Favipiravir Tablets IP 200/400/800 mg
Favilow फेविलो

To be sold on the prescription of medical specialist

PRESCRIBING INFORMATION

WARNINGS

1. **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.**
2. **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.**
3. **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.**
4. **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.**
5. **Examine carefully the necessity of Favipiravir before use.**

1. GENERIC NAME
Favipiravir Tablets IP 200 mg, 400 mg and 800 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Favipiravir Tablets IP 200 mg:
Each film coated tablet contains:
Favipiravir IP 200 mg
Excipients q.s.
Colours: Titanium Dioxide IP
Ferric Oxide (Yellow) USP-NF
Ferric Oxide (Red) USP-NF
Ferrosoferric Oxide USP-NF

Favipiravir Tablets IP 400 mg:
Each film coated tablet contains:
Favipiravir IP 400 mg
Excipients q.s.
Colours: Titanium Dioxide IP
Ferric Oxide (Yellow) USP-NF
Ferric Oxide (Red) USP-NF
Ferrosoferric Oxide USP-NF

Favipiravir Tablets IP 800 mg:
Each film coated tablet contains:
Favipiravir IP 800 mg
Excipients q.s.
Colours: Titanium Dioxide IP,
Ferric Oxide (Yellow) USP-NF,
Ferric Oxide (Red) USP-NF,
Ferrosoferric Oxide USP-NF

3. DOSAGE FORM AND STRENGTH
Favipiravir film-coated tablets 200 mg, 400 mg and 800 mg

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
Favipiravir indicated for the treatment of patients with mild to moderate COVID-19 disease.

4.2 Posology and Method of Administration
The patient will be given a 3,600 mg dose for the first day as a loading dose and subsequently followed by 1,600 mg for maximum up to 14 days depending upon the viral load.

Table 1: Dosage for tablets

	Day 1			Day 2 to max 14 days		
Total daily dose	1800 mg BID			800 mg BID		
Morning	**200 mg**	**400 mg**	**800 mg**	**200 mg**	**400 mg**	**800 mg**
	200 mg X 9 tablets	400 mg X 4 + 200 mg X 1 tab	800 mg X 2 + 200 mg X 1 tab	4 tablets each	2 Tablets each	1 tablet each
Evening	**200 mg**	**400 mg**	**800 mg**	**200 mg**	**400 mg**	**800 mg**
	200 mg X 9 tablets	400 mg X 4 + 200 mg X 1 tab	800 mg X 2 + 200 mg X 1 tab	4 tablets each	2 Tablets each	1 tablet each

Note: Use only as directed by physician.

Use in Special Populations
Use during Pregnancy, Delivery or Lactation
- Do not administer Favipiravir to women known or suspected to be pregnant. (Early embryonic deaths [rats] and teratogenicity [monkeys, mice, rats and rabbits] have been observed in animal studies with exposure levels similar to or lower than the clinical exposure).
- When administering Favipiravir to lactating women, instruct to stop lactating. (The major metabolite of Favipiravir, a hydroxylated form, was found to be distributed in breast milk).

Pediatric Use
Favipiravir has not been administered to children.

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.

Other
It is recommended that the drug should be used only in adults and not on patients with severe liver and renal impairment.

4.3 Contraindications
- Women known or suspected to be pregnant (Early embryonic deaths and teratogenicity have been observed in animal studies).
- Patients with a history of hypersensitivity to any ingredient of the drug.

4.4 Special Warnings and Precautions for Use

Use during Pregnancy, Delivery or Lactation
- 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 gout or a history of gout, and patients with hyper-uricaemia (Blood uric acid level may increase, and symptoms may be aggravated).

Important Precautions
- Although the causal relationship is unknown, psychoneurotic symptoms such as abnormal behaviour after administration of Favipiravir have been reported. For the treatment of children and minors, as a preventive approach in case of an accident due to abnormal behaviour such as fall, patients/their family should be instructed that, after the start of treatment, (i) abnormal behaviour 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 infections may be complicated 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.

4.5 Drug Interactions
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.

Table 2: 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.

4.6 Use in Special Populations

Fertility, Pregnancy and Delivery or Lactation
- 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.
- Do not administer Favipiravir to women known or suspected to be pregnant. (Early embryonic deaths [rats] and teratogenicity [monkeys, mice, rats and rabbits] have been observed in animal studies with exposure levels similar to or lower than the clinical exposure).
- Do not administer to lactating women. If administered, instruct to stop lactating. (The major metabolite of Favipiravir, a hydroxylated form, was found to be distributed in breast milk).

Pediatric Use
Favipiravir has not been administered to children.

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.

Other
It is recommended that the drug should be used only in adults and not on patients with severe liver and renal impairment.

4.7 Effects on Ability to Drive and Use Machines
No data is available on the effect of Favipiravir on ability to drive and use machines.

4.8 Undesirable Effects
Major undesirable effects observed in the clinical studies with Favipiravir used at different doses included:
- Increase of blood uric acid level in 24 subjects (4.79%),
- Diarrhoea in 24 subjects (4.79%),
- Decrease of neutrophil count in 9 subjects (1.80%),
- Increase of AST (GOT) in 9 subjects (1.80%),
- Increase of ALT (GPT) in 8 subjects (1.60%).

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.
- 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.).

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.
- Colitis haemorrhagic

In prospective, multi-center, 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 Umifenovir (Arbidol) 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.

Table 3: Comparison of Anti-viral associated adverse effects

Adverse effects	Favipiravir group (N = 116)		Arbidol group (N = 120)		P value
	Frequency	Cases, n(%)	Frequency	Cases, n(%)	
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 tour (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.

Table 4: 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

Other adverse reactions:

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

Table 5: Adverse reactions observed in clinical studies and the global phase III clinical study (studies conducted with dose levels lower than the approval dosage).

System organ class	≥ 1%	0.5 - < 1%	< 0.5%
Skin and subcutaneous tissue disorders		Rash	Eczema, pruritus
Hepatic disorders	AST (GOT) increased, ALT (GPT) increased, γ-GTP increased		Blood ALP increased, blood bilirubin increased
Gastrointestinal disorders	Diarrhoea (4.79%)	Nausea, vomiting, abdominal pain	Abdominal discomfort, duodenal ulcer, haematochezia, gastritis
Hematologic disorders	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, thoracic and mediastinal disorders			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

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. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on **1800 180 3024** or you can report to MSN Labs on **+918458305295.** By reporting side effects, you can help provide more information on the safety of this product.

4.9 Overdose
There is no human experience of acute over dosage with Favipiravir. Treatment of overdose with Favipiravir should consist of general supportive measures, including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with Favipiravir.

MSN LABORATORIES PRIVATE LIMITED — PACKAGING DEVELOPMENT

Artwork Information		Specification for Printed Leaflet	
		Test	Specification
Brand Name	Favilow	Substrate	Bible Paper
Generic Name	Favipiravir Tablets IP 200/400/800 mg	GSM	40 ± 10%
Pack Style	NA	Mode of supply	Tray Pack
Dimensions	180 x 450 mm ± 2 mm	Pharmacode	3160
Folding Size	90 x 30 mm ± 2 mm	Font Type	NA
Item Code	B32662-02	Font Size (min.)	–
Supersede Code	B32662-01	Developed by	Sridhar
Version	00	Reviewed by	Srilakshmi
Date & Time		Colours	Black
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Customer	NA		

*Pharma code position is not fixed, so it may vary based on the printer's requirement.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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 dependent RNA polymerase (RdRp) involved in SARS CoV2 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.

Pharmacodynamic Properties

Microbiology/Resistance Information

Antiviral Activity

It has a proven *in-vitro* activity against SARS CoV-2. It has a wide therapeutic safety margin for COVID-19 dose.

Authors evaluated the antiviral efficiency of Favipiravir (T-705) against a clinical isolate of 2019-nCoV *in vitro*. Standard assays were carried out to measure the effects of Favipiravir on the cytotoxicity, virus yield and infection rates of 2019-nCoVs. Firstly, the cytotoxicity of the Favipiravir in Vero E6 cells (ATCC-1586) was determined by the CCK8 assay. Then, Vero E6 cells were infected with nCoV- 2019 Beta CoV /Wuhan /WIV04 /2019 at a multiplicity of infection (MOI) of 0.05 in the presence of varying concentrations of the test drugs. DMSO was used in the controls. Efficacies were evaluated by quantification of viral copy numbers in the cell supernatant via quantitative real-time RT-PCR (qRT-PCR) and confirmed with visualization of virus nucleoprotein (NP) expression through immunofluorescence microscopy at 48 h post infection (p.i.) (cytopathic effect was not obvious at this time point of infection). High concentrations of Favipiravir [Half-Effective Concentration ($EC)_{50}$ = 61.88 µM, Half-Cytotoxic Concentration ($CC)_{50}$ > 400 µM, Selectivity Index (SI) > 6.46] were required to reduce the viral infection.

Resistance

No clinical data are available on the development of SARS-CoV-2 resistance to Favipiravir. The cell culture development of SARS-CoV-2 resistance to Favipiravir has not been assessed to date.

Clinical Trials in Subjects with COVID-19

Favipiravir is backed by strong clinical evidence showing encouraging results in patients with mild to moderate COVID-19.

Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study

An outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its caused coronavirus disease 2019 (COVID-19) has been reported in China since December 2019. More than 16% of patients developed acute respiratory distress syndrome, and the fatality ratio was about 1%–2%. No specific treatment has been reported. Herein, we examine the effects of Favipiravir (FPV) versus Lopinavir (LPV)/ritonavir (RTV) for the treatment of COVID-19. Patients with laboratory-confirmed COVID-19 who received oral FPV (Day 1: 1600 mg twice daily; Days 2–14: 600 mg twice daily) plus interferon (IFN)-α by aerosol inhalation (5 million U twice daily) were included in the FPV arm of this study, whereas patients who were treated with LPV/RTV (Days 1–14: 400 mg/100 mg twice daily) plus IFN-α by aerosol inhalation (5 million U twice daily) were included in the control arm. Changes in chest computed tomography (CT), viral clearance, and drug safety were compared between the two groups. For the 35 patients enrolled in the FPV arm and the 45 patients in the control arm, all baseline characteristics were comparable between the two arms. A shorter viral clearance time was found for the FPV arm versus the control arm (median (interquartile range, IQR), 4 (2.5– 9) d versus 11 (8–13) d, P < 0.001). The FPV 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). After adjustment for potential confounders, the FPV arm also showed a significantly higher improvement rate in chest imaging. Multivariable Cox regression showed that FPV was independently associated with faster viral clearance. In addition, fewer adverse reactions were found in the FPV arm than in the control arm. In this open-label nonrandomized control study, FPV showed significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance; if causal, these results should be important information for establishing standard treatment guidelines to combat the SARS-CoV-2 infection.

Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial

No clinically proven effective antiviral strategy exists for the epidemic Coronavirus Disease 2019 (COVID-19). Investigators conducted a prospective, randomized, controlled, open-label multicenter trial involving adult patients with COVID-19. Patients were randomly assigned in a 1:1 ratio to receive conventional therapy plus Umifenovir (Arbidol) (200mg x 3/day) or Favipiravir (1600mg x 2/first day followed by 600mg x 2/day) for 10 days. The primary outcome was clinical recovery rate of Day 7. Latency to relief for pyrexia and cough, the rate of auxiliary oxygen therapy (AOT) or non-invasive mechanical ventilation (NMV) were the secondary outcomes. Safety data were collected for 17 days. 240 enrolled COVID-19 patients underwent randomization; 120 patients were assigned to receive Favipiravir (116 assessed), and 120 to receive Arbidol (120 assessed). Clinical recovery rate of Day 7 does not significantly differ between Favipiravir group (71/116) and Arbidol group (62/120) (P=0.1396, difference of recovery rate: 0.0954; 95% CI: -0.0305 to 0.2213). Favipiravir led to shorter latencies to relief for both pyrexia (difference: 1.70 days, P<0.0001) and cough (difference: 1.75 days, P<0.0001). No difference was observed of AOT or NMV rate (both P>0.05). The most frequently observed Favipiravir-associated adverse event was raised serum uric acid (16/116, OR: 5.52, P=0.0014). Among patients with COVID-19, Favipiravir, compared to Arbidol, did not significantly improve the clinically recovery rate at Day 7. Favipiravir significantly improved the latency to relief for pyrexia and cough. Adverse effects caused Favipiravir are mild and manageable. This trial is registered with Chictr.org.cn (ChiCTR2000030254).

Table 6. 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	**Arbidol group**	**Favipiravir group**	**Arbidol group**
Total patients	(N=71)	(N=74)	(N=78)	(N=73)
Day I	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 (2027)	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	-	-	| (1.28)	6 (8.22)
Day 9	-	-	1 (1.28)	3 (4.11)
Censored		-	23 (29.49)	17 (23.29)
Log-rank P value	< 0.0001		< 0.0001	
Other secondary outcomes				
AOT or NMV*	**Favipiravir group**	**Arbidol 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: Non-invasive mechanical ventilation.

5.2 Pharmacokinetic Properties

Absorption

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 7: Pharmacokinetic parameters of Favipiravir

Dosage		**C_{max} (µg/mL)˙**	**AUC (µg.hr/mL)#**	**T_{max} (hr)$**	**$T_{1/2}$ (hr)@**
1600 mg BID	Day 1	64.56 (17.2)	446.09 (28.1)	1.5 (0.75, 4)	4.8±1.1
600 mg BID	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_{τ}

$ Median (minimum, maximum)

@ Mean±SD

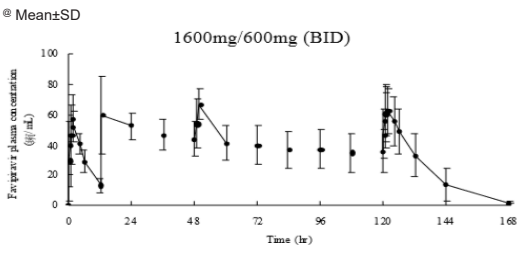

Figure 1: Time course of plasma concentration of Favipiravir (mean ± SD)

Multiple oral administration of Favipiravir for 7 days to a 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.

Distribution

When Favipiravir was orally administered to 20 healthy adult male subjects at 1200 mg twice daily for 1 day followed by 800 mg twice daily for 4 days (1200 mg/800 mg BID) Note 7, 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. The serum protein binding ratio was 53.4 to 54.4% (*in vitro*, centrifugal ultrafiltration) at 0.3 to 30µg/mL.

Animal data:

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.

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). 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-days 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.

Special Populations

Sex, Race and Age

Pharmacokinetic differences based on sex and race have not been evaluated. The antiviral offers broad spectrum RNA virus coverage with clinical improvement noted across age groups 20 to >90 years.

Paediatrics

Favipiravir has not been administered to children. (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).

Patients with Hepatic impairment

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) compared to healthy adult subjects, C_{max} and AUC at day 3 were approximately 2.1 fold and 6.3 fold, respectively.

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 was no inhibitory activity to XO, and weak inhibitory activity to CYP1A2, 2C9, 2C19, 206, 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.

Table 8: 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)**	
				Cmax	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 It03-Q	1200mg twice daily on Day 1, 800mg twice daily on Day 2, 800mg once daily on Day 3	17	Day 1	100 [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]

Table 9: 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)**	
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×	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/O.035mg once daily on Days 1 to Day 5×	1200mg twice daily on Day 1, 800mg twice daily on Days 2 to 4, 800mg once daily on Day 5	25	Day 12∑	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×	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 twice daily 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)

× Results in non-Japanese

∑ Norethindrone

** Ethinylestradiol

6. NONCLINICAL PROPERTIES

Nonclinical Toxicology

Carcinogenesis: Given the short-term administration of Favipiravir for the treatment of COVID-19, long- term animal studies to evaluate the carcinogenic potential of Favipiravir are not required.

Mutagenesis: Studies to evaluate its mutagenic potential have not been conducted.

Teratogenicity: Do not administer Favipiravir to women known or suspected to be pregnant. (Early embryonic deaths [rats] and teratogenicity [monkeys, mice, rats and rabbits] have been observed in animal studies with exposure levels similar to or lower than the clinical exposure.) When administering Favipiravir to lactating women, instruct to stop lactating. (The major metabolite of Favipiravir, a hydroxylated form, was found to be distributed in breast milk.)

Favipiravir is a white to yellow powder which is slightly soluble in water, sparingly soluble in methanol and freely soluble in N, N-Dimethyl formamide.

7. PHARMACEUTICAL PARTICULARS

7.1 Incompatibilities

None

7.2 Packing Information

200 mg Tablets: 34's & 10's count Alu-Alu Blister Pack
400 mg Tablets: 10's count Alu-Alu Blister Pack.
800 mg Tablets: 10's count Alu-Alu Blister Pack.

7.3 Storage and Handling Instructions

Store protected from moisture, at a temperature not exceeding 30°C.

8. PATIENT COUNSELLING INFORMATION

You are being given a medicine called Favipiravir for the treatment of coronavirus disease 2019 (COVID-19). This prescribing information contains information to help you understand the risks and benefits of taking Favipiravir, which you have received or may receive.

Receiving Favipiravir may benefit certain people in the hospital with COVID-19. Talk to your healthcare provider if you have questions.

9. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited
(Formulations Division), Plot No. 42,
Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325,
Telangana, India.

B32662-02

10. DETAILS OF MANUFACTURING LICENCE NUMBER

38/MD/AP/2007/F/CC

11. DATE OF REVISION

August 2021

Favilow 200 / 400 / 800

(Favipiravir Tablets IP 200 / 400 / 800 mg)

Informed consent
(For Emergency Use)

To Whomsoever It May Concern

I,_____ Age_____, Sex_____
R/o_____ hereby give my express consent for receiving Favipiravir tablet, manufactured and marketed by MSN Laboratories Pvt Ltd. Regd. Office at Plot No: C-24, Industrial Estate, Sanathnagar Hyderabad - 18 Telangana, INDIA, for treatment of COVID-19 illness.

My treating doctor _____(name and coordinates) has explained to me in the language I understand that Favipiravir has been approved only for emergency use in India for treatment of mild to moderate COVID-19 by Government (office of DCGI, Ministry of Health and Family Welfare, Govt. of India New Delhi) in the current pandemic situation of COVID-19.

I have also been explained about the possible benefits as well as risks (including the side effects) from the usage of this drug by my treating physician. After which I have made an informed choice to take this Favipiravir tablet willingly and under no undue pressure.

I also confirm that I have had a chance to read or be explained the contents of the Product Information leaflet / sheet that carries all the information on the usage, indication, possible adverse effects and contraindications for Favipiravir.

I understand that if I have questions, concerns, or complaints, or think the treatment has in any way hurt me, I am at liberty to withdraw the consent for my treatment with Favipiravir without giving any reason whatsoever and for can talk to my doctor. I agree to the fact that the data being generated out of my usage of this Favipiravir may be used by MSN laboratories Pvt Ltd. for scientific purposes only.

_____ _____

Physician's signature Name of the Person providing consent

_____

Signature of person providing consent
(Patient, Legally authorized representative, parent, or guardian)

B32679-01

MSN LABORATORIES PRIVATE LIMITED PACKAGING DEVELOPMENT

Artwork Information		Specification for Printed Leaflet	
		Test	Specification
Brand Name	Favilow 200/400/800	Substrate	Maplitho Paper
Generic Name	Favipiravir Tablets IP 200/400/800 mg	GSM	60 ± 10%
Pack Style	NA	Mode of supply	Tray Pack
Dimensions	220 x 300 mm ± 2 mm	Pharmacode	NA
Folding Size	30 x 40 mm ± 2 mm	Font Type	NA
Item Code	B32679-01	Font Size (min.)	–
Supersede Code	B32679-00	Developed by	Sridhar
Version	00	Reviewed by	Srilakshmi
Date & Time		Colours	Black
Country	Domestic		
Customer	NA		