

This prescribing information is English translated from original approval for novel or re-emerging influenza virus infections in Japan.

Revised: November 2017 (4th version)

Standard Commodity Classification No. of Japan

87625

**Storage:** Store at room temperature

**Expiration date:** Do not use after the expiration date indicated on the package

- INFLUENZA ANTIVIRAL AGENT -

Powerful drug/Prescription drug <sup>Note</sup>

Approval No.	22600AMX00533000
Date of listing in the NHI reimbursement price	Not listed in the NHI reimbursement price
<b>Date of initial marketing in Japan</b>	
International birth date	March 2014

# AVIGAN Tablets 200mg

Favipiravir

## AVIGAN

AVIGAN 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.

AVIGAN 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.

### WARNINGS


1. Since early embryonic deaths and teratogenicity have been observed in animal studies for AVIGAN, do not administer the drug to women known or suspected to be pregnant (See "CONTRAINDICATIONS" and "6. Use during Pregnancy, Delivery or Lactation").
2. When administering AVIGAN 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 "6. Use during Pregnancy, Delivery or Lactation"). If pregnancy is suspected during the treatment, instruct to discontinue the treatment immediately and to consult a doctor.
3. AVIGAN is distributed in sperm<sup>1</sup>. 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 "6. Use during Pregnancy, Delivery or Lactation" and "PHARMACOKINETICS, 2. Distribution").
4. 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 (See "CONTRAINDICATIONS", "2. Important Precautions" and "6. Use during Pregnancy, Delivery or Lactation").
5. Examine carefully the necessity of AVIGAN before use.

### CONTRAINDICATIONS

(AVIGAN is contraindicated in the following patients.)

1. Women known or suspected to be pregnant (Early embryonic deaths and teratogenicity have been observed in animal studies [See "6. Use during Pregnancy, Delivery or Lactation"].)
2. Patients with a history of hypersensitivity to any ingredient of the drug

### DESCRIPTION

<b>Brand name</b>	AVIGAN Tablets 200mg
<b>Ingredient/content (Content per tablet)</b>	Favipiravir 200mg
<b>Inactive ingredient</b>	Povidone, colloidal silicon dioxide, low-substituted hydroxypropyl cellulose, crospovidone, sodium stearyl fumarate, hypromellose, titanium dioxide, talc, yellow ferric oxide
<b>Color/dosage form</b>	Light-yellow, film-coated tablet
<b>Appearance</b>	
<b>Size (mm)</b>	Diameter: approx. 8.7 Thickness: approx. 4.3

### INDICATIONS

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

### Precautions

1. AVIGAN 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.
2. AVIGAN is not effective against bacterial infections (See "2. Important Precautions").
3. AVIGAN has not been administered to children (See "7. Pediatric Use").

Note: Use only as directed by a physician.

## DOSAGE AND ADMINISTRATION

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.

### Precautions

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

## PRECAUTIONS

### 1. Careful Administration (AVIGAN 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 “4. Adverse Reactions”])

### 2. Important Precautions

- (1) No clinical study has been conducted to examine the efficacy and safety of AVIGAN 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<sup>2</sup> (See “PHARMACOKINETICS” and “CLINICAL STUDIES”).
- (2) Although the causal relationship is unknown, psychoneurotic symptoms such as abnormal behavior after administration of anti-influenza virus agents including AVIGAN 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.
- (3) 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 (See “Precautions” regarding “INDICATIONS”).

### 3. Drug Interactions<sup>3,4</sup>

AVIGAN 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 (See “PHARMACOKINETICS”).

## Precautions for co-administration

(AVIGAN 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 AVIGAN 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 AVIGAN.	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 <sup>5</sup>	Blood level of AVIGAN may increase, and adverse reactions to AVIGAN may occur.	Interaction with XO may increase blood level of AVIGAN.
Famciclovir Sulindac	Efficacy of these drugs may be reduced.	Inhibition of AO by AVIGAN <sup>3</sup> may decrease blood level of active forms of these drugs.

## 4. Adverse Reactions

AVIGAN 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 “CLINICAL STUDIES”).

(1) 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, delirium, hallucination, delusion, convulsion, etc.)
8. Colitis haemorrhagic

(2) Other adverse reactions <sup>Note 1</sup>

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, $\gamma$ -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

Note 1 Adverse reactions observed in Japanese clinical studies and the global phase III clinical study (studies conducted with dose levels lower than the approval dosage).

**5. Use in the Elderly**

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

**6. Use during Pregnancy, Delivery or Lactation<sup>6,7</sup>**

(1) Do not administer AVIGAN 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 AVIGAN to lactating women, instruct to stop lactating.

(The major metabolite of AVIGAN, a hydroxylated form, was found to be distributed in breast milk.)

**7. Pediatric Use<sup>8</sup>**

AVIGAN 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.)

**8. Precautions concerning Use**

**Precautions regarding dispensing:**

For drugs that are dispensed in a press-through package (PTP), patients should be instructed to remove the drug from the package prior to use. (It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.)

**9. Other Precautions<sup>9,10</sup>**

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.

**PHARMACOKINETICS**

**1. Blood Concentrations**

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 <sub>max</sub> <sup>Note 2</sup> ( $\mu\text{g/mL}$ )	AUC <sup>Note 2, 3</sup> ( $\mu\text{g}\cdot\text{hr/mL}$ )	T <sub>max</sub> <sup>Note 4</sup> (hr)	T <sub>1/2</sub> <sup>Note 5</sup> (hr)
1600 mg/ 600 mg BID	Day 1	64.56 (17.2)	446.09 (28.1)	1.5 (0.75, 4)	4.8 $\pm$ 1.1
	Day 6	64.69 (24.1)	553.98 (31.2)	1.5 (0.75, 2)	5.6 $\pm$ 2.3

Note 2 Geometric mean (CV%)

Note 3 Day 1: AUC<sub>0- $\infty$</sub> , Day 6: AUC<sub>7</sub>

Note 4 Median (minimum, maximum)

Note 5 Mean $\pm$ SD

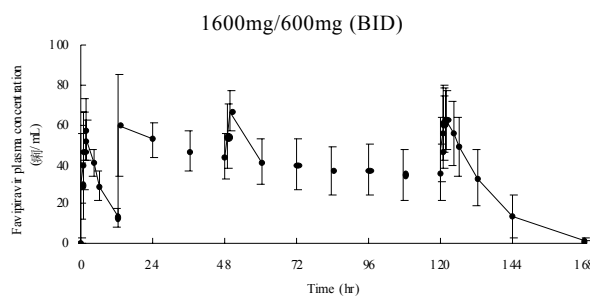


Figure 1 Time course of plasma concentration of favipiravir (mean $\pm$ SD)

Following multiple oral administration of favipiravir for 7 days <sup>Note 6</sup> to an healthy adult who appeared to have little AO activity, the estimated AUC of unchanged drug was 1452.73  $\mu\text{g}\cdot\text{hr/mL}$  on Day 1 and 1324.09  $\mu\text{g}\cdot\text{hr/mL}$  on Day 7<sup>11</sup>.

Note 6 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”.

## 2. Distribution

### Results in non-Japanese

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) <sup>Note 7</sup>, 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. 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.

Note 7 The approved dosage of favipiravir is “1600mg 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 µg/mL.

### Reference: Animal data<sup>12</sup>

When a single dose of <sup>14</sup>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.

## 3. Metabolism<sup>3</sup>

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.

## 4. Excretion<sup>11</sup>

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 <sup>Note 8</sup> 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 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”.

## 5. Patients with liver function impairment<sup>2</sup> (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 1200 mg twice daily for 1 day followed by 800 mg twice daily for 4 days (1200 mg/800 mg BID) <sup>Note 9</sup>, compared to healthy adult subjects, C<sub>max</sub> 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) <sup>Note 9</sup>, compared to healthy adult subjects, C<sub>max</sub> and AUC at day 3 were approximately 2.1 fold and 6.3 fold, respectively.

Note 9 The approved dosage of favipiravir is “1600mg orally twice daily for 1 day followed by 600 mg orally twice daily for 4 days”

## 6. Drug Interactions<sup>3,4</sup>

*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, 2E1 and 3A4. The hydroxylated metabolite showed weak inhibitory activity to CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. Inductive effect of favipiravir on CYP was not observed.

### Drug-drug Interaction Clinical Studies:

#### 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)	
				C <sub>max</sub>	AUC
Theophylline <sup>5</sup> 200mg twice daily on Days 1 to 9, 200mg once daily on Day 10	600mg twice daily on Day 6, 600mg once daily on Days 7 to 10	10	Day 6	1.33 [1.19, 1.48]	1.27 [1.15, 1.40]
			Day 7	1.03 [0.92, 1.15]	1.17 [1.04, 1.31]
Oseltamivir <sup>13</sup> 75mg twice daily on Days 1 to 5, 75mg once daily on Day 6	600mg twice daily on Day 5, 600mg once daily on Day 6	10	Day 6	0.98 [0.87, 1.10]	1.01 [0.91, 1.11]
Raloxifene 60mg once daily on Days 1 to 3 <sup>Note 10</sup>	1200mg twice daily on Day 1, 800mg twice daily on Day 2, 800mg once daily on Day 3	17	Day 1	1.00 [0.90, 1.10]	1.03 [0.95, 1.12]
			Day 3	0.90 [0.81, 0.99]	0.85 [0.79, 0.93]
Hydralazine 5mg once daily on Day 1 and Day 5	1200mg/400mg on Day 1, 400mg twice daily on Days 2 to 4, 400mg once daily on Day 5	14	Day 1	0.99 [0.92, 1.06]	0.99 [0.92, 1.07]
			Day 5	0.96 [0.89, 1.04]	1.04 [0.96, 1.12]

Note 10 Results in non-Japanese

#### Effects of favipiravir on pharmacokinetics of co-administered drugs

Co-administrated drug and dosage	Favipiravir dosage	n	Time of dosing	Parameter ratio for co-administered drug [90% CI] (Co-administered/single administered)	
				C <sub>max</sub>	AUC
Theophylline <sup>5</sup> 200mg twice daily on Days 1 to 9, 200mg once daily on Day 10	600mg twice daily on Day 6, 600mg once daily on Days 7 to 10	10	Day 7	0.93 [0.85, 1.01]	0.92 [0.87, 0.97]
			Day 10	0.99 [0.94, 1.04]	0.97 [0.91, 1.03]
Oseltamivir <sup>13</sup> 75mg twice daily on Days 1 to 5, 75mg once daily on Day 6	600mg twice daily on Day 5, 600mg once daily on Day 6	10	Day 6	1.10 [1.06, 1.15]	1.14 [1.10, 1.18]
Acetaminophen 650mg once daily on Day 1 and Day 5 <sup>Note 11</sup>	1200mg twice daily on Day 1, 800mg twice daily on Days 2 to 4, 800mg once daily on Day 5	28	Day 1	1.03 [0.93, 1.14]	1.16 [1.08, 1.25]
			Day 5	1.08 [0.96, 1.22]	1.14 [1.04, 1.26]

Norethindrone/ Ethinylestradiol combination 1mg/0.035mg once daily on Days 1 to Day 5 Note 11	1200mg twice daily on Day 1, 800mg twice daily on Days 2 to 4, 800mg once daily on Day 5	25	Day 12 Note 12	1.23 [1.16, 1.30]	1.47 [1.42, 1.52]
			Day 12 Note 13	1.48 [1.42, 1.54]	1.43 [1.39, 1.47]
Repaglinide 0.5mg once daily on Day 13 Note 11	1200mg twice daily on Day 1, 800mg twice daily on Days 2 to 4, 800mg once daily on Day 5	17	Day 13	1.28 [1.16, 1.41]	1.52 [1.37, 1.68]
Hydralazine 5mg once daily on Day 1 and Day 5	1200mg/400mg on Day 1, 400mg twice daily on Days 2 to 4, 400mg once daily on Day 5	14	Day 1	0.73 [0.67, 0.81]	0.87 [0.78, 0.97]
			Day 5	0.79 [0.71, 0.88]	0.91 [0.82, 1.01]

Note 11 Results in non-Japanese

Note 12 Norethindrone

Note 13 Ethinylestradiol

### CLINICAL STUDIES

#### Results in non-Japanese

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 1 day followed by 800 mg twice daily for 4 days; 2400 mg/600 mg TID, oral administration of favipiravir 2400mg + 600 mg + 600 mg for 1 day followed by 600 mg three times daily for 4 days)<sup>Note 14</sup>. With regards to the primary endpoint<sup>Note 15</sup>, 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 TID (82 patients) failed to demonstrate significant difference (p=0.414, Gehan-Wilcoxon test).

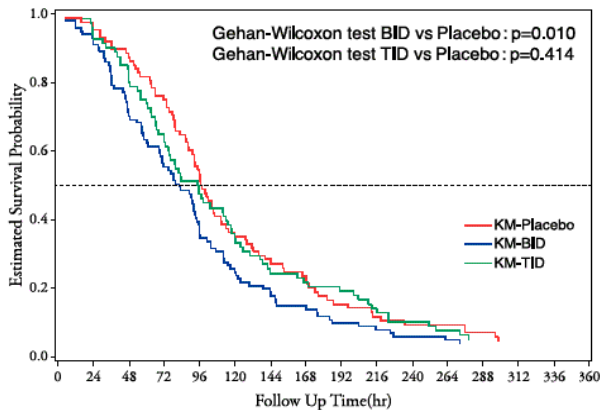


Figure 2 Time to alleviation of influenza symptoms

Note 14 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 15 Time required to alleviate 6 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])<sup>Note 16</sup> with the primary endpoint: the time required to alleviate primary influenza symptoms<sup>Note 17</sup>, were conducted (Study1 and Study2). The results are as follows.

#### Results of primary analysis (ITTI population)

	Study1		Study2	
	Favipiravir (N=301)	Placebo (N=322)	Favipiravir (N=526)	Placebo (N=169)
Number of events	288	306	505	163
Median [95% CI] (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 <sup>Note 18</sup>	0.004		0.303	

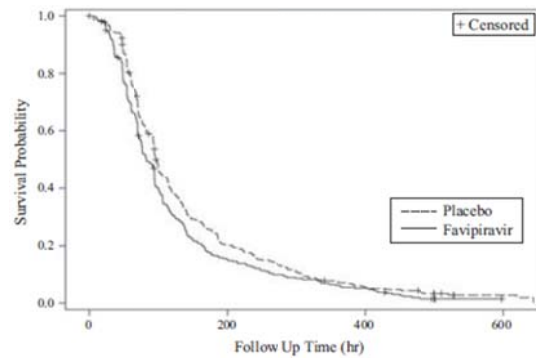


Figure 3 Kaplan-Meier Plot with regard to primary endpoint<sup>Note 17</sup> (ITTI population, Study1)

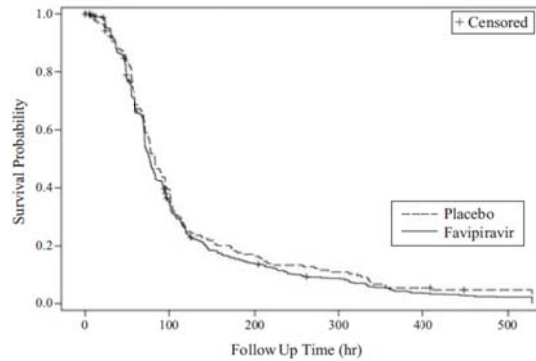


Figure 4 Kaplan-Meier Plot with regard to primary endpoint<sup>Note 17</sup> (ITTI population, Study2)

Note 16 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 17 Time required to alleviate 6 primary influenza symptoms (cough, sore throat, headache, nasal congestion, body aches and pains, fatigue [tiredness]) and resolution of fever. Alleviation was defined as all of the 6 influenza symptoms had been either absent or mild and fever had resolved, with both maintained for at least 21.5 hours.

Note 18 Peto-Peto-Prentice test

#### Reference: Global phase III clinical study (adults)

A global phase III clinical study of favipiravir (the dosage<sup>Note 19</sup> 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% CI) to alleviation of primary influenza symptoms<sup>Note 20</sup> 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 19 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 1 day followed by 600mg orally twice daily for 4 days”.

Note 20 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.)

#### Reference: Phase II clinical study in non-Japanese (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 BID,

oral administration of favipiravir 1200 mg twice daily for 1 day followed by 800 mg twice daily for 4 days; placebo, twice daily) <sup>Note 20</sup>. The median time (95% CI) to alleviation of primary influenza symptoms <sup>Note 21</sup> 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 group 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 19 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 20 Time required to “alleviate” 6 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  $\geq 65$  years old.

## PHARMACOLOGY

### 1. *In vitro* antiviral activity<sup>14, 15</sup>

Favipiravir showed antiviral activity against type A and type B influenza virus laboratory strains with an EC<sub>50</sub> of 0.014–0.55 µg/mL.

The EC<sub>50</sub> 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 EC<sub>50</sub> 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 EC<sub>50</sub> 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<sup>14, 16, 17, 18, 19</sup>

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  $\leq 60$  mg/kg/day.

In 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.

### 3. Mechanism of action<sup>14, 20</sup>

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 µmol/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<sub>50</sub>) of favipiravir RTP on human RNA polymerase II was 905 µmol/L.

### 4. Resistance<sup>14</sup>

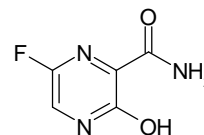
No change of susceptibility of type A influenza viruses to favipiravir was observed after 30 passages in the presence of favipiravir, and no resistant viruses have been selected. In clinical studies including the global phase III study, information about emergence of favipiravir-resistant influenza viruses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

## PHYSICOCHEMISTRY

Nonproprietary name: Favipiravir

Chemical name: 6-Fluoro-3-hydroxypyrazine-2-carboxamide

Structure formula:



Molecular formula: C<sub>5</sub>H<sub>4</sub>FN<sub>3</sub>O<sub>2</sub>

Molecular weight: 157.10

Description: Favipiravir is a white–light yellow powder. It is sparingly soluble in acetonitrile and methanol, slightly soluble in water and ethanol (99.5).

Melting point: 187–193°C

## CONDITIONS FOR APPROVAL

1. Establish and appropriately implement a risk management plan.
2. Since further investigation regarding the efficacy and safety of the drug under utilization is required, conduct an appropriate post marketing surveillance.
3. Do not market the drug unless the Minister of Health, Labour and Welfare requests.
4. When marketing the drug, implement strict distribution management and thorough safety measures so that the drug would not be used for seasonal influenza viral infectious diseases.
5. Take strict and proper measures so that the drug is administered only to patients who are considered appropriate to take the drug only when they are explained in advance about the efficacy and risk in writing and they or their family consent in writing.

## PACKAGING

**AVIGAN Tablets 200mg:** boxes of 100 tablets in press-through packages

## REFERENCES

1. In-house document (Effects on the testis)
2. In-house document (Pharmacokinetics in patients with liver function impairment)
3. In-house document (Metabolism)
4. In-house document (Drug interactions)
5. In-house document (Study of combination therapy with theophylline)
6. In-house document (Reproductive and developmental toxicity study/rats)
7. In-house document (Reproductive and developmental toxicity study/mice, etc.)
8. In-house document (Toxicity study/juvenile dogs, etc.)
9. In-house document (Toxicity study/dogs)
10. In-house document (Testicular toxicity study/mice, etc.)
11. In-house document (High dose repeated administration study)
12. In-house document (*In vivo* kinetics/animal)
13. In-house document (Study of combination therapy with oseltamivir)
14. Takahashi K, et al. *Jpn J Med Pharm Sci.* 2011;66:429.
15. In-house document (Antiviral activity and cross resistance)
16. Ito Y, et al. *Nature.* 2009;460:1021.
17. Watanabe T, et al. *Nature.* 2013;501:551.
18. In-house document (Therapeutic effect/mice)
19. In-house document (Therapeutic effect/immune-deficient mice)
20. Furuta Y, et al. *Antimicrob. Agents Chemother.* 2005;49:981.

## REQUEST FOR LITERATURE SHOULD BE MADE TO:

Please request for the in-house documents cited in the REFERENCES to the following company:

Medical Information Center

Taisho Toyama Pharmaceutical Co., Ltd.

3-25-1, Takada, Toshima-ku, Tokyo 170-8635, Japan

Toll-Free: 0120-591-818

### Distributed by:

Taisho Toyama Pharmaceutical Co., Ltd.

3-25-1, Takada, Toshima-ku, Tokyo 170-8635, Japan

### Manufactured and Marketed by:

TOYAMA CHEMICAL CO., LTD.

2-5, Nishishinjuku 3-chome, Shinjuku-ku, Tokyo 160-0023, Japan