1. NAME OF THE MEDICINAL PRODUCT

Favipiravir MEDITOP 200 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

200 mg favipiravir in each film-coated tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White, round, biconvex, flat

4. CLINICAL PARTICULARS

4.1 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).

4.2 Posology and method of administration

The usual dosage of favipiravir for adults is 1600 mg orally twice daily for l day followed by 600 mg orally twice daily for 4 days. The total duration of administration should be 5 days.

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

Elderly
Because physiological functions are often reduced in the elderly, favipiravir should be used with caution in elderly patients, with monitoring of their general health condition.

Children
Favipiravir has not been administered to children and is therefore not recommended for use in children.

Renal impairment
There are limited data in patients with mild to moderate renal impairment. According to the available data, no dose adjustment is required in this case.

Hepatic impairment
There are limited data in patients with mild to moderate hepatic impairment. In this case, doses other than those recommended have been used: 1200 mg favipiravir twice daily (6 tablets twice daily) orally for 1 day; followed by 800 mg twice daily (4 tablets twice daily) orally for 4 days.

Method of administration
Favipiravir MEDITOP should be taken orally on an empty stomach.

4.3 Contraindications

Hypersensitivity to favipiravir or to any of the excipients listed in section 6.1.
Women known or suspected to be pregnant. (Early embryonic deaths and teratogenicity have been observed in animal studies (See Section 4.6).

4.4 Special warnings and precautions for use

Since early embryonic deaths and teratogenicity have been observed in animal studies with favipiravir, do not administer the drug to women known or suspected to be pregnant (see Sections 4.2 and 4.6).

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 (See Section 4.6). If pregnancy is suspected during the treatment, instruct to discontinue the treatment immediately and to consult a doctor (see Sections 4.3, 4.6 and 5.2).

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 (See Section 4.6 and Section 5.2).

Prior to treatment, explain thoroughly (including in writing) the efficacy and risks of this medicine (including the risk of fetal exposure) to patients and their families. When prescribing the medicinal product, the patient's written consent should be sought (see Sections 4.3, 4.4 and 4.6) after providing written information on the efficacy and risks of this medicinal product (including the risk of fetal harm).

Prior to treatment a careful evaluation is required to decide on the necessity of use of favipiravir.

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 authority decides that this drug can be used against such viruses. When administering the drug, obtain the latest information including authorities' direction of countermeasures against such influenza viruses, and prescribe only to appropriate patients.

Favipiravir has not previously been used in novel or recurrent influenza pandemics. The information on side effects, as well as the results of the clinical trials mentioned below, are from clinical trials in Japan, in which lower doses have been used than the approved dose or the dose used in clinical trials in other countries.

Favipiravir has not been administered to children (see Section 4.2).

No clinical study has been conducted to examine the efficacy and safety of favipiravir with the approved posology. The approved posology 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 (see Sections 5.1 and 5.2).

There is limited experience with the use of favipiravir in the elderly, in patients with underlying diseases (including diabetes, metabolic diseases, chronic respiratory diseases, chronic heart disease) or in patients with compromised immune system, therefore administration should only be performed under close medical supervision (see section 5.2).

Regardless of the administration or the type of anti-influenza virus agents, cases of abnormal behaviour have been reported in patients with influenza virus infection (see "Clinically important side effects"). As a preventive approach to accidents such as fall due to abnormal behaviour, patients and/or their family should be instructed that, (1) abnormal behaviour may occur, and (2) 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. Severe abnormal behaviour leading to fall accidents have been reported more in male children of school age and minors, and it has been known that the symptoms are more likely to occur within 2 days after onset of fever.

Influenza virus infection may be complicated with bacterial infections and 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 antibacterial agents.

Favipiravir should be administered with care when co-administered with drugs in Table 1 below (see Section 4.5).

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

Drugs	**Signs, symptoms and treatment**	**Mechanism and risk factors**
Pyrazinamide	Blood uric acid level increases. When pyrazinamide 1.5g once daily and A favipiravir 1200 mg/400 mg BID was 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 xanthine oxidase (XO) may increase blood level of favipiravir.
Famciclovir Sulindac	Efficacy of these drugs may be reduced.	Inhibition of aldehyde oxidase (AO) by favipiravir may decrease blood level of active forms of these drugs.
Paracetamol	Paracetamol AUC may increase 1.79 times.	The risk of hepatic impairment may slightly increase.

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 (see Section 4.8)).

4.5 Interaction with other medicinal products and other forms of interaction

In vitro results
In vitro: Favipiravir inhibited irreversibly AO in a dose and time dependent manner, and inhibited CYP2C8 in a dose dependent manner. There were no inhibitory activity to XO, and weak inhibitory activity to CYP1A2, 2C9, 2C19, 2D6, 2El and 3A4. The hydroxylated metabolite showed weak inhibitory activity to CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E I and 3A4.
Inductive effect of favipiravir on CYP was not observed.

Drug-drug interaction clinical studies

Table 2.: *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	A UC
Theophylline 200 mg twice daily on Days 1 to 9, 200 mg once daily on Day 10	600 mg twice daily on Day 6, 600 mg once daily on Days 7 to 10	10	Day 6	1.33 (1.19, 1.48)	1.27 (1.15, 1.4 0)
			Day 7	1.03 (0.92, 1.15)	1.17 (1.04, 1.3)
Oseltamivir 75 mg twice daily on Days l to 5, 75 mg once daily on Day 6	600 mg twice daily on Day 5, 600 mg once daily on Day 6	10	Day 6	0.98 (0.87, 1.10)	1.01 (0.91, 1.11l)
Raloxifene 60mg once daily on Days 1 to 3 (*see the Note below*)	1200 mg twice daily on Day 2; 800 mg once daily on Day 3	17	Day 1	1.00 (0.81, 0.99)	1.03 (0.95, 1.12)
			Day 3	0.90 (0.81, 0.99)	0.85 (0.79, 0.93)
Hydralazine 5 mg once daily on Day l and Day 5	1200 mg/400 mg on Day 1; 400 mg twice daily on Days 2 to 4; 400 mg 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)

Note: Results in non-Japanese studies

Table 3.: Effects of fapiravir on 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)	
				Cmax	A UC
Theophylline 200 mg twice daily on Days 1 to 9, 200 mg once daily on Day 10	600 mg twice daily on Day 6; 600 mg 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 (0.9 1, 1.03)
Oseltamivir 75 mg twice daily on Days l to 5, 75 mg once daily on Day 6	600 mg twice daily on Day 5; 600 mg once daily on Day 6	10	Day 6	1.10 (1.06, 1.15)	1.14 (1.1 0, 1.18)
Paracetamol 650 mg once daily on Day l and Day (*see Note 1 below*)	1200 mg twice daily on Day 1; 800 mg twice daily on Days 2 to 4; 800 mg once daily on Day 5	28	Day 1	1.03 (0.93, 1.14)	I.16 (1.08, 1.25)
			Day 5	1.08 (0.96, 1.22)	1.14 (1.04, 1. 26)
Norethindrone / Ethinylestradiol combination 1mg/0.035 mg once daily on Days 1 to 5 *(see Note 1 below)*	1200 mg twice daily on Day 1, 800 mg twice daily on Days 2 to 4; 800 mg once daily on Day 5	25	Day 12 *(see Note 2 below)*	1.23 (1.16, 1.30)	1.47 (1 .42, 1.52)
			Day 12 *(see Note 3 below)*	1.48 (1.42, 1.54)	1.43 (1.39, 1.47)

Repaglinide 0.5mg once daily on Day 13 *(see Note 1 below)*	1200 mg twice daily on Day 1; 800 mg twice daily on Days 2 to 4; 800 mg once daily on Day 5	17	Da y 13	1.28 (1.16, 1.41)	1.52 (1.37, 1.68)
Hydralazine 5 mg once daily on Day 1 and Day 5	1200 mg/400 mg on Day 1; 400 mg twice daily on Days 2 to 4; 400 mg 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)

Note 1: Result s in non-Japan ese
Note 2: Norethindrone
Note 3: Ethinylestradiol

4.6 Fertility, pregnancy and lactation

Pregnancy
Do not administer favipiravir to women known or suspected to be pregnant.
In animal studies early embryonic deaths (in rats) and teratogenicity (in monkeys, mice, rats and rabbits) have been observed with exposure levels similar to or lower than the clinical exposure.

Breast-feeding
When administering favipiravir to lactating women, instruct to stop lactating. The major metabolite of faviriravir, a hydroxylated form, was found to be distributed in breast milk.

Fertility
No data are available on any effect on human fertility.

4.7 Effects on ability to drive and use machines

Favipavir MEDITOP 200 mg tablet has no or negligible influence on the ability to drive and use machines.

4.8 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%) (see Section 5.1).

l) Clinically significant adverse reactions
Abnormal behaviour (frequency unknown): Although the causal relationship is unknown, abnormal behaviour (e.g. suddenly running away, wandering around) leading to a fall accident may occur in patients with influenza virus infection (See Section 4.4).

2) 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:
- Anaphylactic shock
- 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, deliria, hallucination, delusion, convulsion, etc.)
- Colitis haemorrhagic

3) Other adverse reactions

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

Table 4.: *Adverse effects of favipiravir therapy according to organ systems and frequencies*

Organ system	≥1%	0.5 - < 1%	< 0.5%
Blood and lymphatic system disorders	Reduced neutrophil count, reduced white blood cel count		Increased white blood cell count, reduced reticulocyte count, increased monocyte count
Immun system disorders		Rash	Eczema, pruritus
Metabolism and nutrition disorders	Blood uric acid increased (4.79%), blood triglycerides increased	Glucose in urine present	Blood potassium decreased
Nervous system disorder			Dysgeusea, vertigo
Eye disorders			Blurred vision, ophthalmic pain
Cardiac disorders			Supraventricular extrasystole
Respiratory, thoracic and mediastinal disorders			Asthma, oropharyngeal pain, rhinitis, nasopharyngtis, tonsil polyp
Gastrointestinal	Diarrhoea (4.79%)	Nausea, vomiting, abdominal pain	Abdominal discomfort, duodenal ulcer, haematochezia, gastritis
Hepatobiliary disorders	AST (GOT) increased, ALT (GPT) increased, gamma-GTP increased		Blood ALP increased; blood bilirubin increased
Skin and subcutaneous tissue disorders			Pigmentation, lesions
Investigations			Blood creatinine kinase (CPK) increased, blood in the urine

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

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 lll study, information about emergence of favipiravir-resistant influenza viruses has not been obtained.

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. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose
No data are availabée.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use; ATC code: J05AX27

Mechanism of action
Favipiravir showed antiviral activity against type A and type B influenza virus laboratory strains with an EC_{50} of 0.014- 0.55 mcg/ml.
The EC_{50} 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 mcg/ml, respectively.
The EC_{50} 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 mcg/ml.
The EC_{50} against type A and type B influenza viruses resistant to adamantane, oseltamivir and zanamivir was 0.09-0.47 mcg/ml, and no cross resistance was observed.

In mouse infection models inoculated with influenza viruses A (H7N9), A (H1N1) pdm09 or A (H3N2), decrease of virus titres in lung tissues was observed by a 5-day oral administration of favipiravir with a dose of ≤60 mg/kg/day.
ln mouse infection models inoculated with influenza viruses A (H3N2) or A (H5N1), 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.

It is considered that favipiravir is metabolized 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 alpha, beta and gamma, favipiravir RTP (1000 mcmol/l) showed no inhibitory effect on alpha, 9.1-13.5% inhibitory effect on beta and 11.7-41.2% inhibitory effect on gamma. Inhibitory concentration (IC_{50}) of favipiravir RTP on human RNA polymerase II was 905 mcmol/l.

Clinical efficacy and safety
Results of non-Japanese clinical studies
A placebo-controlled phase I/II study in type A or type B influenza patients was conducted (1800 mg/800 mg BID, oral administration of favipiravir 1800 mg twice daily for I day followed by 800 mg twice daily for 4 days; 2400 mg/600 mg Tl D, oral administration of favipiravir 2400mg + 600 mg + 600 mg for 1 day followed by 600 mg three times daily for 4 days) (see Note 14 below). With regards to the primary endpoint (see Note 15 below), favipiravir 1800 mg/800 mg BID (101 patients) demonstrated significant difference in time to alleviation of influenza symptoms compared to placebo (88 patients) (p=0.01, Gehan-Wilcoxon test), but favipiravir 2400 mg/600 mg TIO (82 patients) failed to demonstrate significant difference (p=0.414, Gehan-Wilcoxon test).

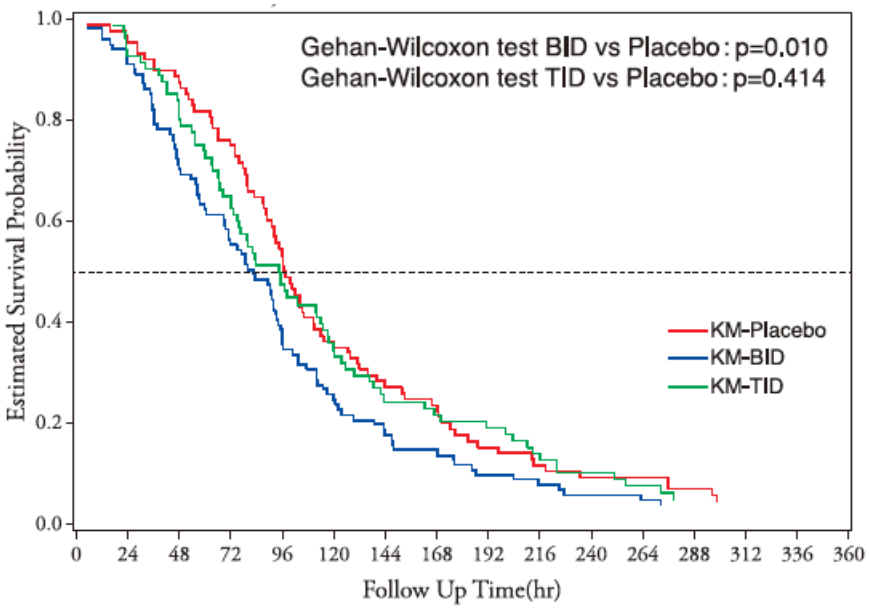

Figure 1.: *Time to alleviation of influenza symptoms*

Note 4: The approved dosage of favipiravir is 1600 mg orally twice daily for 1 day followed by 600 mg orally twice daily for 4 days.
Note 5: Time required to alleviate 7 primary influenza symptoms (cough, sore throat, headache, nasal congestion, body aches and pains, fatigue [tiredness]) and body temperature.

Two placebo-controlled phase III studies in type A or type B influenza patients (oral administration of favipiravir 1800 mg twice daily for 1 day followed by 800 mg twice daily for 4 days (1800 mg/800 mg BID) (*see Note 6 below*) with the primary endpoint: the time required to alleviate primary influenza symptoms (*see Note 7 below*) were conducted (Study I and Study 2). The results are as follows.

Table 5.: *Results of primary analysis (intention to treat (ITT) population)*

	Study 1		**Study 2**	
	Favipiravir (N=301)	**Pla ce bo (N=322)**	**Favipiravir (N=526)**	**Placebo (N= l69)**
Number of events	288	306	505	163
Median (95% Cl) (hours)	84.2 (77.1, 95.7)	98.6 (94.6, 107.1)	77.8 (72.3, 82.5)	83.9 (76 0, 95.5)
p-value *(see Note 8 below)*	0.004		0.303	

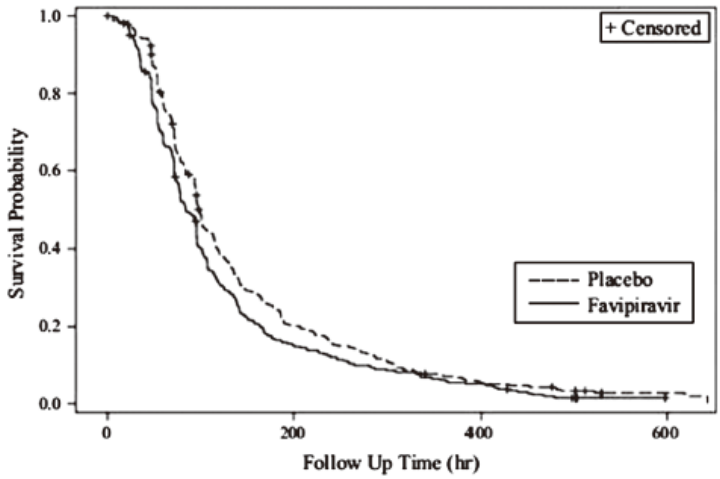

Figure 2.: *Kaplan-Meier Plot with regard to primary endpoint (intention to treat (ITT) population, Study1)* (see Note 8 below)

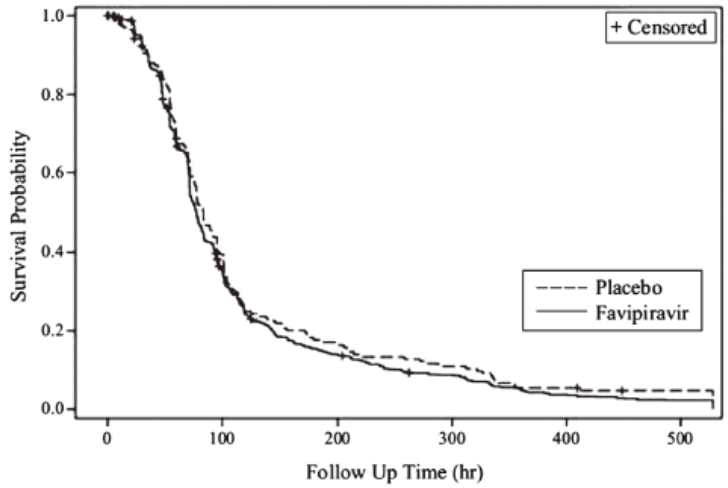

Figure 3.: *Kaplan-Meier Plot with regard to primary endpoint (intention to treat (ITT) population, Study 2)*

Note 6: The approved dosage of favipiravir is 1600 mg orally twice daily for 1 day followed by 600 mg orally twice daily for 4 days.
Note 7: Time required to alleviate 7primary in fluenza symptoms (cough, sore throat, headache, nasal congestion, body aches and pains, fatigue (tiredness) and resolution of fever. Alleviation was defined as all of the 7 influenza symptoms had been either absent or mild and fever had resolved, with both maintained for at least 21.5 hours.
Note 8: Peto-Peto-Prentice test

Global phase III clinical study (adults)
A global phase III clinical study of favipiravir (the dosage (*see Note 9 below*) was different from the approved dosage for adults) versus oseltamivir phosphate (75 mg twice daily for 5 days) was conducted in patients with type A or type B influenza (640 patients (467 patients in Japan, 55 patients in Korea, and 118 patients in Taiwan). The median time (95% Cl) to alleviation of primary influenza symptoms (*see Note 10 below)* was 63.1 hours (55.5, 70.4) for favipiravir group (377 patients) and 51.2 hours (45.9, 57.6) for oseltamivir phosphate group (380 patients). The hazard ratio (95% CI) of favipiravir to oseltamivir phosphate for time to alleviation of primary influenza symptoms was 0.818 (0.707, 0.948), and the efficacy of favipiravir was not demonstrated (p=0.007, log-rank test).

Note 9: 1200 mg + 400 mg on Day 1 followed by 400 mg twice daily for 4 days. The approved dosage of favipiravir is 1600 mg orally twice daily for I day followed by 600 mg orally twice daily for 4 days.
Note 10: Time required for 7 primary influenza symptoms (cough, sore throat, headache, nasal congestion, feeling feverish, body aches and pains, fatigue (tiredness) to alleviate after the start of study drug administration (the time point when all symptoms were scored 1 or below). Alleviation was defined as the state where all of the scores graded by the investigator based on the record of the patient diary remain unchanged for 21.5 hours or longer after all of the scores decrease to 1 or below.

Phase II clinical study in non-Japanese patients (adults)
A placebo-controlled phase II study of favipiravir was conducted in patients with type A or type B influenza (1000 mg/400 mg BID, oral administration of favipiravir 1000 mg twice daily for 1 day followed by 400 mg twice daily for 4 days; 1200 mg/800 mg BlD, oral administration of favipiravir 1200 mg twice daily for 1 day followed by 800 mg twice daily for 4 days; placebo, twice daily) (*see Note 11 below*). The median time (95% CI) to alleviation of primary influenza symptoms was 100.4 hours (82.4, 119.8) for 1000 mg/400 mg BID group (88 patients), 86.5 hours (79.2, 102.1) for 1200 mg/800 mg BID group (121 patients), and 91.9 hours (70.3, 105.4) for placebo group (124 patients). There was no statistically significant difference between either favipiravir groups and placebo group ($p>0.05$, Gehan-Wilcoxon test; A step-down approach was used to regulate the overall type I error rate for the multiple comparisons).

Note 11: The approved dosage of favipiravir is 1600 mg orally twice daily for I day followed by 600 mg orally twice daily for 4 days.
Note 12: Time required to "alleviate" 7 primary influenza symptoms (cough, sore throat, headache, nasal congestion, body aches and pains, fatigue (tiredness) and body temperature, where alleviation was defined as the state where all of the scores and temperature remain unchanged for 21.5 hours or longer after all of the scores decrease to 1 or below and temperature returned to less than 38.0°C for 20 to <65 years old and less than 37.8°C for patients ≥65 years old.

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 l day, then 600 mg twice daily for 4 days followed by 600 mg once daily for 1 day (1600 mg/600 mg BID).

Table 6.: *Pharmacokinetic parameters of favipiravir*

Dosage	**Day**	Cmax (mcg/ml) *Note 13*	AUC (mcg·hr/ml) *Note 13, 14*	Tmax (hr) *Note 15*	T1/2 (hr) *Note 16*
1600 mg/ 600 mg BID	Day I	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 13: Geometric mean (CV%)
Note 14: Day 1: $AUC_{0\text{-}inf}$, Day 6: AUC
Note 15: Median (minimum, maximum)
Note 16: Mean±SD

Following multiple oral administration of favipiravir for 7 days (see Note 17 below) toan healthy adult who appeared to have little AO activity, the estimated AUC of unchanged drug was 1452.73 mcg· hr/ml on Day l and 1324.09 mcg· hr/ml on Day 7.

Note 17: 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 I day followed by 600 mg orally twice daily for 4 days.

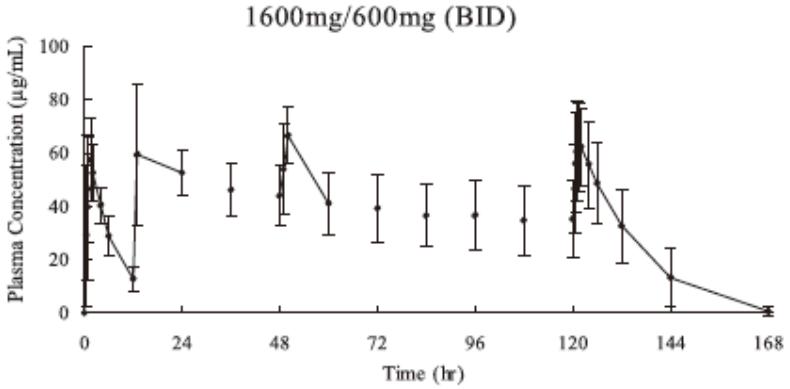

Figure 4: *Time course of plasma concentration of favipiravir* (mean±SD)

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) (see Note 7 below) the geometric mean concentration of the drug in semen was 18.341 mcg/mL on Day 3, and 0.053 mcg/mL on the second day after the treatment. The semen levels became below the limit of quantification (0.02 mcg/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.

Note 18: The approved dosage of favipiravir is 1600 mg orally twice daily for 1 day followed by 600 mg 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 30 mcg/ml.

Biotransformation

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.

Elimination

Favipiravir was mainly excreted as a hydroxylated form into the urine, and little amount unchanged drug was observed. In an oral 7day multiple dose study (see Note 8 below) 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 19: 1200 mg + 400 mg on Day 1, then 400 mg twice daily on Days 2 to 6 followed by 400 mg once daily on Day 7. The approved dosage of favipiravir is 1600 mg orally twice daily for 1 day followed by 600 mg orally twice daily for 4 days.

Special patient groups

Patients with liver function 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) (see Note 9 below) 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) (*see Note 20 below*), compared to healthy adult subjects, Cmax and AUC at day 3 were approximately 2.1fold and 6.3 fold, respectively.

Note 20: The approved dosage of favipiravir is 1600mg orally twice daily for 1 day followed by 600 mg orally twice daily for 4 days.

Use in children and adolescents
Favipiravir has not been used in 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 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 fibre, degeneration necrosis or mine realization of papillary muscle has been reported.

5.3 Preclinical safety data

Pharmacokinetic studies
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.

Teratogenicity and reproductive studies
In animal studies early embryonic deaths (in rats) and teratogenicity (in monkeys, mice, rats and rabbits) have been observed with exposure levels similar to or lower than the clinical exposure.
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
low substitution grade hydroxypropyl cellulose
colloidal silica, anhydrous
sodium stearyl fumarate

Film coating:
poly(vinyl alcohol), titanium dioxide (E 171), Macrogol 3350, talc

6.2 Incompatibilities

Not known.

6.3 Shelf life

6 months.

6.4 Special precautions for storage

Do not store above 25 ºC.
Store in the original packaging in order to protect from moisture.

6.5 Nature and contents of container and special equipment for use, administration or implantation

20 or 40 Favipiravir MEDITOP 200 mg film-coated tablets in PVC/PVdC//l blister and carton.
100 Favipiravir MEDITOP 200 mg film-coated tablets in HDPE container with PP cap and carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Note: + (one cross product)
Classification: Group II
Available only on medical prescription (V).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Meditop Gyógyszeripari Kft.
2097 Pilisborosjenő,
Ady Endre u. 1.
Hungary

8. MARKETING AUTHORISATION NUMBER(S)

OGYI-T-23790/01	20 film-coated tablets
OGYI-T-23790/02	40 db film-coated tablets
OGYI-T-23790/03	100 db film-coated tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28. December 2020.

10. DATE OF REVISION OF THE TEXT

28. December 2020.