MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

INSTRUCTIONS FOR MEDICAL USE OF THE MEDICINAL PRODUCT

CORONAVIR

This medicinal product is registered according to the registration procedure for drugs intended for use in conditions of threat of emergence, occurrence and liquidation of emergency situations. This instruction was prepared on the ground of a limited clinical data amount according to the usage of the drug and will be supplemented as long as new data becomes available.

Registration number:
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 (excluding HIV) drugs
ATX code: J05AX27

PHARMACOLOGY

Pharmacodynamics

Mechanism of action

Favipiravir is a nucleoside analogue. When ingested, favipiravir undergoes intracellular

metabolism to the form of favipiravir ribosyl triphosphate (favipiravir RTF), which selectively blocks the viral RNA polymerase involved in its replication. With respect to human DNA polymerases α, β and γ, 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.

Specific activity in vitro

The antiviral activity of favipiravir against the SARS-CoV-2 virus (*Coronaviridae* family) was investigated *in vitro* on a Vero E6 cell culture. According to the results of the study, the EC_{50} for favipiravir was 61.88 μM, the cytotoxic concentration (CC_{50}) ≥400 μM, the selectivity index (SI) – ≥6.46, respectively.

Regarding SARS-CoV-2 coronavirus (BetaCoV/Hong Kong/VM20001061/2020), isolated from swabs from the nasopharynx and oropharynx obtained from patients with COVID-19 disease from Hong Kong, in an *in vitro* study on Vero E6 cell culture, that favipiravir inhibits viral replication at concentrations above 100 μg/ml.

Favipiravir exhibits antiviral activity against laboratory strains of influenza A and B viruses with half the maximal effective concentration (EC_{50}) in the range of 0.014 to 0.55 μg/ml.

With regard to seasonal strains of influenza A and B viruses, including strains resistant to adamantanes (amantadine, rimantadine), oseltamivir or zanamivir, EC_{50} was 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} was 0.06–3.53 μg/ml.

For strains of influenza A and B viruses resistant to adamantanes, oseltamivir or zanamivir, EC_{50} was 0.09–0.47 μg/ml, no cross-resistance was observed.

Specific activity in vivo

In a model of the development of infection in mice infected with influenza A (H7N9), or A (H1N1) pdm 09, or A (H3N2), a decrease in viral load in lung tissue was observed after oral administration of favipiravir at a dose of ≤60 mg/kg/day in within 5 days.

In a model of the development of infection in mice infected with influenza A (H3N2) or A (H5N1) viruses, the therapeutic effect was observed after oral administration of favipiravir at a dose of 30 mg/kg/day for 5 days.

In a model of the development of infection in mice with severe combined immunodeficiency, infected with the influenza A (H3N2) virus, the therapeutic effect was observed after oral administration of favipiravir at a dose of 30 mg/kg/day for 14 days.

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 was identified.

Clinical trial results

The efficacy of favipiravir in the treatment of novel coronavirus infection (COVID-19) has been studied in two clinical studies:

1) a study of favipiravir versus lopinavir / ritonavir (LPV / RTV), used in combination with inhaled interferon alfa;

2) a study of favipiravir versus umifenovir therapy.

Clinical study of favipiravir versus LPV / RTV used in combination with inhaled interferon alfa

In an open, non-randomized study of favipiravir versus LPV / RTV in patients with laboratory-confirmed SARS-CoV-2 (COVID-19) coronavirus infection, 80 patients with moderate to severe disease took part. In the main group, patients (n=35) received oral favipiravir according to the following scheme: 1600 mg 2 times a day on the 1st day of treatment, followed by 600 mg 2 times a day from the 2nd to the 14th days on the background inhalation use of interferon alpha in the form of an aerosol (at a dose of 5 million units 2 times a day). In the control group, patients (n=45) received a combination of LPV/RTV at a dose of 400 mg/100 mg 2 times a day for 14 days, also against the background of inhalation of interferon alfa in the form of an aerosol at the same dose.

According to the results of computed tomography (CT) of the lungs, clinical improvement in the favipiravir group occurred more rapidly than in the control group: on the 14th day of therapy, clinical improvement was observed in 91.43% of patients in the favipiravir group, while in the control group - only in 62.22% of patients. The median time to virus elimination in the favipiravir group was 4 days (interquartile range (IQR) 2.5–9.0), while in the control LPV / RTV group it was 11 days (IQV 8–13) ($p<0.001$). Antiviral therapy was better tolerated in the favipiravir group: adverse reactions were reported in 11% of patients in the favipiravir group and in 55% of patients in the control group (LPV/RTV).

Clinical study of favipiravir versus umifenovir

In a prospective, open-label, multicenter, randomized study of the efficacy of favipiravir versus umifenovir, 236 patients with novel coronavirus infection (COVID-19 disease) were enrolled: 116 patients (98 with moderate and 18 with severe disease) were included in the favipiravir group and 120 patients (111 of them with moderate and 9 with a severe course of the disease) - in the umifenovir group.

In the main group, patients received oral favipiravir according to the following scheme: 1600 mg 2 times a day on the 1st day of therapy, then 600 mg 2 times a day from the 2nd to the 10th days. In the control group, patients received umifenovir 200 mg 3 times a day for 7-10 days.

Clinical improvement on day 7 of therapy, which was the primary endpoint, was observed in 61.21% of patients in the favipiravir group and 51.67% of patients in the umifenovir group, respectively. For patients with moderate disease, these indicators were: 71.43% (70 of 98) of patients in the favipiravir group and 55.86% (62 of 111) of patients in the umifenovir group. In patients with a severe course of the disease, clinical improvement on the 7th day of therapy occurred in 5.56% (1 of 18) in the favipiravir group, in the umifenovir group the indicator was 0% (0 of 9) (see Table 1).

Table 1. Comparison of indicators of clinical improvement on the 7th day of therapy

Index	Favipiravir	Umifenovir	Frequency difference (95% CI)	p
All patients	n=116	n=120	–	–
Clinical improvement, n (%)	71 (61,21)	62 (51,67)	0,0954 (–0,0305, 0,2213)	0,1396
Patients with a moderate stage of disease	n=98	n=111	–	–
Clinical improvement, n (%)	70 (71,43)	62 (55,87)	0,1557 (0,0271, 0,2843)	0,0199
Patients with severe disease	n=98	n=111	–	–
Clinical improvement, n (%)	1 (5,56)	0 (0,00)	0,0556 (–0,0503, 0,1614)	0,4712

Pharmacokinetics

Absorption

Pharmacokinetic (PK) parameters of favipiravir after oral administration at a dose of 1600 mg 2 times a day on the 1st day of therapy and then 600 mg 2 times from the 2nd to the 5th days and at a dose of 600 mg once a day are presented once in table 2: maximum concentration (C_{max}), area under the pharmacokinetic curve "concentration time" (AUC), time to reach maximum concentrations (T_{max}), half-life ($T_{1/2}$).

Table 2. Pharmacokinetic (PK) parameters of favipiravir

Dosage	Day	C_{max}, mkg/ml[1]	AUC[1, 2], mkg× hr /ml	$T_{max, hr}$ [3]	$T_{1/2, hr}$ [4]
1600 mg /600 mg 2 in day	Day 1	64,56 (17,2)	446,09 (28,1)	1,5 (0,75; 4,0)	4,8±1,1
	Day 6	64,69 (21,1)	553,98 (31,2)	1,5 (0,75; 2,0)	5,6±2,3

[1] Geometric mean (CV%).
[2] Day 1 – $AUC_{0-\infty}$, Day 6 – AUC_t.
[3] Median (minimum; maximum).
[4] Mean ± SD.

Following multiple oral administration of favipiravir for 7 days to an healthy adult who appeared to have little AO activity, the estimated AUC of unchanged drug was 1452,73 μg×hr/ml.

Table 3. Pharmacokinetic parameters of favipiravir after multiple administration at doses of 1600/800 mg and 1800/600 mg

	1600/800 mg twice daily				**1800/600 mg twice daily**			
	Favipiravir		**M1**		**Favipiravir**		**M1**	
	Day 1 (1600 mg)	**Day 5 (800 mg)**	**Day 1 (1600 mg)**	**Day 5 (800 mg)**	**Day 1 (1800 mg)**	**Day 5 (600 mg)**	**Day 1 (1800 mg)**	**Day 5 (600 mg)**
Number of subjects	n=6	n=6	n=6	n=6	n=6	n=6	n=6	n=6
C_{max} (μg/ml)	52,62±11,03	63,42±12,93	18,02±1,13	3,71±0,40	53,52±12,44	32,32±8,06	20,02±4,44	3,50±0,49
T_{max} (hr)	0,75 (0,5, 2,0)	1,0 (1,0, 2,0)	0,88 (0,75, 2,0)	1,50 (0,75, 2,0)	1,0 (0,75, 2,0)	1,0 (0,5, 2,0)	1,0 (0,75, 2,0)	1,0 (0,75, 2,0)
AUC (mkg×hr/ml)	296,33±96,58	570,14±119,41	100,26±11,85	37,89±4,91	309,79±112,14	231,89±85,31	106,18±22,62	31,34±6,11
$T_{1/2}$ (hr)	3,66±0,95	5,02±0,81	3,73±0,57	8,48±2,32	3,58±1,07	4,31±0,74	3,76±0,79	6,27±0,58
CL/F (l/hr)	5,78±1,45	1,46±0,30	–	–	6,79±3,49	3,02±1,53	–	–
Vd/F (l)	28,93±3,25	10,26±0,84	–	–	31,15±4,86	17,66±5,19	–	–

When using favipiravir in healthy volunteers (1600 mg 2 times a day on day 1, followed by 800 mg 2 times a day from days 2 to 5 in the first group, 1800 mg 2 times a day in 1st day followed by 600 mg 2 times a day from 2 to 5 days on the second) Cmax did not decrease after repeated administration of favipiravir compared with that on day 1 (first dose) in the group receiving 1600/800 mg, but decreased afterwards in the 1800/600 mg group.

Distribution

Plasma protein binding ranged from 53.4 to 54.4% (with in vitro ultracentrifugation) at favipiravir concentrations from 0.3 to 30 μg/ml.

With a single oral dose of 14C-labeled favipiravir in monkeys, the drug was well distributed in tissues. Radioactivity in all tissues reached a maximum 30 minutes after administration and changed in parallel with drug concentrations in plasma. The ratio of radioactivity in the lungs and in the plasma was 0.51 30 minutes after administration, the drug was rapidly distributed in the tissues of the respiratory organs, considered as a focus of infection.

After oral administration of favipiravir in 20 healthy volunteers at a dose of 1200 mg twice on day 1 and then 800 mg 2 times a day for 4 days (1200/800 mg 2 times a day), the geometric mean concentration of the drug in the seminal fluid was 18.341 μg/ml on the 3rd day and 0.053 μg / ml one day after the end of therapy. 7 days after the end of therapy, the concentration of the drug in the semen in all volunteers was below the limit of quantitation. The average ratio of the drug concentration indicators in the seminal fluid and in the plasma was 0.53 on the 3rd day and 0.45 one day after the end of therapy.

Metabolism

According to the results of the study, in the cytosol of the human liver, favipiravir is not metabolized by cytochrome P450 (CYP), it is mainly metabolized by AO and partially hydroxylated by xanthine oxidase

(CO). In studies with human liver microsomes, the formation of favipiravir hydroxylate (M1) was 3.98–47.6 pmol/mg protein/min, interindividual differences in AO activity reached a 12-fold maximum. In addition to the hydroxylated form, another metabolite was observed in human plasma and urine -– the glucuronate conjugate favipiravir (M2).

Excretion

Favipiravir was mainly excreted in the hydroxylated form in the urine, the unchanged substance is excreted in a small amount. In a study with repeated oral administration for 7 days in 6 healthy volunteers (at a dose of 1200 mg + 400 mg on the 1st day, 400 mg 2 times a day from the 2nd to the 6th day and 400 mg on the 7^{th} day) day) 48 hours after the last administration, the total proportions of unchanged substance and hydroxylated form excreted in the urine were 0.8% and 53.1%, respectively.

Pharmacokinetics in special patient groups

Patients with impaired liver function

Oral administration of favipiravir by patients (6 patients in a group) with mild and moderate hepatic impairment (classes A and B on the Child – Pugh scale, 6 participants, respectively) 1200 mg 2 times a day for 1 day , and then 800 mg 2 times a day for 4 days (1200 mg / 800 mg) Cmax and AUC on the 5th day were higher than in healthy volunteers. The increase in Cmax and AUC was approximately 1.6 and 1.7 times, respectively, in patients with mild liver dysfunction (class A on the Child–Pugh scale) and 1.4 and 1.8 times, respectively, in patients with moderate liver dysfunction. severity (class B on the Child–Pugh scale) compared with those in healthy volunteers. When taken orally by patients (4 patients) with decompensated liver disease (class C on the Child–Pugh scale, 4 patients) 800 mg 2 times a day on day 1, and then 400 mg 2 times a day for 2 days (800 mg/400 mg 2 times a day) Cmax and AUC on the 3rd day were approximately 2.1 and 6.3 times higher, respectively, compared to those in healthy volunteers.

Indications

- Treatment of new coronavirus infection caused by SARS-CoV-2 virus (COVID-19).

Contraindications

- Pregnancy or the period of breastfeeding (see "Use during pregnancy and during breastfeeding"), the period of planning pregnancy.
- Age under 18 (safety and efficacy in patients under 18 years of age have not been established).
- Hypersensitivity to favipiravir or to any other component of the drug.
- Severe liver dysfunction (class C, 10 or more points on the Child – Pugh scale).

- Severe renal dysfunction (glomerular filtration rate <30 ml / min).

Precautions

Dysfunction of the liver of mild to moderate severity.

• Mild to moderate renal impairment (glomerular filtration rate <60 ml/min and ≥30 ml/min).

• Patients with a history of gout and hyperuricemia.

• Elderly patients. If favipiravir is prescribed, treatment should be carried out under the close supervision of a physician.

• Simultaneous reception with other medications. Favipiravir is not metabolized by cytochrome P450 (CYP), metabolized mainly by AO and partially by ChO. The drug inhibits AO and CYP2C8, but does not induce CYP (see section "Interaction with other medicinal products").

Table 4. Precautions for co-administration

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 2 in 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
Famiclovir Sulindac	Efficacy of these drugs may be reduced	Inhibition of AO by favipiravir may decrease blood level of active forms of these drugs

Use during Pregnancy and lactation

Pregnancy, the period of planning pregnancy and the period of breastfeeding (during the period of therapy with favipiravir and for at least 14 days after the last dose of the drug) are contraindications to the use of the drug.

In preclinical studies, the teratogenicity of favipiravir was observed in all animal species (rats, rabbits, mice, monkeys). In studies of embryofetal development, data were obtained indicating teratogenicity in mice, rats, rabbits and monkeys, and a decrease in the body weight of live fetuses

and the number of live fetuses was found. In the study of pre- and postnatal development, including the effect on the maternal organism, a decrease in the number of living offspring, an increase in the number of dead offspring, a decrease in the survival rate of offspring 4 days after birth, and a decrease in the body weight gain in offspring were noted. In rats, the penetration of favipiravir through the placental barrier and excretion in milk were detected.

In connection with the above data, the use of the drug CORONAVIR in pregnant women (including those with suspected pregnancy) is strictly contraindicated.

Breastfeeding women should stop breastfeeding for the duration of favipiravir treatment and for at least 14 days after the end of the treatment.

Dosage and administration

Treatment with CORONAVIR should be carried out under close medical supervision.

The drug CORONAVIR should be taken orally, 2 times a day (with an interval of no more than 12 hours), not less than 30 minutes before or not earlier than 30 minutes after a meal. For the treatment of a new coronavirus infection caused by the SARS-CoV-2 virus (COVID-19), the following dosage regimen is used: 1800 mg 2 times a day on the 1st day of therapy, then 800 mg 2 times a day from the 2^{nd} on the 10^{th} days of therapy.

It is advisable to consider early drug administration after a COVID-19 diagnosis.

Adverse Reactions

In clinical studies of favipiravir in a population of patients with influenza infection, adverse reactions (including laboratory abnormalities) were observed in 100 (19.96%) of 501 patients included in the general population for safety assessment, of which the most common adverse reactions included an increase in uric acid levels (4.79%), diarrhea (4.79%), decreased neutrophil count (1.80%), increased levels of aspartate aminotransferase (AST) (1.80%) and alanine aminotransferase (ALT) (1.60%).

Table 5. Adverse Reactions Observed in Clinical Trials in Patients with Influenza Infection (Data from Analysis in the Pooled Population Pooled for Safety Assessment)

SOC	**Rate**		
	>1%	**0,5–<1%**	**<0,5%**
Infections and infestations			Rhinitis, Nasopharyngitis
Skin and subcutaneous tissue disorders		Rash	Eczema, Itch
Metabolism and nutrition disorders	Hyperuricaemia		

SOC	Rate		
	>1%	**0,5–<1%**	**<0,5%**
Nervous system disorders			Dizziness
Eye disorders			Ocular pain, Blurring of vision
Respiratory, thoracic and mediastinal disorders			Asthma, Sore throat
Gastrointestinal disorders	Diarrhoea	Nausea, vomiting, abdominal pain	Discomfort abdominal, Ulcer duodenal, Haematochezia, Gastritis
Renal and urinary disorders			Discoloration urine
Investigations	Blood triglycerides increased; Neutrophil count decreased, White blood cell count decreased, AST increased, ALT increased, AST increased, GGT increased	Glucose urine	Blood potassium decreased, White blood cell count increased urrency, lymphocyte count increased, Monocyte count increased; Reticulocyte count decreased, Alkaline phosphatase increased, Bilirubin elevated, Creatine kinase increased

Clinically significant adverse reactions

Abnormal behavior (frequency unknown): Although the causal relationship of this phenomenon with the drug is unknown, patients with influenza infection who received favipiravir experienced abnormal behavior (for example, patients could suddenly run away, wander aimlessly), leading to accidents and risk for life (see section "Special instructions").

Other Antivirals: The following clinically significant adverse reactions have been reported with other influenza virus medications. Patients must be closely monitored, and if any of the following abnormalities are observed, treatment should be discontinued and appropriate measures taken:

• shock, anaphylaxis;

• pneumonia;

• fulminant hepatitis, liver dysfunction, jaundice;

• toxic epidermal necrolysis, Stevens – Johnson syndrome;

• acute kidney damage;

• decrease in the number of leukocytes, decrease in the number of neutrophils, decrease in the number of leukocytes, platelets;

• neurological and psychiatric symptoms (impaired consciousness, delirium, hallucinations, convulsions, etc.);

• hemorrhagic colitis.

Safety of favipiravir in the treatment of coronavirus infection

A safety assessment in patients with COVID-19 was performed in 2 clinical trials of favipiravir:

1) a study of favipiravir versus LPV / RTV used in combination with inhaled interferon alfa;

2) study of therapy with favipiravir in comparison with umifenovir.

Clinical study of favipiravir versus LPV / RTV used in combination with inhaled interferon alfa

Patients in the favipiravir group tolerated therapy well; there were no cases of drug withdrawal due to adverse events (AEs). AEs were found in 4 (11.43%) patients in the favipiravir group, which is significantly less ($p < 0.001$) compared with the LPV / RTV control group - 25 (55.56%). Two out of four patients had diarrhea, one had liver problems, and one had a lack of appetite.

Table 6. AEs identified in a clinical study of favipiravir versus LPV/RTV in COVID-19.

Parameter	Favipiravir (n=35)	LPV/RTV (n=45)	p
Total AE	4 (11,43%)	25 (55,56%)	<0,001
Diarrhea	2 (5,71%)	5 (11,11%)	0,46
Vomiting	0 (0%)	5 (11,11%)	0,06
Nausea	0 (0%)	6 (13,33%)	0,03
Rash	0 (0%)	4 (8,89%)	0,13
Liver and kidney disorders	1 (2,86%)	3 (6,67%)	0,63
Other	1 (2,86%)	2 (4,44%)	1,00

Clinical study of favipiravir versus umifenovir

The most common AEs in this study were abnormalities in blood biochemical parameters (liver enzyme activity), mental symptoms, gastrointestinal symptoms, and elevated serum uric acid (2.50% in the umifenovir group versus 13.79% in the favipiravir group; $p < 0.0001$). A total of 37 AEs were reported in the favipiravir group and 28 in the umifenovir group. The most common AE was an increase in serum uric acid levels (2.50% versus 13.79%, $p = 0.0014$), which was significantly more frequent in the favipiravir group. There were no statistically significant differences in the incidence of other AEs. Most AEs resolved by the time patients were discharged from the hospital.

Table 7. AEs identified in a clinical study of favipiravir versus umifenovir in COVID-19

Parameter	Favipiravir (n=116)	Umifenovir (n=120)	p
Total AE	37 (31,90%)	28 (23,33%)	0,1410
Increased levels of liver enzymes	9 (7,76%)	12 (10,00%)	0,5455
Increased uric acid levels	16 (13,79%)	3 (2,50%)	0,0014
Psychic symptoms	2 (1,72%)	1 (0,83%)	0,6171

Parameter	Favipiravir (n=116)	Umifenovir (n=120)	p
Gastrointestinal disorders	16 (13,79%)	14 (11,67%)	0,6239

Overdose

Single oral doses of favipiravir up to 6,000 mg per day were well tolerated by patients with Ebola virus infection. The intake of 1200 mg (the dose exceeds the recommended 1.5 times) was also well tolerated for 10 days. Higher doses of favipiravir have not been used. There is also no data on cases of overdose in excess of the indicated doses.

In case of an overdose, the use of the drug should be suspended and, if necessary, symptomatic therapy should be used. The antidote to favipiravir is unknown.

Interaction with other drugs

In vitro studies

Favipiravir irreversibly inhibits AO (dose and time dependent) and CYP2C8 (dose dependent). Favipiravir exhibits no inhibitory activity against CO and weak inhibitory activity against CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. The hydroxylated metabolite of favipiravir exhibits weak inhibitory activity against CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4.

Clinical studies of drug interactions

Table 8. Effects of co-administered drugs on pharmacokinetics of favipiravir

Co-administrated drug and dosade	Favipiravir dosage	n	Time of dosing	Parameter ratio for favipiravir (90% CI) (Co-administrated /single administrated)	
				C_{max}	AUC
Theophylline 200 mg twice daily on Days 1 to 9, 200 mg once daily on Day 10	600 mg twice daily on Day 6, 600 mg once daily on Days 7 to 10	10	Day 6	1,33 [1,19; 1,48]	1,27 [1,15; 1,40]
			Day 7	1,03 [0,92; 1,15]	1,17 [1,04; 1,31]
Oseltamivir 75 mg 2 twice daily on Days 1 to 5, 75 mg once daily on Day 6	600 mg twice daily on Day 5, 600 mg once daily on Day 6	10	Day 6	0,98 [0,87; 1,10]	1,01 [0,91; 1,11]
Raloxifene[1] 60 mg once daily on Day 1 to 10	1200 mg twice daily on Day 1, 800 mg twice daily on Day 2, 800 mg once daily on Day 3	17	Day 1	1,00 [0,90; 1,10]	1,03 [0,95; 1,12]
			Day 3	0,90 [0,81;0,99]	0,85 [0,79; 0,93]
Hydralazine 5 mg once daily on Day 1 and Day 5	1200 mg/400 mg on Day 1, 400 mg twice daily on Days 2 to 4, 400 mg once daily on Day 5	14	Day 1	0,99 [0,92; 1,06]	0,99 [0,92; 1,07]
			Day 5	0,96 [0,89; 1,04]	1,04 [0,96; 1,12]

[1] Results in non-Japanese population.

Table 9. Effect of favipiravir on the pharmacokinetics of co-administrated drugs

Препарат, доза	Доза фавипиравира	n	Длительность применения	Отношение ФК показателей препаратов (90% ДИ) (совместное применение/монотерапия)	
				C_{max}	AUC
Theophylline 200 mg twice daily on Days 1 to 9, 200 mg once daily on Day 10	600 mg twice daily on Day 6, 600 mg once daily on Days 7 to 10	10	Day 7	0,93 [0,85; 1,01]	0,92 [0,87; 0,97]
			Day 10	0,99 [0,94; 1,04]	0,97 [0,91; 1,03]
Oseltamivir 75 mg 2 twice daily on Days 1 to 5, 75 mg once daily on Day 6	600 mg twice daily on Day 5, 600 mg once daily on Day 6	10	Day 6	1,10 [1,06; 1,15]	1,14 [1,10; 1,18]
Acetaminophen 650 mg once daily on Day 1 and Day 5[1]	1200 mg twice daily on Day 1, 800 mg twice daily on Days 2 to 4, 800 mg once daily on Day 5	28	Day 1	1,03 [0,93; 1,14]	1,16 [1,08; 1,25]
			Day 5	1,08 [0,96; 1,22]	1,14 [1,04; 1,26]
Norethindrone/Ethinylestradiol combination 1mg/0.035 mg once daily on Days 1 to 5[1]	1200 mg twice daily on Day 1, 800 mg twice daily on Days 2 to 4, 800 mg once daily on Day 5	25	Day 12[2]	1,23 [1,16; 1,30]	1,47 [1,42; 1,52]
			Day 12[3]	1,48 [1,42; 1,54]	1,43 [1,39; 1,47]
Repaglinide 0.5 mg once daily on Day[1]	1200 mg twice daily on Day 1, 800 mg twice daily on Days 2 to 4, 800 mg once daily on Day 5	17	Day 13	1,28 [1,16; 1,41]	1,52 [1,37; 1,68]
Hydralazine 5 mg once daily on Day 1 and Day 5	1200 mg/400 mg on Day 1, 400 mg twice daily on Days 2 to 4, 400 mg once daily on Day 5	14	Day 1	0,73 [0,67; 0,81]	0,87 [0,78; 0,97]
			Day 5	0,79 [0,71; 0,88]	0,91 [0,82; 1,01]

[1] Results in non-Japanese population.
[2] Norethindrone.
[3] Ethinylestradiol

Special warnings

The use of the drug CORONAVIR is possible only under the strict supervision of a physician. 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.

Contraception

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 (see sections "Contraindications" and "Use during pregnancy and during breastfeeding").

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 14 days after its termination (see section "Use during pregnancy and during breastfeeding"). If pregnancy is suspected during therapy with favipiravir, you should immediately stop using the drug and consult a doctor.

Favipiravir 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 7 days after its end. The use of the barrier method (condom) is mandatory. It is necessary to instruct the patient not to have sex with pregnant women (see section "Use during pregnancy and during breastfeeding" and subsection "Pharmacokinetics").

Abnormal behavior

In clinical studies in patients with influenza virus infection, regardless of the class of antiviral drug, there were cases of abnormal behavior (see section "Side effects"). As a preventative approach to accidents such as falls due to abnormal behavior, patients/family members should be instructed that abnormal behavior may develop and that if the patient is being treated on an outpatient basis, family members or caregivers should take preventive measures against accidents for at least 2 days after the onset of the fever. Severe cases of abnormal behavior with the development of life-threatening activities and accidents were more common in children and adolescents within 2 days of the onset of fever.

Bacterial infection

Both influenza infection and novel coronavirus infection (COVID-19) can be complicated by bacterial infections, or bacterial infections can be mistaken for viral infections similar to influenza and novel SARS-CoV-2 coronavirus infection. CORONAVIR is not active against bacterial infections. In the case of a bacterial infection or suspicion of a bacterial infection, appropriate measures should be taken, such as prescribing antibacterial drugs.

Liver dysfunction

Despite the fact that the use of favipiravir in patients with moderate hepatic dysfunction (class B on the Child-Pugh scale) and in patients without hepatic dysfunction did not cause serious adverse reactions, caution should be exercised when prescribing favipiravir in patients with hepatic dysfunction. since under such conditions the exposure of the drug increases. Favipiravir is not recommended for patients with decompensated liver disease.

If severe adverse reactions develop, consider reducing the dose of favipiravir**.**

Impaired renal function

In patients with moderate renal impairment who took part in clinical trials, an increase in uric acid was found due to a decrease in renal clearance, but they did not have any symptomatic manifestations. However, favipiravir should be used with caution in patients with moderate to severe renal impairment.

Children population

The safety and effectiveness of favipiravir in patients under the age of 18 have not been established. However, preclinical studies on juvenile animals do not allow recommending it for admission to pediatric patients.

Phototoxicity

Since preclinical studies in mice and guinea pigs have shown that favipiravir is phototoxic, it is recommended to avoid intense and prolonged exposure to sunlight, exposure to the sun with bare head, and refrain from visiting a tanning bed.

Discoloration of hair and nails

According to preclinical studies in mice, rats and dogs, there is a risk of discoloration of hair and nails with favipiravir.

Other

Animal studies of favipiravir have reported histopathological changes in the testes in rats (12 weeks) and young dogs (7 to 8 months), as well as abnormal findings in semen of mice (11 weeks). Recovery or tendency to recovery was observed after discontinuation of therapy.

According to preclinical studies in mice and rats, saliva may stain yellow.

Influence on the ability to drive vehicles, mechanisms

Studies to study the effect of the drug on the ability to drive and work with mechanisms have not been conducted. If the patient notes symptoms such as dizziness and visual impairment that may affect his ability to concentrate and reaction speed, it is recommended to refuse to drive and perform potentially hazardous activities that require increased concentration and psychomotor speed.

Dosage form

Film-coated tablets, 200 mg.

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, together with instructions for use, is placed in a box made of cardboard box.

Storage conditions

In the dark place at a temperature of no higher than 25 °C.

Shelf life

2 years.

Do not use after the expiration date.

Dispensing rules

Dispensed by prescription.