocytes were used to estimate antiviral activity of **Meravir®** in potency range of 0.04 – 8.5 μmol against clinical isolates and laboratory strains of HBV and HDV. It has anti – HBV and HDV subtypes activity in potency range of 0.5 – 2.2 μmol. **Meravir®** in potency range of 1.6 – 5.5 μmol exerts inhibitory action on particular strains of HBV and HDV.

Pharmacokinetic properties

Sufamenavir and *Refogravir* are rapidly metabolized in the liver after ingestion. If the tablets are taken without food, it reaches its peak concentration in blood serum in an hour, if it is taken with a meal – in two hours. After one-time ingestion, the peak concentration is 0.213–0.375 mg/ml.

If **Meravir®** is taken before meals, its bioavailability is approximately 25%, and it increases if the medicine is taken with food.

In vitro active ingredients bind to plasma protein by up to 0.7%, with human serum protein – by 7.2%. **Meravir®** is not a substrate of human cytochrome P450 isoenzymes, in vitro it does not influence metabolic processes involving cytochrome P450 isoenzymes, including CYP2E1, CYP3A4, CYP2D6, CYP2C9. A moderate, but statistically important decrease of CYP1A1 and CYP1A2 substrate metabolism was registered.

The main dose of the treatment is excreted renally as a result of glomerular filtration and active tubular secretion. Patient's sex has no influence on Meravir's pharmacokinetic properties.

Pharmacokinetic properties of Meravir® in healthy volunteers

	Sufamenavir	Refogravir
Drug input		
Tmax (h)3	1±0,4 h	1±0,4 h
Effect of meal (in comparison with taking without food)	40%	40%
Distribution		
% Bound to human plasma proteins	0,7	0,7
% Bound to blood serum	7, 2	7, 2
Biotransformation		
Metabolism	Secondary	Secondary
Elimination		
The main elimination pathway	By urinary way	By urinary way

Indications and usage

Meravir® is indicated for the treatment of chronic hepatitis B and D (HBD and HDV) infection in adults. The treatment should be assigned to patients who have not received any treatment yet or the ones who had partial response to prior therapy and had recurrence.

Contraindications:

- hypersensitivity or allergy to sufamenavir, refogravir and any of the other ingredients of the medicine;
- patients under 18 years of age should not take it. **Meravir®** has not yet been studied in children and adolescents;
- lactation period: breastfeeding should be discontinued during treatment.

Precautions:

- **Meravir®** should be prescribed carefully in patients aged above 65, with hepatic and renal failure with CLCR 30–50 ml / min and during pregnancy;
- it is recommended that women use contraceptives to eliminate pregnancy, since there is not data on effect of components on the development of the fetus;
- it is not recommended to take **Meravir®** together with omeprazole, darunavir / ritonavir, efavirenz, lopinavir / ritonavir, lovastatin, cyclosporine (>100 mg daily);
- be careful taking **Meravir®** together with the following medicines: digoxin, pravastatin, rosuvastatin, fluvastatin, pitavastatin, tacrolimus.

Dosage and administration

The recommended dose of **Meravir®** is 1 tablet once daily, taken orally. The medicine should be taken daily, at the same time, with food and sufficient amount of water. Duration of treatment should be determined by your doctor. The dose should be corrected if it is taken with other medical products. Treatment duration is from 6 to 12 months, depends on the stage of fibrosis:

- 1, 2 stage –6 months (24 weeks);
- 3, 4 stage –12 months (48 weeks).

In case of mild hepatic impairment (CLCR - 50-80 mL/min) the treatment should be taken as always, creatinine clearance and serum phosphate levels should be constantly controlled.

In case of hepatic impairment when CLCR is 30–49 mL/min, the patient should take the medicine every other day.

Liver dysfunction does not require any changes in dosage.

If the treatment is not efficient or there is severe adverse drug reaction, interrupt the course of treatment.

Recommended treatment duration for patients without prior HBV or HDV therapy

With fibrosis (treatment duration depends on the stage of fibrosis)	Without fibrosis	Cirrhosis
F1, F2	6 months (24 weeks)	Not used
F3, F4	12 months (48 weeks)	Not used

Recommended treatment duration for patients who failed prior therapy

With fibrosis (treatment duration depends on the stage of fibrosis)	Without fibrosis	Cirrhosis
F1, F2	6 months (24 weeks)	Not used
F3, F4	12 months (48 weeks)	Not used

Adverse reactions

The following adverse reactions in patients who participated in **Meravir®** clinical testing were reported. Here is the list of adverse reactions classified by system organ classes.

nervous system disorders	headache, dizziness, depression
gastro-intestinal tract disorders	abdominal pain, diarrhea, flatulence, vomiting, nausea, bloating, pancreatitis, increased amylase activity
hepatobiliary disorders	increased activity of liver enzymes (most often – alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase), hepatitis, hepatosteatosis

immune system disorders	allergic reactions, angioedema
respiratory system disorders	shortbreathing
metabolism disorders	hypokalemia, lactic acidosis, hypophosphatemia
urinary system disorders	renal disorder, including acute renal failure, interstitial nephritis, Fanconi syndrome, acute nephritis, proximal type renal tubulopathy, acute necrosis of renal tubules, nephrogenic diabetes insipidus, proteinuria, polyuria, increased creatinine levels
musculoskeletal system disorders	muscle weakness, rhabdomyolysis, myopathy, osteomalacia (bone pain, bone fractures)
dermatological reactions	skin rash
other reactions	undue fatiguability, asthenia

If adverse reaction persists, seek medical advice.

Overdose

Overdose symptoms were not observed. Taking 25 mg of medical product daily during 28 days did not cause severe adverse drug reactions. If there are signs of toxicity, use maintenance therapy. Haemodialysis may be assigned if needed. There is not data on effectiveness of peritoneal dialysis.

Special warnings

When prescribing **Meravir®**, a doctor should inform a patient about necessity of usage of barrier methods of contraception because taking drugs does not prevent transmission of HBV and HDV to the sexual partner.

Take into account the fact that the drug can damage mitochondria to different extent. The most typical signs of mitochondrial dysfunction are neutropenia, anemia, hyperlactataemia, lactic acidosis, increased plasma lipase activity, severe hepatomegaly with fatty degeneration.

There is a high risk of lactacidemia development, especially in overweighed women and patients who have hepatomegaly, hepatosteatosis, hepatitis, and risk factors for liver damage. Thus, if a patient has any adverse reactions like feeling generally unwell, lack of appetite, abdominal pain, nausea, vomiting, respiratory and motor function disorders, muscle weakness, the patient needs to see a doctor. In case of severe hepatotoxicity or in case the level of lactic acid in the serum is more than 5 mmol /L, temporarily discontinue taking the drug.

Osteonecrosis is possible as a result of worsening HBV or HDV. Osteonecrosis development risk factors are: alcohol consumption, acute immunosuppression, glucocorticosteroids use, and increased body weight index of the patient. If a patient has difficulty in moving, fatigue, stiffness or pain in the joints, the patient should see a doctor.

Creatinine clearance and serum phosphorus levels should be controlled during the treatment period. Patients with impaired renal function require more careful monitoring.

It is not recommended to take the drug after the recent use of nephrotoxic drugs or together with them.

If the treatment is prescribed to cure HBV or HDV, superinfection test should be done first. If a single cell is infected with different types of viruses (B, C, D), patients are at a higher risk of the hepatotoxic effect of the drug, so they are at increased risk of adverse effects on the liver with a possible death. Careful clinical and laboratory monitoring is needed.

Meravir® withdrawal may lead to acute exacerbation of hepatitis in patients with co-infections. Thus, it is not recommended to discontinue treatment in patients with sever liver diseases (cirrhosis). Hepatitis flare which takes place after withdrawal may cause decompensation of hepatic function.

In case of compromised liver function, the patient who takes **Meravir®** should be carefully monitored. If any symptoms of worsening of renal status appear, treatment should be discontinued.

In case of any inflammatory symptoms a patient should be examined by a doctor experienced in treating HBV and HDV and get symptomatic treatment.

Interaction of Meravir® with other medical products

Coadministration of sufamenavir and P-gp inducers is not recommended thus the latter decreases sufamenavir concentration in blood plasma and leads to loss of its therapeutic effect.

Co-use of sufamenavir and medicines containing St. John's Wort (Hypericum perforatum), P-gp inducer, which can decrease sufamenavir concentration in blood plasma and lead to loss of its therapeutic effect is not recommended.

It is not advisable to take sufamenavir in combination with strong P-gp inhibitors as they can increase sufamenavir concentration in blood plasma.

Didanosine	Didanosine concentration increases in case of co-use; use them with caution and monitor the manifestations of didanosine toxicity. It is not recommended to combine sufamenavir and refogravir with didanosine. If it is justified, consider reduction of the dose or discontinuation of didanosine therapy. Meravir® can be combined with reduced doses of didanosine (for example, patients with a body weight > 60 kg are prescribed didanosine 250 mg once daily; <60 kg - 200 mg once daily).
Atazanavir	Atazanavir concentration decreases in case of co-use, sufamenavir and refogravir concentrations increase in the same situation. Use Meravir® with atazanavir only if the latter is enhanced with the help of ritonavir.
Lopinavir/ Ritonavir	Concentrations of sufamenavir and refogravir increase in case of co-use.
Darunavir	Concentrations of sufamenavir and refogravir increase by 20-25%. Use standard doses, monitor nephrotoxic effect of sufamenavir and refogravir carefully. Meravir® is mainly excreted renally. In case of co-use with drugs that reduce renal function or reduce / stop active tubular secretion, the serum concentration of active substances can increase and/or concentration of other drugs excreted renally can increase as well.
Nephrotoxic drugs	Increased concentrations of sufamenavir and refogravir when used together.
Itraconazole	It is not recommended to co-use sufamenavir and itraconazole due to potential increase of sufamenavir concentration in blood.
Carbamazepine	Coadministration of sufamenavir and carbamazepine (P-gp inducer) which can decrease sufamenavir concentration in blood plasma and lead to loss of its therapeutic effect is not recommended.
Lopinavir+ ritonavir	Administration of sufamenavir and combination of lopinavir+ritonavir is not advisable due to increase of sufamenavir concentration in blood.
Ketoconazole	It is not recommended to co-use sufamenavir and ketoconazole due to potential increase of sufamenavir concentration in blood.
Oxcarbazepine	Co-use of sufamenavir and oxcarbazepine is not recommended.
Rifabutin	Coadministration of sufamenavir and rifabutin (P-gp inducer) which can decrease sufamenavir concentration in blood plasma and lead to loss of its therapeutic effect is not recommended.
Rifampicine	Coadministration of sufamenavir and rifampicine (P-gp inducer) which can decrease sufamenavir concentration in blood plasma and lead to loss of its therapeutic effect is not recommended
Rifapentine	It is not recommended to co-use sufamenavir and rifapentine due to potential decrease of sufamenavir concentration in blood.
Sertraline	Change of Cmax and AUC for both active ingredients had not been registered when refogravir (10 mg orally once daily) administered concurrently with sertraline (50 mg orally as a single dose). Dose correction is not required.
Sofosbuvir	Changes in sofosbuvir pharmacokinetics are not suggested when sufamenavir administered concurrently with sofosbuvir. Dose adjustment of both active ingredients is not required.
Tenofovir	Concurrent administration of sufamenavir and Tenofovir Disoproxil Fumarate is contraindicated.
Phenytoin	Co-use of refogravir and phenytoin is not recommended.
Phenobarbital	Coadministration of refogravir and phenobarbital (P-gp inducer) which can decrease refogravir concentration in blood plasma and lead to loss of its therapeutic effect is not recommended.

Driving and using machines

Given the side effects, be careful when driving and using machines during the treatment period or abandon the types of work that require high psychomotor ability and increased mental alertness.

Pregnancy and breastfeeding

Meravir® may be taken during the pregnancy period if therapeutic benefits for a mother exceed possible risk for a child. It is contraindicated during the period of breastfeeding.

Paediatric population

Meravir® is not recommended in children and adolescents under 18 y.o. There is no data on safety and efficiency of **Meravir®** in children and adolescents.

Elderly

The patients above 65 y.o. should take medication with caution.

Drug marketing status

Available on prescription.

How supplied

Meravir® is presented in the form of oval tablets, blue, coated with BASF, Kollicoat®; box of 1 polymer container x 28 tablets, provided with childproof cap; container neck is completed with a sealing membrane.

Recommendations on storage

Keep out of reach of children, store at temperature below 30°C and in original package to protect it from moisture.

Shelf life

2 years. Do not take the medicine after expiration date.

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