FAVUZA (Favipiravir) Tablets

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 treatment. Explain the risks fully and instruct thoroughly to use the most effective contraceptive methods with her partner during and for seven days after the end of 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 the most effective contraceptive methods in sexual intercourse during and for seven 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 risks 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.

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, and the government decides to use the drug as a counter measure against such influenza viruses. When administering the drug, obtain the latest information including government's direction of counter measures against such influenza viruses, and prescribe only to appropriate patients. Favipiravir has not been used for novel or re-emerging influenza virus infections. Information about adverse reactions and clinical study results in this package insert is based on Japanese clinical studies with dose levels lower than the approved dosage and overseas clinical studies.

QUALITATIVE AND QUANTITATIVE COMPOSITION

FAVUZA 200mg Tablets
Each film coated tablet contains:
Favipiravir MS..... 200mg

PHARMACEUTICAL FORM

Tablets

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS:
Novel or re-emerging influenza virus infections (limited to cases in which other anti-influenza virus agents are not effective or insufficiently effective)

POSOLOGY AND METHOD OF ADMINISTRATION
Posology: The usual dosage of favipiravir for adults is 1600mg orally twice daily for 1 day followed by 600mg orally twice daily for 4 days. The total administration period should be 5 days.
Method of Administration: For oral use only.

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

SPECIAL WARNINGS AND PRECAUTIONS FOR 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, and the government decides to use the drug as a countermeasure against such influenza viruses. When administering the drug, obtain the latest information including government's direction of countermeasures against such influenza viruses, and prescribe only to appropriate patients.

Favipiravir is not effective against bacterial infections.

Favipiravir has not been administered to children.

The administration should be started promptly after the onset of influenza-like symptoms.

Careful Administration (favipiravir should be administered with care in the following patients.): Patients with gout or a history of gout, and patients with hyperuricaemia (blood uric acid level may increase), and symptoms may be aggravated.

No clinical study has been conducted to examine the efficacy and safety of favipiravir with the approved dosage. The approved dosage was estimated based on the results of a placebo-controlled phase **I/II** clinical study in patients with influenza virus infection and the pharmacokinetic data from Japanese and overseas studies. Increase of plasma level of favipiravir has been reported in patients with liver function impairment in pharmacokinetic study conducted outside of Japan.

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.

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.

Other Precautions: In animal 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.

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.

Drugs	Signs, Symptoms, and Treatment	Mechanism and 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 11.6mg/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[5]	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[3] may decrease blood level of active forms of these drugs.

PREGNANCY AND LACTATION:
1. 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)
2. When administering to lactating women, instruct to stop lactating. (The major metabolite of favipiravir, a hydroxylated form, was found to be distributed in breast milk)

UNDESIRABLE EFFECTS :
Favipiravir has never been administered with the approved dosage. In Japanese clinical studies and the global phase **III** study (studies conducted with dose levels lower than the approved dosage), adverse reactions were observed in 100 of 501 subjects (19.96%) evaluated for the safety (including abnormal laboratory test values).
Major adverse reactions 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.
1. Shock, anaphylaxis.
2. Pneumonia.

3. Hepatitis fulminant, hepatic dysfunction, jaundice.
4. Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome).
5. Acute kidney injury.
6. White blood cell count decreased, neutrophil count decreased, platelet count decreased.
7. Neurological and psychiatric symptoms (consciousness disturbed, abnormal behavior, deliria, hallucination, delusion, convulsion, etc.).
8. Colitis haemorrhagic.

Other 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).

Use in the Elderly: Since the elderly often have reduced physiological functions, it should be administered with care to them by monitoring their general conditions.
Use during Pregnancy, Delivery or Lactation: Do not administer 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 to lactating women, instruct to stop lactating. The major metabolite, a hydroxylated form, was found to be distributed in breast milk.
Paediatric Use: 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 [60mg/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.)

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES:
ATC Cod: J05AX27

Mechanism of action: It is considered that favipiravir is metabolised 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 905μmol/L.

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

PHARMACOKINETIC PROPERTIES:
Blood Concentrations: The following table shows pharmacokinetic parameters of favipiravir after an oral administration in 8 healthy 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 B.I.D.).

Pharmacokinetic parameters of favipiravir:

Dosage		*C_{max} (μg/mL)	**AUC (μg• hr/mL)	T_{max} (hr)	^^T1/2 (hr)
1600mg/600mg B.I.D.	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_t
$ Median (minimum, maximum)
^^Mean±SD

Distribution: Results in non-Japanese: When favipiravir was orally administered to 20 healthy adult male subjects at 1200mg twice daily for 1 day followed by 800mg twice daily for 4 days (1200mg/800mg B.I.D.) Note 7, the geometric mean concentration of the drug in semen was 18.341μgmL 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 approved dosage of favipiravir is "1600mg orally twice daily for 1 day followed by 600mg orally twice daily for 4 days". The serum protein binding ratio was 53.4 to 54.4% (in-vitro, centrifugal ultrafiltration) at 0.3 to 30μgmL.

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 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. Note 8 1200mg + 400mg on Day 1, then 400mg twice daily on Days 2 to 6 followed by 400mg once daily on Day 7. The approved dosage of favipiravir is "1600mg orally twice daily for 1 day followed by 600mg orally twice daily for 4 days".
Patients with liver function impairment (foreign data): When favipiravir was orally administered to subjects with mild and moderate liver function impairment (Child-Pugh classification A and B, 6 subjects each) at 1200mg twice daily for 1 day followed by 800mg twice daily for 4 days (1200mg/800mg B.I.D.)* , 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 800mg twice daily for 1 day followed by 400mg twice daily for 2 days (800mg/400mg B.I.D.)* No, compared to healthy adult subjects, C_{max} and AUC at day 3 were approximately 2.1 fold and 6.3 fold, respectively.
*The approved dosage of favipiravir is "1600mg orally twice daily for 1 day followed by 600mg orally twice daily for 4 days.

SHELF LIFE
See expiry on the pack.

AVAILABILITY
FAVUZA 200mg tablets in a pack of 30's.

INSTRUCTIONS
Dosage: As advised by the physician.
To be sold on the prescription of registered medical practitioner.
Keep out of reach of children.
Avoid exposure to heat, light and humidity.
Store between 15 to 30°C.
Improper storage may deteriorate the medicine.

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
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فیویوزا ٹیبلٹ
(فیویپیراوِر)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری
سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی

210mm

120mm