MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION
INSTRUCTIONS FOR MEDICAL USE OF THE MEDICINAL PRODUCT

CORONAVIR

Registration number: ЛП-006323

Brand name: CORONAVIR

International non-proprietary name: favipiravir

Dosage form: film-coated tablets

Content

One film-coated tablet contains:
Active ingredient: favipiravir – 200.0 mg.
Inactive ingredients: microcrystalline cellulose type 101, colloidal silicon dioxide, povidone-K25, crospovidone, sodium stearyl fumarate.
Film coat: Opadray II 85F220031 yellow [polyvinyl alcohol, titanium dioxide, macrogol 4000, talc, iron oxide yellow dye].

Description

Round, biconvex, film-coated, tablets, light yellow with a brownish tinge. The core of the tablet in cross-section is from white to light yellow.

Pharmacotherapeutic group: antiviral drugs

ATX code: J05AX27

PHARMACOLOGY

Pharmacodynamics

In vitro antiviral activity

Favipiravir showed antiviral activity against type A and type B influenza virus laboratory strains with an E_{C50} of 0.014-0.55 μg/ml.
For strains of influenza A and B viruses resistant to adamantanes (amantadine, rimantadine), oseltamivir or zanamivir, EC_{50} is 0.03–0.94 and 0.09–0.83 μg/ml, respectively. For influenza A viruses (including strains resistant to adamantanes, oseltamivir or zanamivir), such as type A swine influenza and type A avian influenza, including highly pathogenic strains (including H5N1 and H7N9), the EC_{50} is 0.06–3.53 μg/ml.
For strains of influenza A and B viruses resistant to adamantanes, oseltamivir or zanamivir, EC_{50} is 0.09–0.47 μg/ml, no cross-resistance was observed.
Favipiravir inhibits the SARS-CoV-2 virus that causes novel coronavirus infection (COVID-19). The EC50 in Vero E6 cells is 61.88 μM which corresponds to 9.72 μg/ml.

Mechanism of action

Favipiravir is metabolized in cells to a ribosyl triphosphate form (favipiravir RTF), and that favipiravir RTF selectively inhibits RNA-dependent RNA polymerase involved in influenza virus replication. Favipiravir RTF at a concentration of 1000 μmol/L did not show an inhibitory effect on DNA polymerase α, but showed an inhibitory effect on DNA polymerase β in the range from 9.1 to 13.5% and γ in the range from 11.7 to 41.2%, respectively. The inhibitory concentration (IC_{50}) of favipiravir RTF for human RNA polymerase II was 905 μmol/L.

Resistance

There were no changes in the sensitivity of influenza type A virus to favipiravir after 30 passages of the virus in the presence of favipiravir, no resistant virus strains were isolated. In clinical studies, no cases of influenza virus strains resistant to favipiravir were identified.

Pharmacokinetics

Absorption

Favipiravir is readily absorbed in the gastrointestinal tract. Time taken to reach the maximum concentration (T_{max}) is 1.5 hours.

Distribution

Plasma protein binding is about 54%

Metabolism

Favipiravir is mostly metabolized by aldehyde oxidase and is partly metabolized to hydroxylated form by xanthine oxidase. RTF of favipiravir is metabolized in cells. A glucoronate conjugate was observed in human plasma and urine as a metabolite other than the hydroxylated form.

Excretion

Favipiravir was mainly excreted by the kidneys as an active metabolite hydroxylat, the unchanged substance is excreted in a small amount. The half-life ($T_{1/2}$) is about 5 hours.

Patients with impaired liver function

Oral administration of favipiravir by patients with mild and moderate hepatic impairment (classes A and B on the Child-Pugh scale) C_{max} and AUC was approximately 1.5 and 1.8 times, respectively compared with those in healthy volunteers. When taken orally by patients with decompensated liver disease (class C on the Child–Pugh scale) C_{max} and AUC were approximately 2.1 and 6.3 times higher, respectively.

Patients with impaired renal function

In patients with moderate renal impairment (glomerular filtration rate <60 ml/min and ≥30 ml/min) the residual concentration ($C_{through}$) of favipiravir increased by 1.5 times. Favipiravir has not been studied at patients with severe renal impairment (glomerular filtration rate <30 ml / min).

Indications

Treatment of new coronavirus infection (COVID-19).

Contraindications

Hypersensitivity to favipiravir or to any other component of the drug.
Severe liver dysfunction (class C on the Child-Pugh scale).
Severe renal dysfunction (glomerular filtration rate <30 ml/min).
Pregnancy or the period of planning a pregnancy.
The period of breastfeeding.
Children under than 18 years.

Precautions

Patients with a history of gout and hyperuricemia (possibly increased blood uric acid levels and worsening symptoms).
Elderly patients
Patients with mild and moderate hepatic impairment (classes A and B on the Child-Pugh scale).
Patients with moderate renal impairment (glomerular filtration rate <60 ml/min and ≥30 ml/min).

Use during Pregnancy and lactation

Early embryonic death and teratogenicity have been observed in animal studies with exposure levels similar to or lower than the clinical exposure.
CORONAVIR is contraindicated to pregnant women, as well as to men and women during pregnancy planning. When administering CORONAVIR to women of childbearing potential (include menopause less than 2 years), confirm a ***negative pregnancy test*** result before starting the treatment. A repeated pregnancy test must be performed after the end of treatment. Necessary to use the most effective contraceptive (condom with spermicide) during the treatment and after treatment (for 1 months for women and for 3 months for men).
Breastfeeding women should stop breastfeeding for the duration of favipiravir treatment and for at least 7 days after the end of the treatment, since the main metabolite of favipiravir passes into breast milk.

Dosage and administration

The drug CORONAVIR should be taken orally 30 minutes before meals.
For the treatment of a new coronavirus infection caused by the SARS-CoV-2 virus (COVID-19), the following dosage regimen is used:
o for patients having bodyweight <75 kg: 1600 mg (8 tablets) twice daily on the 1st day of therapy, then 600 mg (3 tablets) twice daily from the 2nd to the 10th days of therapy respectively;
o for patients having bodyweight ≥75 kg: 1800 mg (9 tablets) twice daily on the 1st day of therapy, then 800 mg (4 tablets) twice daily from the 2nd to the 10th days of therapy respectively.
The drug should be taken after the diagnosis confirmed by the laboratory and / or in the presence of characteristic clinical symptoms.
The total duration of the course of treatment is 10 days or until confirmation of the elimination of the virus, if it occurs earlier (two consecutive negative results of PCR studies, obtained with an interval of at least 24 hours).

Adverse Reactions

Adverse reactions were observed in 70 (63.9 %) of 108 patients in clinical trial of CORONAVIR, and they include: Hyperuricaemia in 43 patients (39.8 %), ALT increased in 36 patients (33.33 %), AST increased in 24 patients (22.2 %), Diarrhea in 16 patients (14.8%), Creatine kinase increased in 15 patients (13.9%), Hyperglycemia in 11 patients (10.2%), Sinus bradycardia in10 patients (9.3 %), Nausea in 9 patients (8.3 %), Abdominal pain in 8 patients (7.4 %), Epigastric pain in 7 patients (6.5 %), Blood lactate dehydrogenase increased in 6 patients (5.6%), Headache in 4 patient (3.7%), Skin rash in 4 patients (3.7 %), Hyperbilirubinemia in 4 patients (3.7 %), Sinus tachycardia in 3 patients (2.8%), Hematuria in 2 patients (1.9%), Increased sweating of the feet in 1 patient (0.9%), Chilliness of feet in 1 patient (0.9%), Muscle weakness in 1 patient (0.9%), Pain in eyes in 1 patient (0.9%), Dizziness in 1 patient (0.9%), Vomiting in 1 patient (0.9%), Blood pressure increased in 1 patient (0.9%), Ferritin increased in 1 patient (0.9 %), Hypercreatininaemia in 1 patient (0.9%), Leukocyturia in 1 patient (0.9%), Bilirubinuria in 1 patient (0.9%), Urobilinogen urine increased in 1 patient (0.9%), Proteinuria in 1 patient (0.9%), Glycosuria in 1 patient (0.9%), Thrombocytosis in 1 patient (0.9%), Cylindruria in 1 patient (0.9%).
Adverse reactions observed in Clinical Trials in Patients with Influenza Infection (Data from Analysis in the Pooled Population Pooled for Safety Assessment) are presented in the table 1.
Estimation of the frequency of adverse events listed as follows is defined using the WHO classification: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1. Adverse Reactions

System organ class	Adverse reactions
Blood and lymphatic system disorders	*Common:* Neutrophil count decreased, Leukopenia *Rare:* Lymphocyte count increased, Monocytosis, Reticulocytopenia
Metabolism and nutrition disorders	*Common:* Hyperuricemia, Hypertriglyceridemia *Uncommon:* Glucosuria *Rare:* Hypokalemia
Immune system disorders	*Uncommon:* Rash *Rare:* Eczema, Itch
Respiratory, thoracic and mediastinal disorders	*Rare:* Bronchial asthma, Sore throat, Rhinitis, Nasopharyngitis
Gastrointestinal disorders	*Common:* Diarrhoea *Uncommon:* Nausea, Vomiting, Abdominal pain *Rare:* Discomfort abdominal, Ulcer duodenal, Haematochezia, Gastritis
Hepatobiliary disorders	*Common:* Increased ALT activity, Increased AST activity, Increased glutamyl transferase activity *Rare:* Increased activity of alkaline phosphatase (ALP), Increased concentration of bilirubin in the blood
Others	*Rare:* Abnormal behavior, Increased activity of creatine phosphokinase, Hematuria, Laryngeal polyp, Hyperpigmentation, Impaired taste sensitivity, Hematoma, Blurred vision, Eye pain, Vertigo, Supraventricular extrasystoles, Chest pain

Overdose
There are no reports of an overdose with favipiravir.

Interaction with other drugs
CORONAVIR is not metabolized by cytochrome P450 (CYP), it is mainly metabolized by aldehyde oxidase and partially hydroxylated by xanthine oxidase. CORONAVIR irreversibly inhibits aldehyde oxidase and CYP2C8 but does not induce cytochrome P450.

Table 2. Drug interaction.

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Pyrazinamide	Blood uric acid level increases. When pyraxinamide 1.5 g once daily and favipiravir 1200 mg/400 mg twice a day were administered, the blood uric acid level was 11.6 mg/dL when pyrazinamide was administered alone, and 13,9 mg/dL in combination with favipiravir	Reabsorption of uric acid in the renal tubule is additively enhanced
Repaglinide	Blood level of repaglinide may increase, and adverse reactions to repaglinide may occur	Inhibition of CYP 2C8 increases blood level of repaglinide
Theophylline	Blood level of favipiravir may increase, and adverse reactions to favipiravir may occur	Interaction with XO may increase blood level of favipiravir
Famciclovir Sulindac	Efficacy of these drugs may be reduced	Inhibition of AO by favipiravir may decrease blood level of active forms of these drugs

Special warnings
With the development of side effects when using the drug, it is must be informed immediately in the prescribed order for the implementation of measures for pharmacovigilance.
Before using the drug CORONAVIR, the patient must be provided with full information about its effectiveness and risks associated with the use (including the risk of affecting the embryo and fetus), and obtain written consent for its use.
Since early embryonic death and teratogenicity have been observed in animal studies of favipiravir, the use of CORONAVIR in women with established or probable pregnancy is unacceptable.
1) When prescribing favipiravir to women with preserved reproductive potential, it is necessary to obtain a ***negative pregnancy test result*** before starting treatment. It is necessary to explain to the patient the risks of teratogenicity and instruct to use the most effective methods of contraception throughout the entire period of therapy and for at least 1 month after its termination (condom with spermicide). If pregnancy is suspected during therapy with favipiravir, you should immediately stop using the drug and consult a doctor.
2) CORONAVIR enters the semen. Male patients when using the drug CORONAVIR should use the most effective methods of contraception throughout the entire period of therapy and for at least 3 months after its end. The use of the barrier method (condom with spermicide) is mandatory. It is necessary to instruct the patient not to have sex with pregnant women.
3) When distributed in the human body, the drug CORONAVIR passes into breast milk. When prescribing the drug to lactating women, it is necessary to explain the risks and instruct them to stop breastfeeding during the treatment and within 7 days after its end.

Influence on the ability to drive vehicles, mechanisms
Should be careful when driving and operating machinery.

Dosage form
Film-coated tablets, 200 mg.
10 tablets in a blister strip of a combined film (polyvinyl chloride / polyvinylidene chloride) and varnished aluminum foil.
50 tablets in a polymer jar (made of polyethylene) for medicines, sealed with a polymer lid (made of polypropylene) with a first opening control.
A label made of label paper or writing paper or a self-adhesive label is attached to the jar.
Each can or 5 blister packs together with instructions for use are placed in a box made of cardboard box.

Storage conditions
At a temperature of no higher than 25 °C.
Keep out of the reach of children.

Shelf life
2 years.
Do not use after the expiration date.

Dispensing rules
Dispensed by prescription.

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