Evopravir®
(Favipiravir)

ایوپراوِر

COMPOSITION
Each film coated tablet contains:
Favipiravir.....200mg
(As per innovator's specs.)

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.

DESCRIPTION
Evopravir tablet contains Favipiravir which is a pyrazinecarboxamide derivative with activity against RNA viruses. The use of favipiravir 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.

CLINICAL PHARMACOLOGY

Mechanism of Action
The mechanism of action of favipiravir is novel compared to existing influenza antivirals that primarily prevent entry and exit of the virus from cells. Favipiravir functions as a prodrug and undergoes ribosylation and phosphorylation intracellularly to become the active ribosyl triphosphate form (favipiravir-RTP). The active favipiravir-RTP selectively inhibits RNA polymerase and prevents replication of the viral genome.

There are several hypotheses as to how favipiravir-RTP interacts with RNA dependent RNA polymerase (RdRp). Some studies have shown that when favipiravir-RTP is incorporated into a nascent RNA strand, it prevents RNA strand elongation and viral proliferation. Studies have also found that the presence of purine analogs can reduce favipiravir's antiviral activity, suggesting competition between favipiravir-RTP and purine nucleosides for RdRp binding. Although favipiravir was originally developed to treat influenza, the RdRp catalytic domain (favipiravir's primary target), is expected to be similar for other RNA viruses. This conserved RdRp catalytic domain contributes to favipiravir's broad-spectrum coverage.

Pharmacodynamics
1. In vitro antiviral activity
Favipiravir showed antiviral activity against type A and type B influenza virus laboratory strains with an EC50 of 0.014—0.5 5 µg/ mL.

The EC50 against seasonal type A and type B influenza viruses including strains resistant to adamantane (amantadine and rimantadine), oseltamivir or zanamivir was 0.03—0.94 and 0.09—0.83 µg/ mL, respectively.
The EC50 against type A influenza viruses (including strains resistant to adamantane, oseltamivir or zanamivir) such as swine-origin type A and avian-origin type A including highly-pathogenic strains (including H5N1 and H7N9) was 0.06—3.53 µg/ mL.

The EC50 against type A and type B influenza viruses resistant to adamantane, oseltamivir and zanamivir was 0.09—0.47 µg/ mL, and no cross resistance was observed.

2. Therapeutic effect in animal models
In mouse infection models inoculated with influenza viruses A (H7N9), A (H1N1) pdm09 or A (H3N2), decrease of virus titers in lung tissues was observed by a 5-day oral administration of favipiravir with a dose of ≤60 mg/kg/day.

In mouse infection models inoculated with influenza viruses A (H3N2) or A (H5N 1), therapeutic effect was observed by a 5-day oral administration of favipiravir with a dose of 30 mg/kg/day.

In a SCID mouse infection model inoculated with an influenza virus A (H3N2), therapeutic effect was observed by a 14-day oral administration of favipiravir with a dose of 30 mg/kg/day.

3. 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.

Pharmacokinetics

Absorption
The bioavailability of Favipiravir is almost complete at 97.6%. The mean Cmax for the recommended dosing schedule of Favipiravir is 51.5 ug/mL.

Distribution
The apparent volume of distribution of Favipiravir is 15 - 20 L. Favipiravir is 54% plasma protein-bound. Of this fraction, 65% is bound to serum albumin and 6.5% is bound to α1-acid glycoprotein.

Metabolism
Favipiravir is extensively metabolized with metabolites excreted mainly in the urine. The antiviral undergoes hydroxylation primarily by aldehyde oxidase and to a lesser extent by xanthine oxidase to the inactive metabolite, T705M1.

Excretion
Favipiravir's metabolites are predominantly renally cleared. The elimination half-life of Favipiravir is estimated to range from 2 to 5.5 hours.

INDICATIONS
Evopravir is indicated in the treatment of novel or re-emerging influenza virus infections (limited to cases in which other influenza antiviral drugs are ineffective or not sufficiently effective).

DOSAGE AND ADMINISTRATION

Adult dosage
The usual dosage of Favipiravir for adults is 1600 mg orally twice daily for 1 day followed by 600 mg orally twice daily for 4 days. The total administration period should be 5 days.

Dosage adjustment

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

Pediatric Patients
Favipiravir has not been administered to children.

Patients with liver function impairment
According to studies, 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, Cmax 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, Cmax 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 600 mg orally twice daily for 4 days.

Administration requirements
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.

CONTRAINDICATIONS
• Women known or suspected to be pregnant
• Patient with a history of hypersensitivity to any ingredient of the drug.

WARNINGS & PRECAUTIONS
• Since early embryonic deaths and teratogenicity have been observed in animal studies for Favipiravir, do not administer the drug to women with known or suspected to be pregnant.
• 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 drug to male patients, explain fully the risk and instruct thoroughly to use most effective contraceptives methods in sexual intercourse during and for 7 days after the end of treatment (men must wear condom). It is instructed 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.
• 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.
• Patients with gout or a history of gout, and patients with hyperuricaemia (Blood uric acid level may increase, and symptoms may be aggravated. Favipiravir should be administered with cautions in the patients.
• 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.
• Regardless of the administration or the type of anti-influenza virus agents, cases of abnormal behavior have been reported in patients with influenza virus infection. As a preventive approach to accidents such as fall due to abnormal behavior, patients/their family should be instructed that, (i) abnormal behavior may occur, and (ii) when patients are treated at home, guardians and others should take preventive measures against accidents such as fall for at least 2 days after onset of fever.
• 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.

ADVERSE REACTIONS
• Abnormal behavior (frequency unknown): Although the causal relationship is unknown, abnormal behavior (e.g. suddenly running away, wandering around) leading to a fall accident

may occur in patients with influenza virus infection.

• 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.).
• Colitis haemorrhagic.

Other adverse reactions:
Hypersensitivity: Rash, eczema, pruritus.
Hepatic: AST (GOT) increased, ALT (GPT) increased, γ-GTP increased, Blood ALP increased, blood bilirubin increased.
Gastrointestinal: Diarrhoea, 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, 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.

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.

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.

USE IN SPECIAL POPULATIONS
Pregnancy
Do not administer Favipiravir to women known or suspected to be pregnant.

Nursing mother
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.)

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

Children
Favipiravir has not been administered to children.

OVER DOSAGE
Favipiravir is known to be teratogenic; therefore, administration of favipiravir should be avoided in women if pregnancy is confirmed or suspected. Toxicity information regarding favipiravir in humans is not readily available.

PRESENTATION
Evopravir 200 mg: Pack of 30 Tablets.

INSTRUCTIONS
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, email us at
reports@pharmevo.biz

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

ہدایات:
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
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