For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Fabiflu™

Favipiravir Tablets 200 mg

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 risks (including the risk of exposure to fetus) to patients or their family members and written informed consent from each patient/ or his representative prior to administration of the drug shall be obtained by the prescriber.

Examine carefully the necessity of favipiravir before use.

Label Claim
Each film-coated tablet contains
Favipiravir 200 mg
Excipient(s) q.s.
Colours: Titanium Dioxide USP NF & Ferric oxide yellow USP NF
For the full refer list of excipients,

PHARMACEUTICAL FORM
Film-coated tablet

PRODUCT DESCRIPTION
Yellow coloured, film coated round shaped, tablets plain on both sides.

CLINICAL PARTICULARS
Therapeutic indications
For the treatment of patients with mild to moderate COVID-19 disease.
From the clinical trial, limited efficacy data for Fabiflu 200mg Tablets in the age group 18 to 30 years old, and >60 years old for the treatment of patients with mild to moderate COVID-19 disease.

Posology and Method of Administration
The recommended dosage of favipiravir for adults is 1800 mg orally twice daily on 1st day followed by 800 mg orally twice daily, up to maximum of 14 days.

Note: Use only as directed by a physician.

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

Pediatric Use
Favipiravir has not been administered to children.

Contraindications
- **Women known or suspected to be pregnant (Early embryonic deaths and teratogenicity have been observed in animal studies.**
- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.
- Lactating women
- Severe hepatic impairment
- Severe renal impairment

Special Warnings and Precautions for Use

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 risks (including the risk of exposure to fetus) in writing to patients or their family members and obtain their written consent.

Examine carefully the necessity of favipiravir before use.

Careful Administration
Favipiravir should be administered with care in the following patients:-
Patients with history of abnormalities in metabolism of uric acid or having Gout. (Blood uric acid level may increase, and symptoms may get aggravated.)

Important Precautions
Although the causal relationship is unknown, psychoneurotic symptoms such as abnormal behavior after administration of anti-influenza virus agents including favipiravir have been reported. For the treatment of children and minors, as a preventive approach in case of an accident due to abnormal behavior such as fall, patients/their family should be instructed that, after the start of treatment with anti-influenza virus agents, (i) abnormal behavior may be developed, and (ii) guardians and others should make an arrangement so that children/minors 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.

Viral infection may be complicated or confused with bacterial infections. In case of bacterial infection or suspected to be bacterial infection, appropriate measures should be taken, such as administration of anti-bacterial agents.

Interaction with other medicinal products and other forms of interaction
Favipiravir is not metabolized by cytochrome P-450(CYP), mostly metabolized by aldehyde oxidase (AO), and partly metabolized by xanthine oxidase (XO). The drug inhibits AO and CYP2C8, but does not induce CYP. Precautions for co-administration

Table 1: Favipiravir should be administered with care when co-administered with the following drugs

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Pyrazinamide	Blood uric acid level increases. When pyrazinamide 1.5g once daily and favipiravir 1200 mg /400 mg BID 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 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.

Fertility, Pregnancy and lactation

Fertility
In animal toxicity studies, histopathological changes of testis in rats (12 weeks old) and young dogs (7 to 8 months old), and abnormal findings of sperm in mice (11 weeks old) have been reported. Recovery or tendency of recovery has been observed in those studies after the administration was suspended. In fertility study in rats, effects on the testis and sperm and decreased fertility were observed in males and anestrus was observed in females at the high-dose.

Pregnancy
Do not administer favipiravir to women known or suspected to be pregnant.
(Early embryonic deaths [rats] and teratogenicity [mouse, rat, rabbit and monkey] have been observed in animal studies with exposure levels similar to or lower than the clinical exposure.)

Lactation
Do not administer to lactating women
(The major metabolite of favipiravir, a hydroxylated form, was found to be distributed in breast milk.)

Effects on ability to drive and use machines
No data are available.

Undesirable effects

Clinical Safety
Glenmark has conducted a phase 3, randomised, multi-center, open-label, clinical study evaluating the efficacy and safety of favipiravir with standard supportive care versus standard supportive care alone in the treatment of subjects with mild to moderate COVID-19.

Table 2: Summary of Adverse Events (AEs) by Treatment Group and System Organ Class (SOC & PT)- Safety Population

System Organ Class Preferred Term	Statistics	FAVIPIRAVIR (N=73)	CONTROL (N=75)	Total (N=148)
Any SOC Number of subjects with any AE	n (%) (y)	26 (35,6) (29)	6 (8,0) (7)	32 (21,6) (36)
Investigations	n (%) (y)	17 (23,3)	2 (2,7) (2)	19 (12,8) (20)
Blood Lactate Dehydrogenase Increased	n (%) (y)	1 (1,4) (1)	0 0	1 (0,7) (1)
Blood Uric Acid Increased	n (%) (y)	12 (16,4) (12)		12 (8,1) (12)
Liver Function Test Abnormal	n (%) (y)	5 (6,8) (5)	2 (2,7) (2)	7 (4,7) (7)
Gastrointestinal Disorders	n (%) (y)	2 (2,7) (3)	2 (2,7) (2)	4 (2,7) (5)
Diarrhoea	n (%) (y)	1 (1,4) (1)	0	1 (0,7) (1)
Gastrointestinal Disorder	n (%) (y)	1 (1,4) (1)	2 (2,7) (2)	3 (2,0) (3)
Vomiting	n (%) (y)	1 (1,4) (1)	0	1 (0,7) (1)
Metabolism And Nutrition Disorders	n (%) (y)	3 (4,1) (3)	1 (1,3) (1)	4 (2,7) (4)
Dyslipidaemia	n (%) (y)	1 (1,4) (1)	1 (1,3) (1)	2 (1,4) (2)
Hyperglycaemia	n (%) (y)	1 (1,4) (1)	0	1 (0,7) (1)
Hypokalaemia	n (%) (y)	1 (1,4) (1)	0	1 (0,7) (1)
Infections And Infestations	n (%) (y)	2 (2,7) (2)	0	2 (1,4) (2)
Pneumonia Viral	n (%) (y)	2 (2,7) (2)	0	2 (1,4) (2)
Blood And Lymphatic System Disorders	n (%) (y)	1 (1,4) (1)	0	1 (0,7) (1)
Leukocytosis	n (%) (y)	1 (1,4) (1)	0	1 (0,7) (1)
General Disorders And Administration Site Conditions	n (%) (y)	1 (1,4) (1)	0	1 (0,7) (1)
Asthenia	n (%) (y)	1 (1,4) (1)	0	1 (0,7) (1)
Immune System Disorders	n (%) (y)	0	1 (1,3) (1)	1 (0,7) (1)
Drug Hypersensitivity	n (%) (y)	0	1 (1,3) (1)	1 (0,7) (1)
Respiratory, Thoracic And Mediastinal Disorders	n (%) (y)	0	1 (1,3) (1)	1 (0,7) (1)
Acute Respiratory Distress Syndrome	n (%) (y)	0	1 (1,3) (1)	1 (0,7) (1)
Skin And Subcutaneous Tissue Disorders	n (%) (y)	1 (1,4) (1)	0	1 (0,7) (1)
Rash	n (%) (y)	1 (1,4) (1)	0	1 (0,7) (1)

1. At each level of summarization a subject was counted once if the subject reported one or more events in a given level of summarization.
2. Adverse event terms were coded using MedDRA version 23.0.
3. Percentages were based on the total number of subjects in safety population in each treatment.
4. y was the total number of events and n was the number of subjects with at least one event, in safety population in each treatment.
5. SOCs were sorted with descending order of incidence in Total Column.

The subjects with TEAEs were 26 (35.6%) in the favipiravir group and 6 (8.0%) in the control group. One serious adverse event (SAE), acute respiratory distress syndrome, was reported in 1 subject in the control group, which was fatal and causality was assessed as not related. A total of 21 subjects had TEAEs which were considered related to study drug in the favipiravir group [21 (28.8%)]. The majority of the subjects had AEs of mild intensity 25 (16.9%) [favipiravir group: 20 (27.4%); control group: 5 (6.7%)] and 6 subjects had AEs of moderate intensity [favipiravir group: 6 (8.2%); control group: none]. The most commonly reported AEs in subjects by system organ class (SOC) across the 2 treatment groups were investigation disorders (19 [12.8%]; 17 [23.3%] in favipiravir group, and 2 [2.7%] in control group), followed by gastrointestinal, and metabolism and nutritional disorders (4 [2.7%]; 2 [2.7%] each in favipiravir group, and control group) and (4 [2.7%]; 3 [4.1%] in favipiravir group, and 1 (1.3%) in control group), followed by infections and infestations (2 [1.4%]; 2 [2.7%] in favipiravir group, and none in control group).

Favipiravir was safe and well tolerated and the most common AEs reported were in line with known adverse effect of the drug. Most common AE in the favipiravir group was asymptomatic, and transient increase in uric acid which generally resolved on first follow-up. No severe or serious adverse event or death was noted in the favipiravir group.

Clinical studies with favipiravir used at different doses
The major undesirable effects observed in clinical studies with favipiravir used at different doses included:
- Increase of blood uric acid level (4.79%)
- Diarrhea (4.79%)
- Decrease of neutrophil count (1.80%)
- Increase of AST (SGOT) (1.80%)
- Increase of ALT (SGPT) (1.60%)

A. *Adverse reactions**
If the following adverse reactions occur, appropriate measures should be taken according to the symptoms.

	≥ 1%	0.5 - < 1%	< 0.5%
Hypersensitivity		Rash	Eczema, pruritus
Hepatic	AST (GOT) increased, ALT (GPT) increased, γ-GTP increased		Blood ALP increased, blood bilirubin increased
Gastrointestinal	Diarrhoea (4.79%)	Nausea, vomiting, Abdominal pain	Abdominal discomfort, duodenal ulcer, haematochezia, gastritis
Hematologic	Neutrophil count decreased, white blood cell count decreased		White blood cell count increased, reticulocyte count decreased, monocyte increased
Metabolic disorders	Blood uric acid increased (4.79%), Blood triglycerides increased	Glucose urine present	Blood potassium decreased
Respiratory			Asthma, oropharyngeal pain, rhinitis, nasopharyngitis
Others			Blood CK (CPK) increased, blood urine present, tonsil polyp, pigmentation, dysgeusia, bruise, vision blurred, eye pain, vertigo, supraventricular extrasystoles
*Adverse reactions observed in Japanese clinical studies and the global phase III clinical study (studies conducted with dose levels lower than the approval dosage).			

B. *Clinically significant adverse reactions (similar drugs)*
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.
1. Shock, anaphylaxis
2. Pneumonia
3. Hepatitis fulminant, hepatic dysfunction, jaundice
4. Toxic epidermal necrolysis (TEN), oculo-muco-cutaneous syndrome (Stevens-Johnson syndrome)
5. Renal failure acute
6. White blood cell count decreased, neutrophil count decreased, platelet count decreased
7. Neurological and psychiatric symptoms (consciousness disturbed, deliria, hallucination, delusion, convulsion, etc.)

Abnormal behaviour:
Abnormal behaviour (such as sudden movement or wandering) that could result in falls etc. may occur in patients infected with influenza, although the existence of a causal relationship between these symptoms and this drug is currently unclear.
8. Colitis haemorrhagic

In prospective, multicenter, comparative trial with 240 subjects, 37 incidences of antiviral-associated adverse effects (AE) were detected in the favipiravir group (dose used: 1600 mg twice a day on first day; 600 mg twice a day from second day up to a maximum of 10 days) and 28 incidences in the control group. All observed AE incidences were mild. Increased serum uric acid (3 (2.50%) vs 16 (13.79%), P=0.0014) were more common in patients of the favipiravir group. No statistical difference was observed for the frequency of abnormal liver function tests (LFT), psychiatric symptom reactions and digestive tract reactions (nausea, acid reflux, flatulence). Most of these adverse reactions disappeared by the time patients being discharged. Antiviral-associated adverse effects of favipiravir were mild and manageable. *Chang C et al. (2020)*

Comparison of Anti-viral associated adverse effects

Adverse effects	Favipiravir group (N=116)		Control group (N=120)		P value
	Frequency	Cases, n (%)	Frequency	Frequency	
Total	43	37 (31.90)	33	28 (23.33)	0.1410
Abnormal LFT	10	10 (8.62)	12	12 (10.00)	0.7156
Raised serum uric acid	16	16 (13.79)	3	3 (2.50)	0.0014
Psychiatric symptom reactions	5	5 (4.31)	1	1 (0.83)	0.1149*
Digestive tract reactions	16	16 (13.79)	17	14 (11.67)	0.6239
*Fisher's exact test was used for comparison between groups.					

In a study of favipiravir versus Lopinavir /ritonavir for the treatment of COVID-19, the total number of adverse reactions in the favipiravir arm (dose used: 1600 mg twice a day on first day; 600 mg twice a day from second day up to a maximum of 14 days) was four (11.43%), which was significantly fewer than the 25 adverse reactions (55.56%) in the control arm (P < 0.001). Two patients had diarrhea, one had a liver injury, and one had a poor diet in the favipiravir arm. Meanwhile, there were five patients with diarrhea, five with vomiting, six with nausea, four with rash, three with liver injury, and two with chest tightness and palpitations in the control arm. *Cai Q et al (2020)*

Statistics of adverse reactions after medication [Favipiravir versus Lopinavir /ritonavir]

Characteristic	Treatment		
	Favipiravir (N=35)	Lopinavir/ ritonavir (N=45)	*P value*
Total no. of adverse reactions	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 injury	1 (2.86%)	3 (6.67%)	0.63
Others	1 (2.86%)	2 (4.44%)	1.00

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Overdose
No data are available.

PHARMACOLOGICAL PROPERTIES
ATC Code - J05AX27.

Pharmacodynamic properties
Mechanism of action:
Favipiravir is a prodrug that is metabolized in cells to the active form favipiravir-ribosyl triphosphate form (favipiravir RTP), which selectively inhibits RNA polymerase involved in viral replication. Inhibitory concentration (IC_{50}) of favipiravir RTP on human RNA polymerase II was 905 μmol/L.

Pharmacodynamic effects
In vitro antiviral activity
Favipiravir effectively inhibits SARS-CoV-2 infection in Vero E6 cells (half maximal effective concentration (EC_{50}) = 61.88 μmol/L, half maximal cytotoxic concentration (CC_{50}) > 400 μmol/L, selectivity index (SI) > 6.46).

Therapeutic effect in animal models
In EBOV-infected mice models, lacking the type I IFN-alpha/beta receptor (IFNAR-/-), treatment with favipiravir 300 mg/kg/day initiated 6 days post infection induced rapid virus clearance, reduced biochemical parameters of disease severity, and prevented a lethal outcome in 100% of the animals.

Resistance
No information about emergence of favipiravir-resistant viruses is available.

Clinical efficacy
Glenmark has conducted a phase 3, randomised, multi-center, open-label, clinical study evaluating the efficacy and safety of favipiravir with standard supportive care versus standard supportive care alone in the treatment of subjects with mild to moderate COVID-19.

Time until cessation of oral shedding of SARS-CoV-2 virus
For the ITT population, out of 147 subjects, a total of 138 subjects [70 (97.2%) subjects in the favipiravir group and 68 (90.7%) subjects in the control group], achieved the event of cessation of oral shedding of SARS-CoV2 virus. The median time to cessation of oral shedding of SARS-CoV2 virus was 5 days (95% CI: 4 days, 7 days) in the favipiravir group compared with 7 days (95% CI 5 days, 8 days) in the control group (p=0.129). A 28.6 % faster viral clearance (by 2 days) was seen in the favipiravir group compared with the control group.

The HR (favipiravir/control) for time to cessation of oral shedding of SARS-CoV2 virus was 1.36 (95% CI: 0.944, 1.979; p=0.098).

Moderate COVID-19 Subgroup (Time until cessation of oral shedding of SARS-CoV-2 virus)
Out of 58 subjects, a total of 51 subjects [favipiravir group 27 (96.4%) subjects, and control group 24 (80.0%) subjects] achieved the event of cessation of oral shedding of SARS-CoV2 virus. The median time to cessation of oral shedding of SARS-CoV2 virus was 4.5 days (95% CI: 3 days, 7 days) in the favipiravir group compared with 6.5 days (95% CI: 3 days, 14 days) in the control group (p=0.067).

The HR (favipiravir/control) for time to cessation of oral shedding of SARS-CoV2 virus was 1.855 (95% CI: 0.991, 3.471).

Mild COVID-19 Subgroup (Time until cessation of oral shedding of SARS-CoV-2 virus)
Out of 89 subjects, a total of 87 subjects [favipiravir group: 43 (97.7%) and control group: 44 (97.8%)], achieved the event of cessation of oral shedding of SARS-CoV2 virus. The median time to cessation of oral shedding of SARS-CoV2 virus was 6 days (95% CI: 4 days, 8 days) in the favipiravir group compared with 7 days (95% CI: 5 days, 7 days) in the control group (p=0.853).

The HR (favipiravir/control) for time to cessation of oral shedding of SARS-CoV2 virus was 1.145 (95% CI: 0.716, 1.833).

Time from Randomization to Clinical Cure Based on Clinician Assessment:
For the ITT population, out of 102 subjects who had baseline clinical signs and symptoms, a total of 97 subjects [favipiravir group 51 (96.2%) and control group 46 (93.9%)], achieved clinical cure. The median time to clinical cure was 3 days (95% CI: 3 days, 4 days) in the favipiravir group compared with 5 days (95% CI: 4 days, 6 days) in the control group which was statistically significant (p=0.030).

The HR (favipiravir/control) for time to clinical cure was statistically significant 1.749 (95% CI:1.096, 2.792) (p=0.019).

Time to first time use of high flow supplemental oxygen/non-invasive ventilation/mechanical ventilation/extracorporeal membrane oxygenation
Fourteen subjects [favipiravir group 7 (100%), and control group 7 (100%)], required high flow supplemental oxygen/non-invasive ventilation/mechanical ventilation/extracorporeal membrane oxygenation. The median time to first time use of high flow supplemental oxygen/non-invasive ventilation/mechanical ventilation/extracorporeal membrane oxygenation was 5 days (95% CI: 1 day, 6 days) in the favipiravir group compared with 2 days (95% CI: 1 day, 4 days) in the control group. (p=0.065)

The HR (favipiravir/control) for time to first time use of high flow supplemental oxygen/non-invasive ventilation/mechanical ventilation/extracorporeal membrane oxygenation was 0.065 (95% CI: 0.005, 0.809) (p=0.034) was statistically significant, favouring the favipiravir group compared with the control group.

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Time from Randomization to Hospital Discharge
For the ITT population, out of 147 subjects, a total of 138 subjects [favipiravir group70 (97.2%) and control group 68 (90.7%)], got discharged The median time to hospital discharge was 9 days (95% CI: 7 days, 10 days) in the favipiravir group compared with 10 days (95% CI: 8 days, 12 days) in the control group (p=0.108).

The HR (favipiravir/control) for time to hospital discharge was 1.406 (95% CI: 0.974, 2.030) (p=0.069).

Rate of Clinical Cure
On Day 14, the proportion of subjects achieving clinical cure, was higher in the favipiravir group: 49 (92.5%) as compared with the control group: 43 (87.8%) (p=0.643).

*Rate of SARS-CoV2 RT-PCR negativity in both oropharyngeal swab and nasopharyngeal swab*On Day 14, the proportion of subjects achieving SARS-CoV2 RT-PCR negativity was higher in favipiravir group 66 (91.7%) as compared with the control group 60 (80.0%) (p=0.074).

Favipiravir with standard supportive care was found to be more effective compared with standard supportive care alone in terms of time to clinical cure, RT-PCR negativity, and hospital discharge in the mild to moderate COVID-19 population enrolled in the study. A faster virological cure, statistically significant faster clinical cure, delay in progression of disease as measured by delayed requirement of supplemental oxygen (high flow supplemental oxygen/non-invasive ventilation/mechanical ventilation/extracorporeal membrane oxygenation) was observed in the favipiravir group compared with the control group.

Clinical studies (published)
In prospective, multicenter, comparative trial with 240 patients with chest CT imaging and laboratory-confirmed COVID-19 infection, aged 18 years or older were randomly assigned to either conventional therapy + favipiravir or control drug. The primary outcome was clinical recovery rate of day 7. Duration of fever, cough relief latency, and auxiliary oxygen therapy or noninvasive mechanical ventilation rate were the secondary outcomes. 120 patients were assigned to favipiravir group (116 assessed) and 120 to control group (120 assessed). In ordinary COVID-19 patients; 7 day's clinical recovery rate was 55.86% in the control group and 71.43% in the favipiravir group (P = 0.0199). The latency to fever reduction and cough relief in favipiravir group was significantly shorter than that in control group (both P<0.0001). No statistical difference was observed of auxiliary oxygen therapy or noninvasive mechanical ventilation rate (both P>0.05). Favipiravir significantly improved time-to-relief for fever and cough. *Chang C et al. (2020)*

Table 3: Comparison of time to relief for pyrexia, cough relief time and other secondary outcomes.

Variables	Time to relief for pyrexia		Cough relief time	
	Favipiravir group	Control group	Favipiravir group	Control group
Total patients	**(N = 71)**	**(N = 74)**	**(N = 78)**	**(N = 73)**
Day 1	15 (21.13)	2 (2.70)	1 (1.28)	3 (4.11)
Day 2	23 (32.39)	8 (10.81)	2 (2.56)	1 (1.37)
Day 3	19 (26.76)	18 (24.32)	23 (29.49)	7 (9.59)
Day 4	10 (14.08)	15 (20.27)	20 (25.64)	11 (15.07)
Day 5	1 (1.41)	16 (21.62)	10 (12.82)	12 (16.44)
Day 6	-	5 (6.76)	10 (12.82)	10 (13.70)
Day 7	-	3 (4.05)	3 (3.85)	3 (4.11)
Day 8	-	-	7 (8.97)	6 (8.22)
Day 9	-	-	1 (1.28)	3 (4.11)
Censored	-	-	1 (1.28)	17 (23.29)
Log-rank P value	< 0.0001		< 0.0001	
Other secondary outcomes				
AOT or NMV*	**Favipiravir group**	**Control group**	**Rate ratio (95% CI)**	**P value**
Total patients	N= 116	N= 120		
With auxiliary, n (%)	21 (18.10)	27 (22.50)	-0.0440 (-0.1464, -0.0585)	0.4015
Patients with hypertension and/or diabetes	N = 42	N = 35		
With auxiliary, n (%)	9 (21.43)	10 (28.57)	-0.0714 (-0.2658, 0.1230)	0.4691
All-cause mortality	0 (0.00)	0 (0.00)	/	/
Dyspnea after taking medicine, n (%)	4 (3.45)	14 (11.67)	/	0.0174
Respiratory failure, n (%)	1 (0.86)	4 (3.33)	/	0.3700*

*Fisher's exact test was used for comparison between groups.
AOT: Auxiliary oxygen therapy.
NMV: Noninvasive mechanical ventilation.

In another open label study; favipiravir (FPV) has proven to be superior to lopinavir/ritonavir in treatment of COVID-19 positive patients. The results from a total of 80 patients indicated that favipiravir had more potent antiviral action than that of lopinavir (LPV)/ritonavir. A shorter viral clearance time was found for the favipiravir arm versus the control arm (median (interquartile range, IQR), 4 (2.5–9) days versus 11 (8–13) days, p < 0.001). The favipiravir arm also showed significant improvement in chest imaging compared with the control arm, with an improvement rate of 91.43% versus 62.22% (p = 0.004). Multivariable cox regression showed that favipiravir was independently associated with faster viral clearance. *Cai Q et al (2020)*

Viral response to the antiviral therapy
The Kaplan-Meier survival curves for the length of time until viral clearance for both kinds of antiviral therapy were presented in Figure below. The median time of viral clearance for the patients treated with favipiravir (FPV), designated as Group A, was estimated to be 4 d (IQR: 2.5–9), which was significantly shorter than the time for patients in the control group, designed as Group B, which was 11 d (IQR: 8–13) (P < 0.001). *Cai Q et al (2020)*

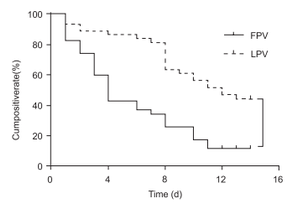


Figure 1: Kaplan-Meier survival curves for the length of time until viral clearance for both kinds of antiviral therapy (P < 0.001)

On Day 14 after treatment, the improvement rates of the chest CT changes in the group with viral clearance within 7 d of treatment were significantly higher than those of the patients with viral clearance after 7 d of treatment (Figure 2)

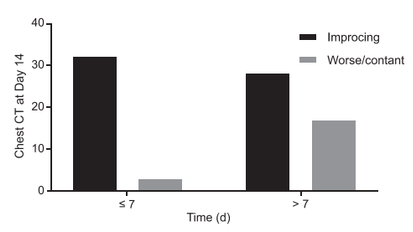


Figure 2: Time of viral shedding and improving chest CT scan on Day 14 after treatment.

Two placebo-controlled phase III studies in type A or type B influenza patients (oral administration of favipiravir 1800 mg twice daily for 1 day followed by 800 mg twice daily for 4 days [1800 mg /800 mg BID])^ with the primary endpoint: the time required to alleviate primary influenza symptoms ^^, were conducted (Study 1 and Study 2). The results are as follows:

Table 4 Results of primary analysis (ITT population)

	Study 1		Study 2	
	Favipiravir (N=301)	**Placebo (N=322)**	**Favipiravir (N=526)**	**Placebo (N=169)**
Number of events	288	306	505	163
Median [95% CI (hours)	84.2 [77.1, 95.7]	98.6 [94.6, 107.1]	77.8 [72.3, 82.5]	83.9 [76.0, 95.5]
p-value"	0.004		0.303	

"Peto-Peto-Prentice test

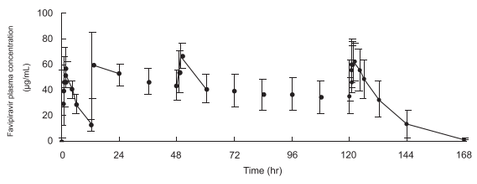
Pharmacokinetic properties

Absorption
Blood Concentrations
The following table shows pharmacokinetic parameters of favipiravir after an oral administration in 8 healthy adults at 1600 mg twice daily for 1 day, then 600 mg twice daily for 4 days followed by 600 mg once daily for 1 day (1600 mg/600 mg BID).

Table 5 Pharmacokinetic parameters of favipiravir

Dosage		C_{max} (μg/mL)#	AUC (μg hr/mL)#^	T_{max} (hr)*	$T_{1/2}$ (hr)+
1600 mg/ 600 mg 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
# Geometric mean (CV%) ^ Day 1: $AUC_{0-\infty}$, Day 6: AUC, * Median (minimum, maximum) +Mean±SD					

1600mg/600mg (BID)
Figure 3: Time course of plasma concentration of favipiravir (mean±SD)



Following multiple oral administration of favipiravir for 7 days[x] to an healthy adult who appeared to have little AO activity, the estimated AUC of unchanged drug was 1452.73 μg·hr/mL on Day 1 and 1324.09 μg·hr/mL on Day 7.

[x]1200 mg + 400 mg on Day 1, then 400 mg twice daily on Days 2 to 6 followed by 400 mg once daily on Day 7. The approved dosage of favipiravir is "1600 mg orally twice daily for 1 day followed by 600 mg orally twice daily for 4 days".

Studies from healthy Japanese volunteers showed that the maximum plasma concentration of favipiravir occurred at 0.5 to 2 hours after oral administration, and then decreased rapidly with a short half-life time of 2–5.5 hours.

Distribution
The plasma protein binding of favipiravir was 54% in humans. The bound percentages of favipiravir to human serum albumin and α1-acid glycoprotein were 65.0% and 6.5%, respectively. Favipiravir's apparent volume of distribution ranges from 15 to 20 L and is likely restricted to vascular and extra vascular fluids.

Metabolism
Favipiravir is mostly metabolized by aldehyde oxidase (AO), and partly to a hydroxylated form by xanthine oxidase (XO). In studies using human liver microsomes, formation of the hydroxylate ranged from 3.98 to 47.6 pmol/mg protein/min, with an inter-individual variation of AO activity by 12 times at maximum. 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 6 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.

Specific Populations
Patients with Hepatic Impairment
Increase of plasma level of favipiravir has been reported in patients with liver function impairment in a clinical safety and pharmacokinetic study conducted outside of Japan.

When favipiravir was orally administered to subjects with mild and moderate liver function impairment (Child-Pugh classification A and B, 6 subjects each) at 1200 mg twice daily for 1 day followed by 800 mg twice daily for 4 days (1200 mg/800 mg 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, 4 subjects) at 800 mg twice daily for 1 day followed by 400 mg twice daily for 2 days (800 mg/400 mg BID), compaired to healthy adult subjects, C_{max} and AUC at day 3 were approximately 2.1 fold and 6.3 fold, respectively.

Patients with renal function impairment
In patients with moderate renal function impairment (GFR <60ml/min and ≥30ml/min) the remaining favipiravir concentration (C_{trough}) increased 1.5 fold versus that of patients with no renal function impairment. The use of the drug has not been studied in patients with severe renal impairment or terminal stage of renal impairment (GFR <30ml/min).

Drug Interaction Studies
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. Inductive effect of favipiravir on CYP was not observed.

Drug-drug Interaction Clinical Studies:
Effects of co-administered drugs on pharmacokinetics of favipiravir

Co-administrated drug and dosage	Favipiravir dosage	n	Time of dosing	Parameter ratio for favipiravir (90% CI) (Co-administered/single administered)	
				C_{max}	AUC
Theophylline 200mg twice daily on Days 1 to 9, 200mg once daily on Day 10	600mg twice daily on Day 6, 600mg 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 75mg twice daily on Days 1 to 5, 75mg once daily on Day 6	600mg twice daily on Day 5, 600mg once daily on Day 6	10	Day 6	0.98 [0.87, 1.10]	1.01 [0.91, 1.11]
Raloxifene 60mg once daily on Days 1 to 3[Ω]	1200mg twice daily on Day 1, 800mg twice daily on Day 2, 800mg 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 5mg once daily on Day 1 and Day 5	1200mg/400mg on Day 1, 400mg twice daily on Days 2 to 4, 400mg 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]
[Ω] Results in non-Japanese					

Effects of favipiravir on pharmacokinetics of co-administered drugs

Co-administrated drug and dosage	Favipiravir dosage	n	Time of dosing	Parameter ratio for co-administered drug [90% CI] (Co-administered/single administered)	
				C_{max}	AUC
Theophylline 200mg twice daily on Days 1 to 9, 200mg once daily on Day 10	600mg twice daily on Day 6, 600mg 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 75mg twice daily on Days 1 to 5, 75mg once daily on Day 6	600mg twice daily on Day 5, 600mg once daily on Day 6	10	Day 6	1.10 [1.06,1.15]	1.14 [1.10,1.18]
Acetaminophen 650mg once daily on Day 1 and Day 5[x]	1200mg twice daily on Day 1, 800mg twice daily on Days 2 to 4, 800mg 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/0.035mg once daily on Days 1 to Day 5[x]	1200mg twice daily on Day 1, 800mg twice daily on Days 2 to 4, 800mg once daily on Day 5	25	Day 12[Σ]	1.23 [1.16,1.30]	1.47 [1.42,1.52]
			Day 12**	1.48 [1.42,1.54]	1.43 [1.39,1.47]
Repaglinide 0.5mg once daily on Day 13[x]	1200mg twice daily on Day 1, 800mg twice daily on Days 2 to 4, 800mg once daily on Day 5	17	Day 13	1.28 [1.16,1.41]	1.52 [1.37,1.68]
Hydralazine 5mg once daily on Day 1 and Day 5	1200mg/400mg on Day 1, 400mg twicedaily on Days 2 to 4, 400mg 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]
[x] Results in non-Japanese [Σ] Norethindrone ** Ethinylestradiol					

Preclinical safety data
In pharmacokinetic study, when a single dose of ^{14}C-favipiravir was orally administered to monkeys, it was distributed broadly in tissues. Radioactivity of each tissue peaked in 0.5 hours after the administration and changed in parallel with the radioactivity in plasma. The ratio of radioactivity in lung tissues to that in plasma was 0.51 in 0.5 hours after the administration, and the drug was distributed rapidly to respiratory tissues which were considered infection site. Radioactivity in kidney was higher than that in plasma, with a ratio of 2.66. Radioactivity in each tissue, except bones, decreased to ≤2.8% of the peak within 24 hours after the administration.

The toxicity profile of favipiravir was assessed in the repeat-dose oral toxicity studies in rats and dogs up to 4-week duration and in monkeys in 2-week duration. At the no-observed–adverse-effect-levels [NOAEL] dose (rats, 32 mg/kg/day; dogs, 10 mg/kg/day; monkeys, 100 mg/kg/day) in these studies, the AUC in humans was approximately 0.58 to 0.87 times that in rats, approximately 0.23 to 0.27 times that in dogs, and approximately 0.9 to 1.3 times that in monkeys, and the C_{max} in humans was approximately 0.75 to 0.87 times that in rats, approximately 0.21 to 0.24 times that in dogs, and approximately 2.1 to 2.2 times that in monkeys.

Favipiravir was non-genotoxic in various in vitro and in vivo studies. No carcinogenicity studies have been conducted and it not required as Favipiravir is indicated for a short period in clinical setting. In fertility study in rats, effects on the testis and sperm and decreased fertility were observed in males and anestrus was observed in females at the high-dose. In embryofetal developmental study, favipiravir was found to be teratogenic in all animal species (mouse, rat, rabbit and monkey) tested at systemic exposures equivalent to systemic exposure achieved in human at the proposed dosing regimen.

Juvenile Animal Study
In a one month study with juvenile dogs [8 weeks old], death cases have been reported after day 20 with a dosage [60 mg/kg/day] which was lower than the lethal dosage for young dogs [7 to 8 months old]. In juvenile animals [6-day-old rats and 8-week-old dogs], abnormal gait, atrophy and vacuolation of skeletal muscular fiber, degeneration/necrosis/mineralization of papillary muscle have been reported.

PHARMACEUTICAL PARTICULARS

List of excipients
Excipients - L-Hydroxy propyl cellulose, Colloidal Silicon Dioxide, Povidone K 30, Purified Water, Crospovidone, Sodium Stearyl Fumarate, Opadry 03A520072 Yellow.

Incompatibilities
None Reported

Shelf life
24 Months

Special precautions for storage
Store at a temperature not exceeding 30°C

Nature and contents of container
Alu-Alu Blister Packaging

Pack Size(s)
1 x 34s and 5 x 1 x 34s

Special precautions for disposal and other handling
Keep all medicines out of reach of children./ Jauhi ubat kanak-kanak
Disposal and other handling, as per the local regulatory guidance
Controlled medicine/ Ubat terkawal

Date of Revision:
22/09/2021

Product Registration Holder:
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TM Trade Mark