Piravir™
[Favipiravir]

پِراوِر

Tablets 200mg

Favipiravir is a viral RNA polymerase inhibitor that has demonstrated efficacy against a broad spectrum of RNA viruses. It has also demonstrated promising clinical evidence, with positive results in mild to moderate COVID-19 cases.
Favipiravir can be used for coronavirus patients with co-morbid conditions such as diabetes and heart disease. It offers rapid reduction in viral load and provides faster symptomatic and radiological improvement. Favipiravir provides a substitute for compassionate use in COVID-19 based on its mechanism of action inhibiting virus RNA-dependent RNA polymerase (RdRp) and safety data in clinical studies. Its definite dosage and duration of therapy for COVID-19 is still under clinical investigation.
Dosage studied for COVID-19 infection in published clinical trials is:

	Day 1	Day 2 to min Day 7[a] or max Day 14[b]
Total Daily Dose	1600mg BID	600mg BID
Morning	8 Tablets (1600mg)	3 Tablets (600mg)
Evening	8 Tablets (1600mg)	3 Tablets (600mg)

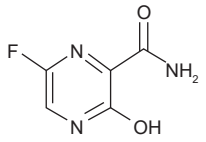
Further, the dose of Favipiravir Tablets for the treatment of COVID-19 as approved by DCGI is:

	Day 1	Day 2 to max Day 14
Total Daily Dose	1800mg BID	800mg BID
Morning	9 Tablets (1800mg)	4 Tablets (800mg)
Evening	9 Tablets (1800mg)	4 Tablets (800mg)

At higher doses proposed for COVID-19, QT interval monitoring, LFT monitoring and plasma level monitoring of the drug may be needed.

(a) Chen, C., Huang, J., Cheng, Z., Wu, J., Chen, S., Zhang, Y., ... & Yin, P. (2020). Favipiravir versus arbidol for COVID-19: a randomized clinical trial. MedRxiv.
(b) Cai, Q., Yang, M., Liu, D., Chen, J., Shu, D., Xia, J., ... & Yang, Y. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering 2020. S2095809920300631, doi, 10.

DESCRIPTION
Piravir contains Favipiravir which is a new antiviral drug that selectively and potently inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses. Chemically, Favipiravir is 6-Fluoro-3-hydroxypyrazine-2-carboxamide. Its molecular formula is $C_5H_4FN_3O_2$ and the structural formula is:



Favipiravir

QUALITATIVE AND QUANTITATIVE COMPOSITION
Piravir (Favipiravir) Tablets are available for oral administration as:

Piravir Tablets 200mg
Each film-coated tablet contains:
Favipiravir…200mg

CLINICAL PHARMACOLOGY
Mechanism of Action
It is considered that 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 (IC_{50}) of Favipiravir RTP on human RNA polymerase II was 905 μmol/L.

Pharmacokinetics
Absorption
The following table shows pharmacokinetic parameters of Favipiravir after an oral administration in adults at 1600mg twice daily for 1 day, then 600mg twice daily for 4 days followed by 600mg once daily for 1 day (1600mg / 600mg BID).

Pharmacokinetic parameters of Favipiravir

Dosage		C_{max} (μg/mL)	AUC (μg.hr/mL)	T_{max} (hr)	$T_{1/2}$ (hr)
1600mg / 600mg BID	Day 1	64.56 (17.2)	446.09 (28.1)	1.5 (0.75, 4)	4.8±1.1
	Day 6	64.69 (24.1)	553.98 (31.2)	1.5 (0.75, 2)	5.6±2.3

Distribution
When Favipiravir was orally administered to adult male subjects at 1200mg twice daily for 1 day followed by 800mg twice daily for 4 days (1200mg / 800mg BID), the geometric mean concentration of the drug in semen was 18.341μg/mL on Day 3, and 0.053μg/mL on the second day after the treatment. The semen levels became below the limit of quantification (0.02μg/mL) in all subjects in 7 days after the end of the treatment. The mean ratio of the drug concentration in semen to that in plasma was 0.53 on Day 3 and 0.45 on the second day after the treatment.

Metabolism
Favipiravir was not metabolized by cytochrome P-450 (CYP), mostly metabolized by aldehyde oxidase (AO), and partly metabolized to a hydroxylated form by xanthine oxidase (XO). A glucuronate conjugate was observed in human plasma and urine as a metabolite other than the hydroxylated form.

Excretion
Favipiravir was mainly excreted as a hydroxylated form into the urine, and little amount unchanged drug was observed. In an oral 7 day multiple dose study with healthy adults, cumulative urinary excretion ratio of the unchanged drug and the hydroxylated form was 0.8% and 53.1%, respectively, during 48 hours after the last administration.

Special population
Patients with hepatic impairment
When Favipiravir was orally administered to subjects with mild and moderate liver function impairment (Child-Pugh classification A and B) at 1200mg twice daily for 1 day followed by 800mg twice daily for 4 days (1200mg / 800mg BID), compared to healthy adult subjects, C_{max} and AUC at day 5 were approximately 1.6 fold and 1.7 fold, respectively in subjects with mild liver function impairment, and 1.4 fold and 1.8 fold, respectively in subjects with moderate liver function impairment.
When Favipiravir was orally administered to subjects with severe liver function impairment (Child-Pugh classification C) at 800mg twice daily for 1 day followed by 400mg twice daily for 2 days (800mg / 400mg BID), compared to healthy adult subjects, C_{max} and AUC at day 3 were approximately 2.1 fold and 6.3 fold, respectively.

Elderly
Since the elderly often have reduced physiological functions, Favipiravir should be administered with care to them by monitoring their general conditions.

THERAPEUTIC INDICATIONS
Piravir (Favipiravir) is indicated for treatment of novel or re-emerging pandemic influenza virus infections (Limited to cases in which other influenza antiviral drugs are ineffective or not sufficiently effective).

DOSAGE AND ADMINISTRATION
The usual adult dosage for treatment of influenza virus infection is 1600mg of Favipiravir administered orally twice daily on Day 1, followed by 600mg orally twice daily from Day 2 to Day 5. The total treatment duration should be 5 days.

CONTRAINDICATIONS
Favipiravir is contraindicated in:
- Patients with known hypersensitivity to Favipiravir or to any excipient of the product.
- Women known and suspected to be pregnant.

ADVERSE REACTIONS
The following clinically significant adverse reactions have been reported with other anti-influenza virus agents. Patients should be carefully monitored, and if any abnormality is observed, the treatment should be discontinued and appropriate measures should be taken.
Shock, anaphylaxis, pneumonia, hepatitis fulminant, hepatic dysfunction, jaundice, toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson Syndrome), acute kidney injury, white blood cell count decreased, neutrophil count decreased, platelet count decreased, neurological and psychiatric symptoms (consciousness disturbed, abnormal behavior, deliria, hallucination, delusion, convulsion, etc.) and colitis hemorrhagic.

If the following adverse reactions occur, appropriate measures should be taken according to the symptoms:
AST (GOT) increased, ALT (GPT) increased, γ-GTP increased, diarrhea, neutrophil count decreased, white blood cell count decreased, blood uric acid increased, blood triglycerides increased, rash, nausea, vomiting, abdominal pain, glucose urine present, eczema, pruritus, blood ALP increased, blood bilirubin increased, abdominal discomfort, duodenal ulcer, haematochezia, gastritis, white blood cell count increased, reticulocyte count decreased, monocyte increased, blood potassium decreased, asthma, oropharyngeal pain, rhinitis, nasopharyngitis, blood CK (CPK) increased, blood urine present, tonsil polyp, pigmentation, dysgeusia, bruise, vision blurred, eye pain, vertigo and supraventricular extrasystoles.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

WARNINGS
- Since early embryonic deaths and teratogenicity have been observed in animal studies for Favipiravir, do not administer the drug to women known or suspected to be pregnant.
- When administering Favipiravir to women of child-bearing potential, confirm a negative pregnancy test result before starting the treatment. Explain fully the risks and instruct thoroughly to use most effective contraceptive methods with her partner during and for 7 days after the end of the treatment. If pregnancy is suspected during the treatment, instruct to discontinue the treatment immediately and to consult a doctor.
- Favipiravir is distributed in 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 7 days after the end of the treatment (men must wear a condom). In addition, instruct not to have sexual intercourse with pregnant women.
- Prior to the treatment, explain thoroughly the efficacy and risk (including the risk of exposure to fetus) to patients or their family members.
- Examine carefully the necessity of Favipiravir before use.

PRECAUTIONS
- Favipiravir is a drug, the use of which is considered only when there is an outbreak of novel or re-emerging influenza virus infections in which other anti-influenza virus agents are not effective or insufficiently effective.
- Favipiravir is not effective against bacterial infections.
- Favipiravir is not recommended for use in children.
- Favipiravir should be administered with care in patients with gout or a history of gout, and patients with hyperuricaemia (Blood uric acid level may increase, and symptoms may be aggravated).
- Increase plasma level of Favipiravir has been reported in patients with liver function impairment.
- Psychoneurotic symptoms such as abnormal behavior after administration of Favipiravir have been reported. Patients / their family should be instructed that after the start of treatment abnormal behavior may be developed, and patients are not left alone for at least 2 days when they are treated at home. Since similar symptoms associated with influenza encephalopathy have been reported, the same instruction as above should be given.
- Influenza virus infection may be complicated with bacterial infections or may be confused with influenza-like symptoms. In case of bacterial infection or suspected to be bacterial infection, appropriate measures should be taken, such as administration of anti-bacterial agents.

Pregnancy
Early embryonic deaths and teratogenicity have been observed in animal studies with exposure levels similar to or lower than the clinical exposure. Do not administer Favipiravir to women known or suspected to be pregnant.

Nursing Mothers
The major metabolite of Favipiravir, a hydroxylated form, was found to be distributed in breast milk. When administering Favipiravir to lactating women, instruct to stop lactation.

DRUG INTERACTIONS
In vitro: Favipiravir inhibited irreversibly AO in a dose and time dependent manner, and inhibited CYP2C8 in a dose dependent manner. There were no inhibitory activity to XO, and weak inhibitory activity to CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. The hydroxylated metabolite showed weak inhibitory activity to CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4.
Favipiravir should be administered with care when co-administered with the following drugs:

Drugs	Signs	Mechanism & Risk Factors
Pyrazinamide	Blood uric acid level increases. When pyrazinamide 1.5g once daily and Favipiravir 1200mg / 400mg BID were administered, the blood uric acid level was 11.6 mg/dL when pyrazinamide was administered alone, and 13.9mg/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 CYP2C8 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.

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Piravir (Favipiravir) Tablets 200mg are available in blister pack of 20's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
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