MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

INSTRUCTION

FOR MEDICAL USE

AVIFAVIR

This pharmaceutical product is approved according to the registration procedure for the drugs intended for use in the state or preparedness of emergency. The instruction is prepared based on limited clinical data and will be amended as new data becomes available. The use of the drug is possible only in inpatient care.

Registration number: LP-006225-290520

Trade name: AVIFAVIR

International Non-proprietary or Group Name: Favipiravir

Pharmaceutical dosage form: Film-coated tablets

Composition: 1 tablet contains:

- *Active substance:* Favipiravir, 200 mg;
- *Excipients:* microcrystalline cellulose 102; sodium croscarmellose; povidone K-30; magnesium stearate; silicon dioxide colloidal;
- *Opadray II 85F38183 yellow film shell:* polyvinyl alcohol, macrogol, iron oxide yellow, talc, titanium dioxide.

Description: Round concave brown-yellow film coated tablets. The tablet core is white or almost white – yellowish at the cross section.

Pharmacotherapeutic group: antiviral agent

ATC code: J05AX27

Pharmacological properties

Pharmacodynamics

In vitro antiviral activity

Favipiravir showed antiviral activity against type A and type B influenza virus laboratory strains with an a half maximal effective concentration (EC50) of 0.014–0.55 μg/mL. The EC50 against seasonal type A and type B influenza viruses including strains resistant to adamantane (amantadine and rimantadine), oseltamivir or zanamivir was 0.03–0.94 and 0.09–0.83 μg/mL, respectively.

The EC50 against type A influenza viruses (including strains resistant to adamantane, oseltamivir or zanamivir) such as swine-origin type A and avian-origin type A including highly-pathogenic strains (including H5N1 and H7N9) was 0.06–3.53 μg/mL.

The EC50 against type A and type B influenza viruses resistant to adamantane, oseltamivir and zanamivir was 0.09–0.47 μg/mL, and no cross resistance was observed.

Favipiravir inhibits the SARS-CoV-2 virus that causes a new coronavirus infection (COVID-19). The EC50 in Vero E6 cells is 61.88 μmol, which corresponds to 9.72 μg/ml.

Mechanism of action

Favipiravir is metabolized in cells to a ribosyl triphosphate form (favipiravir RTP) and that favipiravir RTP selectively inhibits RNA polymerase involved in influenza viral replication. With regards to the activity against human DNA polymerases α , β and γ , favipiravir RTP (1000 μmol/L) showed no inhibitory effect on α , 9.1-13.5% inhibitory effect on β and 11.7-41.2% inhibitory effect on γ . Inhibitory concentration (IC50) of favipiravir RTP on human RNA polymerase II was 905 μmol/L.

Resistance

No change of susceptibility of type A influenza viruses to favipiravir was observed after 30 passages in the presence of favipiravir, and no resistant viruses have been selected. In conducted clinical studies, information about emergence of favipiravir-resistant influenza viruses has not been obtained.

Pharmacokinetics

Absorption

Favipiravir is rapidly absorbed taken orally. Time to reach maximum concentration (T_{max}) 1,5 h.

Distribution

Plasma protein binding is about 54 %.

Metabolism

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

Excretion

Favipiravir is mainly excreted by the kidneys as an active metabolite of hydroxylate, a small amount remains unchanged. Half-life (T1/2) is about 5h.

Patients with hepatic impairment

Increase of Cmax and AUC after favipiravir administration by patients with mild and moderate hepatic impairment (Child-Pugh A and B class) were 1.5-fold *и* 1.8-fold accordingly, comparing to healthy subjects. Cmax and AUC in patients with severe hepatic impairment (Child-Pugh C class) increased 2.1-fold and 6.3-fold, accordingly.

Patients without impaired renal function

After administration of favipiravir by patients with a moderate decrease in glomerular filtration rate (GFR <60 ml / min and ⩾ 30 ml / min), the residual concentration Ctrough increased 1.5-fold compared to patients without impaired renal function. The drug has not been studied in patients with severe and terminal stages of chronic kidney disease (GFR <30 ml / min).

Indications

Novel coronavirus infection (COVID-19) treatment.

Contraindications

- Hypersensitivity to favipiravir or any ingredient of AVIFAVIR.
- Severe hepatic impairment (Child-Pugh C class).
- Severe and terminal stages of impaired renal function (GFR <30 ml / min).
- Pregnancy or pregnancy planning .
- Period of breastfeeding.
- Age under 18 years.

Precautions

Patients with gout or a history of gout, and patients with hyperuricaemia (Blood uric acid level may increase, and symptoms may be aggravated., elderly patients, patients with mild and moderate hepatic impairment (Child-Pugh A and B class), patients without moderate impaired renal function (GFR < 60 ml/min and ⩾ 30 ml/min).

Use in pregnancy and breast-feeding period

Early embryonic deaths and teratogenicity have been observed in nonclinical studies at similar to clinical or lower doses.

AVIFAVIR is contraindicated in pregnant women, as well as men and women during pregnancy planning. When prescribing AVIFAVIR to women capable of childbearing (including postmenopausal women less than 2 years old), it is necessary to confirm a negative pregnancy test result before treatment. A repeated pregnancy test shall be carried out after taking the drug. Effective methods of contraception (condom with spermicide) shall be used while taking the drug and after treatment completion: 1 month for women and 3 months for men.

When taking AVIFAVIR, lactating women shall stop breastfeeding for the time of drug administration and 7 days after withdrawal, as the primary metabolite of favipiravir penetrates into breast milk.

Dosage and Administration

Orally, 30 minutes before meal. AVIFAVIR is prescribed as inpatient treatment.

New coronavirus infection (COVID-19)

AVIFAVIR is prescribed for adults according to the standard regimen depending on the patient's body weight:

For the patients with body weight less than 75 kg: 1600 mg 2 times on Day 1, then 600 mg 2 times per day on Days 2 to 10.

For the patients with body weight of 75 kg and over: 1800 mg 2 times on Day 1, then 800 mg 2 times per day on Days 2 to 10.

Total duration of treatment shall be 10 days or till the virus elimination is confirmed, depending on what is earlier (two sequential negative PCR tests with a minimum interval of 24 hours).

Side effects

In a clinical study of AVIFAVIR, adverse reactions were observed in 6 out of 60 patients (10%), including vomiting in 2 (3.3%) patients, nausea in 1 (1.7%) patient, increased activity of alanine aminotransferase (ALT) and increased activity of aspartate aminotransferase (AST) in 1 (1.7%) patient and chest pain in 1 (1.7%) patient. These adverse reactions, except for chest pain of unknown origin, are consistent with the known adverse drug reactions of favipiravir presented in Table 1.

The assessment of the frequency of adverse reactions is based on the WHO classification: very common (⩾1/10); common (⩾1/100, <1/10); uncommon (⩾1/1000, <1/100); rare (⩾1/10000, <1/1000); very rare (<1/10000), frequency unknown (it is not possible to determine the frequency from the available data).

Table 1. Adverse reactions

Classification by diseases, organs and systems	***Adverse reactions***
Blood and lymphatic system disorders	*Common:* neutropenia, leukopenia *Rare:* leukocytosis, monocytosis, reticulocytopenia
Metabolism and nutrition disorders	*Common:* hyperuricemia, hypertriglyceridemia *Uncommon:* glucosuria *Rare:* hypokalemia
Nervous system disorders	*Uncommon:* rash *Rare*: eczema, itching
Respiratory, thoracic and mediastinal disorders	*Rare:* bronchial asthma, sore throat, rhinitis, nasopharyngitis
Gastrointestinal tract disorders	*Common*: diarrhea *Uncommon:* nausea, vomiting, abdominal pain *Rare:* abdominal discomfort, duodenal ulcer, bloody stools, gastritis
Liver and biliary tract disorders	*Common*: increased activity of aspartate aminotransferase (ACT), increased activity of alanine aminotransferase (ALT), increased activity of gamma-glutamyltransferase (γ-GT) *Rare:* increased activity of alkaline phosphatase (ALP), creatine phosphokinase (CPK) in the blood, increased bilirubin levels in the blood
Other	*Rare:* abnormal behavior, increased activity of creatine phosphokinase (CPK), hematuria, polyps on the tonsils, hyperpigmentation, taste disorders, hematomas, blurred vision, eye pain, dizziness, supraventricular extrasystole

Overdose

There are no reports of an overdose with favipiravir.

Drug interactions

AVIFAVIR is not metabolized by cytochrome P450, mostly metabolized by aldehyde oxidase, and partly metabolized by xanthine oxidase. AVIFAVIR inhibits aldehyde oxidase and CYP2C8, but does not induce cytochrome P450

Table 2. Drug-drug interactions

Medicinal products	*Signs, symptoms, and treatment*	*Mechanism of action and risk factors*
Pyrazinamide	hyperuricemia	Additionally an increase in the reabsorption of uric acid in the renal tubules was noted
Repaglinide	The concentration of Repaglinide in the blood may increase, and adverse reactions to Repaglinide may develop	Inhibition of CYP2C8 leads to increase in the concentration of Repaglinide in the blood
Theophylline	The concentration of favipiravir in the blood may increase, adverse reactions to favipiravir may develop	Drug interaction with xanthine oxidase can lead to increase in the concentration of favipiravir in the blood
Famciclovir, sulindak	The effectiveness of these medications may be reduced	Favipiravir inhibition of aldehyde oxidase can lead to a decrease in the concentration of active forms of these drugs in the blood

Special Precautions

The use of the drug is permitted for inpatient care only.

The development of an adverse reaction should be reported duly in order to conduct the pharmacovigilance activities.

Before prescription of AVIFAVIR, the written information about efficacy and risks associated with the use of the drug (including the risk of exposure to the embryo and fetus) shall be provided to the patient and written consent to use the drug shall be obtained.

As embryonic deaths and teratogenicity have been observed in nonclinical studies in animals AVIFAVIR shall not be prescribed to pregnant and presumably pregnant women.

1) AVIFAVIR is contraindicated in pregnant women, as well as men and women during pregnancy planning. When prescribing AVIFAVIR to women capable of childbearing (including postmenopausal women less than 2 years old), a negative pregnancy test result shall be confirmed before treatment. A repeated pregnancy test shall be carried out after taking the drug. Men and women who are capable of childbearing shall be fully explained the risks and carefully instructed of the use of effective methods of contraception while taking the drug and within 1 month after treatment completion (condom with spermicide). Under the assumption of a possible pregnancy, it is necessary to immediately stop taking the drug and consult a doctor.

2) Distributing in a human body AVIFAVIR penetrates into sperm. When administering the drug to male patients, explain fully the risks and instruct thoroughly to use most effective contraceptive methods in sexual intercourse during and for 3 months after the end of the treatment (condom with spermicide). In addition, men shall be instructed not to have sexual intercourse with pregnant women.

3) Distributing in a human body AVIFAVIR penetrates into breast milk. When prescribing the drug to breastfeeding women, they shall be fully explained the risks and carefully instructed to avoid breastfeeding during drug administration and for 7 days after withdrawal.

Effects on ability to drive and use machines

Care should be taken when driving vehicles and working with mechanisms.

Dosage form

Film-coated tablets, 200 mg.

10 tablets in blister pack made from polyvinylchloride film and printed lacquered aluminum foil.

40 capsules in a PE bottle sealed with a tamper-proof cap with moisture acceptor.

One cardboard pack (package) contains one bottle or 1, or 4 blister packs including patient information leaflet.

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

Shelf life: 1 year. Do not use after the expiration date indicated on the package.

Prescription status

Prescription only