FACT SHEET FOR HEALTH CARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF FAVIPIRAVIR
FOR TREATMENT OF COVID-19 PATIENTS

Badan POM, the Indonesia Food and Drug Administration, has issued an Emergency Use Authorization (EUA) to permit the emergency use of favipiravir for the management of adult patients (aged 18 years and older) with mild to moderate COVID-19, combined with standard supportive care.

The Emergency Use Authorization of favipiravir is for the management of adult patients (aged 18 years and older) with mild to moderate COVID-19, combined with standard supportive care.

ADMINISTRATION:
Favipiravir must be administered by a healthcare professional pursuant to a valid prescription of a licensed practitioner.

Favipiravir must be administered orally.

The optimal dosing and duration of treatment is unknown.

The suggested dose under this EUA for favipiravir to treat adults patients with mild to moderate COVID-19 is in accordance with the available clinical trials and current available guideline on the procedure for the treatment of COVID-19, which is: **1600 mg orally twice daily for first day followed by 600 mg orally twice daily on subsequent days until 7 to 14 days, based on clinical consideration by prescriber. The total administration period should not be more than 14 days.** The suggested dose and duration may be updated as data from clinical trials becomes available.

Health care providers must submit a report on all medication errors and ALL SERIOUS ADVERSE EVENTS related to favipiravir, See specific reporting instructions below.

WARNING
1. **Since early embryonic death and teratogenicity have been observed in animal studies for favipiravir, DO NOT administer the drug to women known or suspected to be pregnant (See Contraindication Section, Use in Pregnancy and Lactation Section and Pharmacological Properties Section).**
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, discontinue treatment immediately and consult to Doctor.**
3. **Favipiravir is distributed in sperm. When administering the drug to male patients, explain fully the risk of the drug and instructed thoroughly to use most effective contraception method in sexual intercourse during the treatment and for 7 days after treatment (men must wear a condom). In addition, instruct not to have sexual intercourse with pregnant woman. (See Warnings and Precautions Section and Pharmacological Properties Section).**
4. **Prior to the treatment, explain thoroughly the efficacy and the risk (including the risk of exposure to fetus) of favipiravir written to patient and his/her family members and informed consent should be obtained prior to the start of the treatment.**
5. **Examine carefully the necessity of favipiravir before use.**

For information on clinical trials that are testing the use of favipiravir in COVID-19, please see www.clinicaltrials.gov.

INSTRUCTIONS FOR ADMINISTRATION

This section provides essential information on the use of favipiravir under this EUA for the management of adult patients (aged 18 years and older) with mild to moderate COVID-19, combined with standard supportive care.

Please refer to this fact sheet for information on use of favipiravir under the EUA.

COMPOSITION

Each tablet contains favipiravir 200 mg.

CONTRAINDICATIONS

- Favipiravir should not be used in a pregnant woman or women may possibly be pregnant.
- Hipersensitivity to the any of the excipients in favipiravir tablet.

DOSING

The optimal dosing and duration of treatment is unknown.

Favipiravir must be administered orally.

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The suggested dose under this EUA for favipiravir to treat adults patients with mild to moderate COVID-19 is in accordance with the available clinical trials and current available guideline on the procedure for the treatment of COVID-19, which is: **1600 mg orally twice daily for first day followed by 600 mg orally twice daily on subsequent days until 7 to 14 days, based on clinical consideration by prescriber. The total administration period should not be more than 14 days.**

The suggested dose and duration may be updated as data from clinical trials becomes available.

METHOD OF ADMINISTRATION

Careful Administration:
Favipiravir should be administered with care in Patients with gout or a history of gout, and atients with hyperuricaemia (Blood uric acid level may increase, and symptoms may be aggravated.

Special Populations:

Elderly population (>65 years of age)
Since the elderly often have reduced physiological functions, Favipiravir should be administered with care to them by monitoring their general conditions.

Pediatrics population (<18 years of age)
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.

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, 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.

WARNINGS AND PRECAUTIONS

Administration of favipiravir should be careful for patients, such as:

- Woman of childbearing potential should have negative result test of pregnancy before the treatment started. If pregnancy occur during the treatment, the treatment should be stopped.
- When favipiravir is going to be used in breastfeeding women, breast-feeding must be stopped due to active metabolite of favipiravir distributed in human milk.
- Favipiravir is distributed in sperm. When the drug is going to be used in man, give thorough explanation about the risk dan instructs:
  - to use most effective contraception method in sexual intercourse during the treatment and for 7 days after treatment (men must wear a condom),
  - not to have sexual intercourse with pregnant woman.
- Although causal effect correlation have not known, psychoneurotic symptoms, such as abnormal behaviors, were reported after administering favipiravir. Their families must be made aware of the following precautionary points to avoid rare accidents such as falls due to abnormal behaviour. Patients or their families should be informed to take preventive measures after favipiravir administration such as to look after for at least 2 days after patients if they are treated at home.
- Favipiravir should be given with caution in gout patients or patients who has a history of gout, hiperuricemia patients since uric acid can be increased and worsening the symptoms.
- Favipiravir should be given with caution to elderly patients and monitored regularly.
- The administration favipiravir in children have not been established.
- In *in-vitro* study, favipiravir inhibited the current hERG at the Cmax which 3 times higher than Cmax in human dose, so that the risk of QT interval prolongation of favipiravir at therapeutic dose considered to be low.

DRUG INTERACTIONS

Favipiravir is mostly metabolized by aldehyde oxidase (AO), and partly metabolized by xanthine oxidase (XO). Favipiravir is not metabolized by cytochrome P-450 (CYP).

Favipiravir inhibits AO and CYP2C8, but does not induce CYP. According the in-vitro studies, Favipiravir inhibited irreversibly aldehyde oxidase (AO) in a dose and time dependent manner, and inhibited CYP2C8 in a dose dependent manner. There were no inhibitory

activity to XO, and weak inhibitory activity to CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. The hydroxylated metabolite showed weak inhibitory activity to CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4.

Favipiravir should use with caution if given concomitantly with the drug below:

Drug	Signs and symptoms	Mechanism and risk factors
Pyrazinamide	Increase uric acid in blood. At dose 1500 mg once daily and favipiravir 1200 mg/400 mg twice daily, uric acid concentration in blood reach 11.6 mg/dL when administer pyrazinamide alone, and become 13.9 mg/dL when administered in combination.	Increasing of reabsorption of uric acid in renal tubular.
Repaglinide	Blood concentration of repaglinide may increase, and adverse reaction towards repaglinide may occur.	Inhibition of CYP2C8 cause increasing of repaglinide concentration in blood.
Theophylline	Blood favipiravir concentration may increase, and adverse reaction towards favipiravir may occur.	Interaction with xantin oksidase (XO) can increase favipiravir concentration in blood.
Famciclovir, Sulindac	Efficacy of these drugs may be reduced.	Inhibition of AO by favipiravir may decrease blood level of active forms of these drugs.
Chloroquine (Substrate of CYP2C8)	Potential interaction	Clinically significance have not known.
Oseltamivir	Potential interaction	Clinically significance have not known.

ADVERSE EFFECTS

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%), diarrhea 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%).

Others adverse event are shock, pneumonia, hepatitis fulminant, liver dysfunction, jaundice, toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute renal disturbance, decrease in white blood cell, neutrophil, and thrombocyte, neurologic symptoms, psychiatric, duodenum bleeding.

The adverse effect were reported after administration favipiravir in lower dose than stated in Dosing section, such as:

	≥ 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

PHARMACOLOGICAL PROPERTIES

Preclinical Studies

The non-clinical pharmacological data of favipiravir were not specific to shown the effect of favipiravir on the SARS-Cov-2 virus. However, since the mechanism of favipiravir is suggested to be by the selective inhibition of RNA polymerase in the influenza virus leading to antiviral activity, it can be presumed the same mechanism of action for SARS-Cov-2 virus.

The bioavailability of favipiravir in female mice were similar between oral and intravenous administration, with the oral bioavailability of 97.6%.

The distribution of favipiravir following a single oral dose in male rats revealed maximum radioactivity levels were reached at 0.5 to 1 hours after dosing in all tissues, including to the cerebrum. Following a single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir to male rats, the maximum radioactivity levels (mean) were reached in the trachea and lungs (trachea, 20.5 µg eq./g; lung, 21.7 µg eq./g) at 0.5 and 1 hour after dosing. Following a single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir to male monkeys, the maximum radioactivity levels were reached at 0.5 hours after dosing.

A single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir was administered to rats to investigate the main metabolites. At 0.5, 4, and 8 hours after dosing, favipiravir (accounting for 84.36%-93.53% of the radioactivity recovered) was mainly detected in the plasma, cerebrum, and skeletal muscle; and favipiravir (28.33%-69.50%) and M1 (10.75%-34.44%) were mainly detected in the lungs, liver, kidney, and testis.

Following a single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir to fasted male rats, the cumulative radioactivity excretion rate (mean) in urine and feces, up to 96 hours was 83.06% and 19.97%, of the dosed radioactivity, respectively. Favipiravir was also found to be excreted through milk in lactating rats.

Favipiravir had effects on nonclinical reproductive and developmental toxicity. Favipiravir can exert a toxic effect on male and female reproduction by reducing fertility in both male and female

animals. In male animals, favipiravir can cause reproductive organ abnormalities. Favipiravir also exerts a toxic effect on embryos which is characterized by an increase in embryo mortality in early pregnancy. The reproductive effects of favipiravir are seen at doses ranging from 30 mg / kg or more.

Pharmacokinetics Properties

Blood concentration

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).

Pharmacokinetic parameters of favipiravir

Dosage		C_{max} Note 2 (μg/mL)	AUC Note 2, 3 (μg·hr/mL)	T_{max} Note 4 (hr)	$T_{1/2}$ Note 5 (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

Note 2 Geometric mean (CV%)
Note 3 Day 1: $AUC_{0-\infty}$, Day 6: AUC_{τ}
Note 4 Median (minimum, maximum)
Note 5 Mean±SD

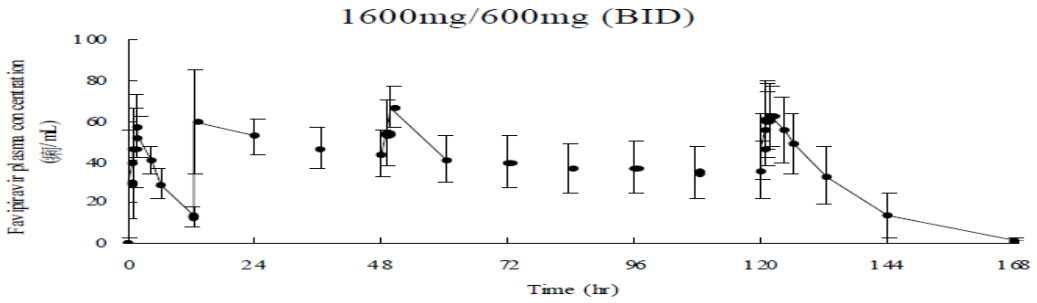

Figure 1 Time course of plasma concentration of favipiravir (mean±SD)

Following multiple oral administration of favipiravir for 7 days (see Note below) 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.

Note:
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 7-14 days".

Distribution

Animal studies showed that favipiravir distributed widely in the body (including cerebrum), except in intestine, cecum and hair.

Study in non-Japanese population, the geometric mean concentration of the drug in semen was 18.341 μg/mL on Day 3, and 0.053 μg/mL on the second day after the treatment 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). The semen levels became below the limit of quantification (0.02 μg/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 30 μg/mL.

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 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) 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.

Clinical Studies

Clinical data of favipiravir for treatment of COVID-19 are still limited. There are 2 clinical trials and 1 observational study supported the safety and efficacy of favipiravir for treatment of COVID-19.

An open-label, non-randomized control study of favipiravir compared with lopinavir/ritonavir in 80 mild to moderate adult COVID-19 patients[1)] showed the median time of viral clearance for the patients treated with FPV was estimated to be 4 days (2.5–9 days), which was significantly shorter than the time for patients in the control group which was 11 days (8–13 days) (P < 0.001).

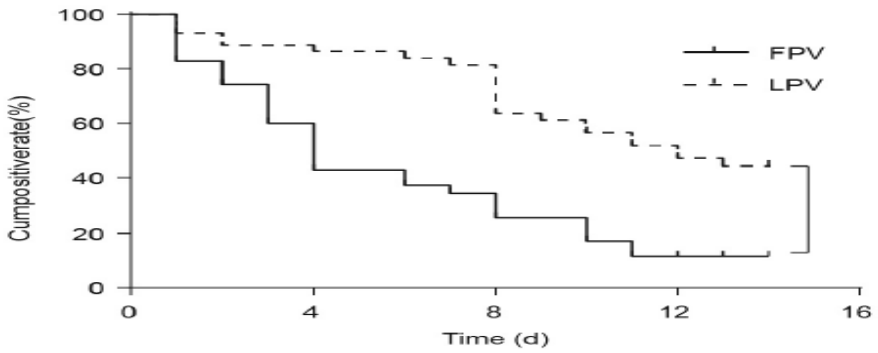

Fig. 3. Kaplan-Meier survival curves for the length of time until viral clearance for both kinds of antiviral therapy ($P < 0.001$).

In addition, favipiravir showed significant improvement in chest imaging compared with the lopinavir/ritonavir, with an improvement rate of 91.43% versus 62.22% at day 14 after treatment (p<0.004).

Table 2
Chest CT changes in patients with COVID-19 after treatment.

Chest CT changes	COVID-19 patients (N = 80)		
	FPV (N = 35)	LPV/RTV (N = 45)	P value
Day 4 after treatment			
Improve	8 (22.86%)	8 (17.78%)	
Worse	9 (25.71%)	15 (33.33%)	
Constant	18 (51.43%)	22 (48.89%)	0.42
Day 9 after treatment[a]			
Improve	18 (56.25%)	16 (35.55%)	
Worse	8 (25.00%)	16 (35.55%)	
Constant	6 (18.75%)	13 (28.90%)	0.11
Day 14 after treatment			
Improve	32 (91.43%)	28 (62.22%)	
Worse	1 (3.23%)	9 (20.00%)	
Constant	2 (6.45%)	8 (17.78%)	0.004

[a] For three patients in the FPV arm, the lung CT scan on Days 6–9 after medication was not carried out.

This study showed smaller adverse reactions of favipiravir than lopinavir/ritonavir (11.4% vs 55.56%). The most frequent adverse reactions in favipiravir reported in this study was Diarrhea, while in lopinavir/ritonavir were nausea and vomiting.

A prospective, multicenter, open-label, randomized clinical trial of favipiravir compared with Arbidol (umivenofir) in 240 COVID-19 patients[2)] showed that 7 days clinical recovery rate favipiravir better than Arbidol (71.43% vs 55.86%) and the difference was statistically significant (P = 0.0199). the clinical recovery rate in critical patients were not showed in critical patients in both favipiravir or Arbidol treatments.

Table 2. Comparison of 7 day's clinical recovery rate of favipiravir and arbidol in COVID-19 patients.

Variables	Favipiravir group	Arbidol group	Rate ratio (95% CI)	P value
Total patients	**(N = 116)**	**(N = 120)**		0.1396
Recovered, n (%)	71 (61.21)	62 (51.67)	0.0954 (-0.0305, 0.2213)	
Ordinary patients	**(N = 98)**	**(N = 111)**		
Recovered, n (%)	70 (71.43)	62 (55.86)	0.1557 (0.0271, 0.2843)	0.0199
Critical patients	**(N = 18)**	**(N = 9)**		
Recovered, n (%)	1 (5.56)	0 (0.00)	0.0556 (-0.0503, 0.1614)	0.4712
Patients with hypertension and/or diabetes	**(N = 42)**	**(N = 35)**		
Recovered, n (%)	23 (54.76)	18 (51.43)	0.0333 (-0.1904, 0.2571)	0.7704

The duration of fever in the favipiravir group was shorter than that in the Arbidol group (4 days vs 7 days, p <0.0001). Cough relief time was also shorter with favipiravir than Arbidol (8 days vs 9 days). The percentage of patients requiring supplemental oxygen / ventilator was smaller in the favipiravir group compared to arbidol (21.59% vs 45.69%). The percentage of patients with respiratory failure / dyspnea was also smaller in the favipiravir group than in the Arbidol group (respiratory failure: 0.86% vs 3.33%; dyspnea: 3.45% vs 11.67%).

The most frequent adverse events reported in favipiravir treatment in this study were increase of serum uric acid, abnormal LFT (AST and/or ALT), digestive tract reactions. Psychiatric symptom reactions also reported in 2 cases after receiving favipiravir.

The dose used in the both clinical trials above was 1600 mg twice daily on the first day and then continued with 600 mg twice daily until 7 to 14 days.

The observational study of favipiravir was conducted in Japan involving total 2,158 COVID-19 patients.[3)] A total of 2,158 cases were registered from 407 hospitals on May 15, 2020. In 92.8% of the patients, favipiravir was dosed at 2 doses of 1,800 mg orally on the first day followed by 800 mg orally twice a day on subsequent days. The rest of patients received doses of 1600 mg twice on day 1 and continued with 600 mg twice daily. The median duration was 11 days.

Based on the severity of the COVID-19 disease, favipiravir showed efficacy in patients with mild to moderate COVID-19 for clinical improvement parameters and length of stay. The data reported here suggest that the vast majority of patients with mild and moderate disease have recovered from the illness, whereas poor prognosis is not uncommon among those with severe disease.

Table 3. Clinical status and outcome stratified by severity of illness

(a) Clinical status at 7 days after start of favipiravir therapy

n		Improved	Unchanged	Worsened
1,713	Mild	574 (73.8%)	102 (13.1%)	102 (13.1%)
	Moderate	498 (66.6%)	91 (12.2%)	159 (21.3%)
	Severe	75 (40.1%)	59 (31.6%)	53 (28.3%)

(b) Clinical status at 14 days after start of favipiravir therapy

n		Improved	Unchanged	Worsened
1,282	Mild	506 (87.8%)	36 (6.2%)	34 (5.9%)
	Moderate	469 (84.5%)	37 (6.7%)	49 (8.8%)
	Severe	91 (60.3%)	22 (14.6%)	38 (25.2%)

(c) Clinical outcome one month from hospital admission

n		Died in hospital	Transferred for escalation of care	Still in hospital	Transferred for de-escalation of care	Discharged alive
1,918	Mild	42 (5.1%)	35 (4.2%)	160 (19.3%)	81 (9.8%)	512 (61.7%)
	Moderate	110 (12.7%)	66 (7.6%)	248 (28.7%)	71 (8.2%)	369 (42.7%)
	Severe	71 (31.7%)	10 (4.5%)	82 (36.6%)	28 (12.5%)	33 (14.7%)

The most common adverse events were hyperuricemia (335 patients; 15.52%) followed by liver injury or liver function test abnormalities (159 patients; 7.37%), rash (1.44%) and Diarrhea (0.74%).

Storage Condition

Store at room temperature (below 30 ^{O}C).

Shelf Life

The shelf life of Avigan (favipiravir) stored at room temperature (below 30 ^{O}C) was 10 years.

INSTRUCTIONS FOR HEALTH CARE PROVIDERS

As the health care provider administering **favipiravir**, you should, provide your patients with the Fact Sheet titled "Emergency Use Authorization (EUA) of **favipiravir Informasi Produk untuk Pasien** (Fact Sheet for Patients and Parent/Caregivers)" and communicate the following information to the patient:

1. That the Badan POM has authorized emergency use favipiravir
2. That the patient has the option to accept or refuse administration of favipiravir
3. The potential consequences of refusing favipiravir
4. The significant known and potential risks and benefits of favipiravir, as supplied under this EUA.
5. The alternative products that are available and their benefits and risks, including clinical trials.

If providing this information will delay the administration of Favipiravir to a degree that would endanger the lives of patients, the information must be provided to the patients as soon as practicable after favipiravir is administered.

If the drug is dispensed separate from the pack for inpatient use, the dispensing container should clearly identify the drug and dosage strength.

MANDATORY REQUIREMENTS FOR FAVIPIRAVIR ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION:

In order to mitigate the risks of using this approved product for an unapproved use under EUA and to optimize the potential benefit of favipiravir, the following items are required. Use of favipiravir under this EUA is limited to the following (all requirements **must** be met):

1. Adult patients with COVID-19.
2. As the health care provider, communicate to your patient or parent/caregiver information consistent with the **"Informasi Produk untuk Pasien"** prior to the patient receiving favipiravir. Health care providers (to the extent practicable given the circumstances of the emergency) must document in the patient's medical record that the patient/caregiver has been:
    - Given the **"Informasi Produk untuk Pasien"**
    - Informed of alternatives to receiving authorized favipiravir and
    - Informed that favipiravir is authorized for the use of treatment of adult patients with COVID-19 under this Emergency Use Authorization.
3. The prescribing health care provider and/or the provider's designee are/is to provide responses to requests from Badan POM for information about adverse events and medication errors following receipt of favipiravir.
4. The prescribing health care provider and/or the provider's designee are/is responsible for reporting medication errors and adverse events (death, serious adverse events*) occurring during favipiravir treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "**Favipiravir Treatment under Emergency Use Authorization (EUA)."** in the description section of the report.
    - Submit adverse event reports to:

      Pusat Farmakovigilans/MESO Nasional

      Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif

      Badan Pengawas Obat dan Makanan https://e-meso.pom.go.id/ADR
    - Submitted reports should include in the field name, "Describe Event, Problem, or Product Use/Medication Error" the statement **"Favipiravir Treatment under EUA"**

    *Serious Adverse Events are defined as:

    - death;
    - a life-threatening adverse event;
    - inpatient hospitalization or prolongation of existing hospitalization;

- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly

Additional Requirement for Use under this EUA

5. Additional requirements for reporting of patient outcomes, in addition to safety, may be required as a condition of use under this EUA.

APPROVED AVAILABLE ALTERNATIVES

There are no approved available alternative products. The health care provider should visit https://clinicaltrials.gov/ to determine whether enrollment of the patient(s) in a clinical trial is more appropriate than product use under this EUA.

AUTHORITY FOR ISSUANCE OF THE EUA

Indonesia Government has declared an emergency situation as a result of pandemic outbreak of COVID-19 that justifies the emergency need of using favipiravir as an treatment option in this situation. In response to that situation, the Badan POM has issued an Emergency Use Authorization (EUA) for the use of the Badan POM-approved product favipiravir for treatment of adult patients with COVID-19. As a health care provider, you must comply with the mandatory requirements of the EUA listed above.

Although limited scientific information is available, it is reasonable to believe that favipiravir may be effective for treatment of adult patients with COVID-19, as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency. Serious adverse events related to the use of favipiravir must be reported to Badan POM through Pusat Farmakovigilans/MESO Nasional, Badan Pengawas Obat dan Makanan online http://e- meso.pom.go.id/ADR. Please include in the field name, "Describe Event, Problem, or Product Use/Medication Error" the following statement: **Favipiravir Treatment under Emergency Use Authorization (EUA).**

This EUA for favipiravir will end when the Badan POM determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

HARUS DENGAN RESEP DOKTER
ON MEDICAL PRESCRIPTION ONLY

Favipiravir tablets are available in the following strengths and packages
200 mg in package of Box, 1 Pillow Packing @ 10 Blister @ 10 Tablet

Manufactured by Fujifilm Toyama Chemical Co., Ltd., Toyama Factory, Japan for Dr. Reddy's Laboratories Limited, India

Secondary packaged, Registered and imported by Beta Pharmacon, Indonesia

References:

1) Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental treatment with favipiravir for COVID19: an open-label control study. Engineering. 2020. In press. doi pubmed
2) Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, Chen S. Favipiravir versus Arbidol for COVID-19: a randomized clinical trial. medRxiv 2020:2020.03.17.20037432. doi.
3) Preliminary Report of the Favipiravir Observational Study in Japan: Favipiravir Observational Study Group (https://www.kansensho.or.jp/uploads/files/ topics/2019ncov/ covid19_ casereport_en_200529.pdf)

INFORMASI PRODUK UNTUK PASIEN DAN ORANG TUA/PENGASUH

PENGGUNAAN FAVIPIRAVIR UNTUK PENGOBATAN COVID-19 RINGAN HINGGA SEDANG PADA PASIEN DEWASA (USIA 18 TAHUN ATAU LEBIH)

AVIGAN®
FAVIPIRAVIR
TABLET SALUT SELAPUT

Anda diberikan obat favipiravir untuk pengobatan COVID-19. Informasi Produk (PIL) ini mengandung informasi yang dapat membantu Anda untuk mengetahui manfaat dan risiko penggunaan favipiravir yang sudah atau akan anda terima.

Belum ada obat yang disetujui oleh Badan Pengawas Obat dan Makanan (Badan POM) untuk mengobati COVID-19 secara spesifik. Penggunaan favipiravir dapat bermanfaat bagi pasien COVID-19 yang dirawat di rumah sakit. Baca Informasi Produk ini untuk mengetahui informasi mengenai favipiravir. Bicarakan kepada tenaga kesehatan yang merawat Anda apabila ada pertanyaan lebih lanjut. Hal ini merupakan pilihan Anda untuk menggunakan favipiravir atau menghentikannya.

1. **Avigan/Favipiravir tidak boleh digunakan pada wanita hamil (Lihat kontraindikasi). Penelitian pada hewan menunjukkan pemberian favipiravir dapat menyebabkan kematian pada janin dan berpotensi menimbulkan efek samping pada janin apabila dikonsumsi oleh ibu hamil (memiliki efek teratogenik)**
2. **Penggunaan pada wanita yang berpotensi hamil harus dipastikan dulu hasil uji kehamilan negatif sebelum pengobatan dimulai. Jika terjadi kehamilan saat pengobatan berlangsung, pengobatan harus segera dihentikan dan langsung konsultasi ke dokter.**
3. **AVIGAN/ favipiravir terdistribusi dalam sperma. Jika obat diberikan pada pasien pria, agar menggunakan metode kontrasepsi yang paling efektif dengan pasangannya selama dan untuk 7 hari setelah pengobatan berakhir (harus menggunakan kondom). Selain itu, tidak melakukan hubungan seksual dengan wanita hamil.**

PEMERIAN

Tablet salut selaput, berwarna putih

APA YANG TERKANDUNG DALAM AVIGAN®?

Tiap tablet salut selaput mengandung
Favipiravir …….. 200 mg

APAKAH COVID-19?

COVID-19 merupakan penyakit yang disebabkan oleh virus yang disebut coronavirus. Jenis coronavirus ini belum diketahui sebelumnya. Virus baru ini pertama kali ditemukan di Wuhan, Provinsi Hubei, China pada Desember 2019. Penyebaran dari orang ke orang telah dilaporkan di luar Hubei dan di negara selain China, termasuk di Indonesia. Anda dapat menderita COVID-19 melalui kontak dengan orang yang memiliki virus tersebut.

APA GEJALA DARI COVID-19?

Gejalanya adalah demam, batuk dan sesak nafas yang dapat timbul 2-14 hari setelah terpapar virus. Jika Anda mengalami **kesulitan bernafas, nyeri atau sesak yang terus-menerus di dada, kebingungan atau kesulitan berdiri atau bibir atau wajah pucat kebiruan segera hubungi petugas kesehatan**.

Penyakit COVID-19 memiliki rentang keparahan dari sangat ringan (termasuk beberapa laporan kasus tanpa gejala) hingga parah, dan termasuk penyakit yang mengakibatkan kematian. Informasi yang ada sejauh ini menunjukkan sebagian besar penyakit COVID-19 bersifat ringan, namun penyakit serius dapat terjadi dan dapat menyebabkan beberapa kondisi medis Anda lainnya menjadi lebih buruk. Orang yang lebih tua dan orang dari segala usia dengan kondisi medis kronis yang parah, seperti penyakit jantung, penyakit paru-paru dan diabetes, berisiko lebih tinggi dirawat di rumah sakit apabila terjangkit COVID-19.

APA ITU AVIGAN® (favipiravir)?

Avigan, atau yang juga dikenal dengan favipiravir merupakan obat antivirus yang memperoleh izin edar di Jepang untuk pengobatan influenza dimana obat anti virus influenza yang lain tidak efektif atau kurang memadai. Saat ini, obat Avigan belum tersedia di Indonesia. Satu tablet Avigan mengandung favipiravir 200 mg.

Belum ada bukti yang cukup untuk membuktikan kemanfaatan Avigan untuk terapi COVID-19. Namun obat ini sudah digunakan dalam penelitian untuk mengobati beberapa pasien COVID-19, termasuk pasien yang dirawat di rumah sakit. Favipiravir digunakan untuk menghentikan virus COVID-19 agar tidak menyebar di dalam tubuh Anda, sehingga dapat membantu Anda merasa lebih baik.

Favipiravir merupakan obat yang masih dalam pengujian sehingga belum diketahui pasti khasiatnya untuk mengobati COVID-19. Badan POM memberikan izin penggunaan emergency (darurat) favipiravir untuk mengobati COVID-19, tetapi penggunaan darurat ini diperbolehkan hanya untuk pasien COVID-19 dewasa dengan tingkat keparahan ringan hingga sedang. Informasi khasiat dan keamanan penggunaan Avigan untuk pasien COVID-19 masih sangat terbatas.

APA YANG HARUS SAYA BERITAHUKAN KEPADA TENAGA KESEHATAN SEBELUM SAYA MEMINUM FAVIPILAVIR:

Beritahukan petugas kesehatan jika Anda:

- Memiliki alergi, termasuk alergi terhadap favipiravir atau bahan lainnya yang terkandung dalam obat ini
- Memiliki penyakit ginjal atau hati atau hepatitis
- Memiliki diabetes atau riwayat gula darah rendah

- Sedang hamil atau merencanakan kehamilan
- Sedang menyusui
- Memiliki penyakit yang serius
- Memiliki penyakit gout, hiperurisemia (kadar asam urat darah tinggi)
- Sedang mengonsumsi obat-obatan lainnya, khususnya pirazinamid, repaglinid, teofilin, famsiklovir, sulindak, klorokuin, oseltamivir

SIAPA YANG TIDAK BOLEH MENGGUNAKAN FAVIPIRAVIR?

Jangan menggunakan favipiravir jika Anda sedang atau diduga hamil atau menyusui. Selain itu, jangan digunakan apabila Anda memiliki riwayat reaksi alergi terhadap favipiravir

BAGAIMANA SAYA MENGKONSUMSI FAVIPIRAVIR?

Favipiravir diberikan kepada Anda untuk diminum melalui mulut setiap hari pada dosis yang disarankan dokter. Dosis optimal favipiravir untuk mengobati COVID-19 belum diketahui. Anda akan diberikan tablet favipiravir hingga maksimum 14 hari berdasarkan pertimbangan dokter.

Apabila Anda sedang menyusui, maka diharuskan untuk menghentikan menyusui karena favipiravir dapat terdistribusi dalam air susu ibu.

Favipiravir terdistribusi dalam sperma. Jika Anda merupakan pasien pria, maka Andan diharuskan untuk menggunakan metode kontrasepsi yang paling efektif (seperti kondom) selama masa pengobatan dan 7 hari setelah pengobatan berakhir. Anda juga diharuskan untuk tidak melakukan hubungan seksual dengan wanita yang sedang hamil.

APA EFEK SAMPING PENTING YANG MUNGKIN TERJADI DARI KONSUMSI FAVIPIRAVIR?

Semua obat dapat mempunyai beberapa efek samping. Tingkat keparahan dan gejala efek samping yang muncul mungkin akan bervariasi. Efek samping yang paling umum dilaporkan adalah gangguan saluran cerna berupa diare, mual, muntah, sakit perut, perut tidak nyaman, radang perut, tukak lambung. Favipiravir juga dapat menyebabkan gangguan hati, penurunan produksi sel darah merah, gejala/simptom neurologi, dan psikiatri. Pada beberapa orang, favipiravir dapat menyebabkan gatal dan eksim

APA PILIHAN PENGOBATAN LAINNYA?

Seperti favipiravir, Badan POM telah mengizinkan penggunaan darurat klorokuin fosfat dan hydroxyklorokuin sulfate untuk mengobati pasien dewasa dan remaja dengan berat 50 kg atau lebih yang dirawat di rumah sakit dengan COVID-19. Lihat www.pom.go.id untuk informasi tentang penggunaan darurat klorokuin dan hidroksiklorokuin sulfat. Sebagai tambahan, dokter dapat menjelaskan kepada Anda tentang uji klinis yang sedang dilakukan terhadap obat-obat untuk pengobatan COVID-19.

BAGAIMANA JIKA SAYA MEMUTUSKAN UNTUK TIDAK MENGKONSUMSI FAVIPIRAVIR?

Ketika Anda memutuskan untuk mengkonsumsi favipiravir atau tidak, Anda akan diberikan perawatan lain yang memungkinkan termasuk oksigen, cairan dan obat-obatan tergantung pada kondisi Anda dan ditetapkan oleh dokter. Manfaat favipiravir dalam pengobatan COVID-19 belum dapat dipastikan. Bahkan jika Anda menggunakan favipiravir persis seperti yang diarahkan untuk mengobati COVID-19, masih ada kemungkinan penyakit Anda tidak membaik.
Merupakan pilihan Anda untuk diobati atau tidak dengan favipiravir. Anda dapat memutuskan untuk tidak mendapatkannya atau menghentikannya kapan saja. Itu tidak akan mengubah perawatan medis rutin Anda jika Anda memutuskan untuk tidak mengkonsumsinya.

APA YANG HARUS SAYA HINDARI SAAT MENGKONSUMSI FAVIPIRAVIR?

Beberapa obat lain dapat berinteraksi dengan favipiravir dan menyebabkan masalah bagi Anda. Beri tahu dokter Anda apa obat lain yang Anda pakai, termasuk obat-obatan bebas dan suplemen makanan.

BAGAIMANA JIKA SAYA HAMIL ATAU MENYUSUI?

Avigan atau favipiravir memiliki sifat teratogenik artinya obat ini berpotensi menimbulkan efek samping apabila dikonsumsi oleh ibu hamil. Penelitian pada hewan menunjukkan adanya peningkatan cacat lahir atau keguguran bayi secara tiba-tiba. Anda harus menghindari kemungkinan hamil selama meminum favipiravir.
Selain itu, Anda tidak diperbolehkan menyusui selama meminum favipiravir karena obat ini dapat masuk ke dalam air susu sehingga kemungkinan dapat menimbulkan risiko efek samping pada bayi yang disusui. Jika Anda hamil atau menyusui, diskusikan pilihan Anda dan kondisi spesifik Anda dengan dokter Anda.

BAGAIMANA SAYA MELAPORKAN EFEK SAMPING FAVIPIRAVIR?

Hubungi dokter Anda jika Anda mengalami efek samping apapun yang dirasakan setelah penggunaan favipiravir. Laporkan efek samping ke:

Pusat Farmakovigilans

Direktorat Pengawasan Keamanan, Mutu dan Ekspor Impor Obat Narkotika, Psikotropika, Prekursor, dan Zat Adiktif
Badan Pengawas Obat dan Makanan Republik Indonesia
Melalui pos: Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Tel: +62-21-4244755 Ext. 111; 4244691 Ext. 1072
Fax: +62-21-42883485
Website: http://e-meso.pom.go.id/

BAGAIMANA SAYA MENYIMPAN FAVIPIRAVIR?

Favipiravir disimpan pada tempat yang aman jauh dari jangkauan bayi dan anak-anak.
Simpan di tempat yang kering, pada suhu ruang (di bawah 30^{o}C), jauh dari panas dan cahaya matahari. Perhatikan instruksi penyimpanan pada kemasan produk atau tanyakan pada apoteker Anda

BERAPA LAMA FAVIPIRAVIR DAPAT DIGUNAKAN SELAMA DISIMPAN?

Jangan menggunakan favipiravir setelah tanggal kedaluwarsa yang tercantum pada kemasan. Tanggal kedaluwarsa pada hari terakhir bulan dan tahun tercantum.

BAGAIMANA SAYA MEMPEROLEH INFORMASI LEBIH LANJUT?

- Tanyakan pada petugas layanan kesehatan
- Kunjungi website pom.go.id

KEMASAN:

Favipiravir tablet tersedia dalam kekuatan 200 mg dan kemasan Dus, 1 pouch @ 10 Blister @ 10 tablet.

HARUS DENGAN RESEP DOKTER

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