

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

Revised: June 2024 (2nd version)

Storage: Store at room temperature  
Shelf Life: 10 years

Standard Commodity Classification  
No. of Japan  
87625

- ANTIVIRAL AGENT -  
Favipiravir

Powerful drug, Prescription-only drug <sup>Note)</sup>

# AVIGAN Tablets 200mg

|                                    |                  |
|------------------------------------|------------------|
| Approval No.                       | 22600AMX00533000 |
| Date of Initial Marketing in Japan | -                |

Note) Caution - Use only pursuant to the prescription of a physician, etc.

## 〈Novel or re-emerging influenza virus infections〉

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 electronic package insert is based on Japanese clinical studies with dose levels lower than the approved dosage and overseas clinical studies.

## 1. WARNINGS

### 〈SFTS virus infections〉

**1.1** Drug should be administered under inpatient control by a physician with adequate knowledge of drug at a medical institution where a medical care system for severe infectious diseases is in place and adequate measures can be taken in the event of an emergency.

### 〈Common indication〉

**1.2** 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 1.4, 2.1, and 9.5.]

**1.3** 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 10 days after the end of the treatment. If pregnancy is suspected during the treatment, instruct to discontinue the treatment immediately and to consult a doctor. [See 9.4.1.]

**1.4** 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 consent. [See 1.2, 2.1, and 9.5.]

### 〈Novel or re-emerging influenza virus infections〉

**1.5** Examine carefully the necessity of AVIGAN before use.

## 2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)

**2.1** Women known or suspected to be pregnant [See 1.2, 1.4, and 9.5.]

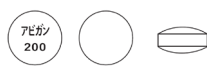
**2.2** Patients with a history of hypersensitivity to any ingredient of the drug

## 3. COMPOSITION AND PRODUCT DESCRIPTION

### 3.1 Composition

|                   |  |
|-------------------|--|
| Brand name        | AVIGAN Tablets 200mg   |
| Active ingredient | Per tablet<br>Favipiravir 200mg  |
| Excipients        | Povidone, colloidal silicon dioxide, low-substituted hydroxypropyl cellulose, crospovidone, sodium stearyl fumarate, hypromellose, titanium dioxide, talc, yellow ferric oxide |

### 3.2 Product Description

|                   |   |
|-------------------|---|
| Brand name        | AVIGAN Tablets 200mg  |
| Color/dosage form | Light-yellow, film-coated tablet  |
| Appearance        |  |
| Size (mm)         | Diameter: approx. 8.7, Thickness: approx. 4.3   |

## 4. INDICATIONS

- Novel or re-emerging influenza virus infections (limited to cases in which other anti-influenza virus agents are not effective or insufficiently effective.)
- Severe fever with thrombocytopenia syndrome (SFTS) virus infections

## 5. PRECAUTIONS CONCERNING INDICATIONS

### 〈Novel or re-emerging influenza virus infections〉

**5.1** 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.

**5.2** AVIGAN is not effective against bacterial infections. [See 8.3.]

### 〈Common indication〉

**5.3** AVIGAN has not been administered to children. [See 9.7.]

## 6. DOSAGE AND ADMINISTRATION

### (Novel or re-emerging influenza virus infections)

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.

### (SFTS virus infections)

The usual dosage of favipiravir for adults is 1800 mg orally twice daily for 1 day followed by 800 mg orally twice daily for 9 days. The total administration period should be 10 days.

## 7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION

### (Novel or re-emerging influenza virus infections)

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

7.2 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. [See 16.1.1 and 17.1.1.]

### (SFTS virus infections)

7.3 The administration should be started promptly after the onset of symptoms of SFTS virus infection.

## 8. IMPORTANT PRECAUTIONS

### (Common indication)

8.1 Hepatic function disorder may occur. Hepatic function tests should be performed before and during administration, and patients should be carefully monitored. [See 9.3.1, 9.3.2 and 11.1.4.]

8.2 Regardless of the administration or the type of anti-influenza virus agents, cases of abnormal behavior have been reported in patients with influenza virus infection.

As a preventive approach to accidents such as fall due to abnormal behavior, patients/their family should be instructed that, (i) abnormal behavior may occur, and (ii) when patients are treated at home, guardians and others should take preventive measures against accidents such as fall for at least 2 days after onset of fever.

Severe abnormal behavior 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. [See 11.1.1.]

8.3 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 5.2.]

## 9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

### 9.1 Patients with Complication or History of Diseases, etc.

#### 9.1.1 Patients with gout or a history of gout, and patients with hyperuricaemia

Blood uric acid level may increase, and gout attack may occur. [See 11.2.]

### 9.3 Patients with Hepatic Impairment

#### 9.3.1 Patients with Severe Hepatic Impairment (Child-Pugh classification C)

Administration is not recommended. The acceptability of drug administration should be judged carefully considering the risks and benefits. The exposure of drug increased markedly, and adverse reactions may occur strongly. [See 8.1 and 16.6.1.]

#### 9.3.2 Patients with mild and moderate Hepatic Impairment (Child-Pugh classification A and B)

Risks should be carefully investigated before the start of administration, and the drug should be administered with

care. Drug exposure may be increased, and adverse reactions may be severe. [See 8.1 and 16.6.1.]

## 9.4 Patients with Reproductive Potential

### 9.4.1 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 10 days after the end of the treatment. If pregnancy is suspected during the treatment, instruct to discontinue the treatment immediately and to consult a doctor. [See 1.3 and 9.5.]

## 9.5 Pregnant Women

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<sup>3,4)</sup>. [See 1.2, 1.4, 2.1, and 9.4.1.]

## 9.6 Breast-feeding Women

Consider continuation or discontinuation of breast-feeding, taking into account the therapeutic benefits and the benefits of breast-feeding. The major metabolite of AVIGAN, a hydroxylated form, was found to be distributed in human breast milk.

## 9.7 Pediatric Use

No clinical studies in children have been conducted. In a one month study with juvenile dogs [8 weeks old], fatal 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<sup>3)</sup>. [See 5.3.]

## 9.8 Geriatric Use

Administer AVIGAN while monitoring the patient's condition. In general, physiological function is often decreased.

## 10. INTERACTIONS

AVIGAN is mostly metabolized by aldehyde oxidase (AO), and partly metabolized by xanthine oxidase (XO). The drug inhibits AO and cytochrome P-450 (CYP) 2C8<sup>4,5)</sup>. [See 16.4 and 16.7.1.]

### 10.2 Precautions for Co-administration (This drug should be administered with caution when co-administered with the following.)

| Drugs   | Signs, Symptoms, and Treatment   | Mechanism and Risk Factors  |
|---|--|---|
| Pyrazinamide  | Blood uric acid level increases. When pyrazinamide 1.5 g 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.                             |
| Drugs metabolized by CYP2C8<br>Repaglinide<br>etc.<br>[See 16.7.2.] | Blood level of the drug mentioned on the left may increase, and adverse reactions to the drug mentioned on the left may occur.   | Inhibition of CYP2C8 increases blood level of the drug mentioned on the left.                     |
| Theophylline <sup>6)</sup><br>[See 16.7.2.]                         | Blood level of AVIGAN may increase, and adverse reactions to AVIGAN may occur.   | Interaction with XO may increase blood level of AVIGAN.   |
| Famciclovir<br>Sulindac   | Efficacy of these drugs may be reduced.  | Inhibition of AO by AVIGAN <sup>4)</sup> may decrease blood level of active forms of these drugs. |

## 11. ADVERSE REACTIONS

The following adverse reactions may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

### 11.1 Clinically Significant Adverse Reactions

#### 11.1.1 Abnormal behavior (frequency unknown)

Although the causal relationship is unknown, abnormal behavior (e.g. suddenly running away, wandering around) leading to a fall accident may occur in patients with influenza virus infection. [See 8.2.]

#### 11.1.2 Shock, anaphylaxis (frequency unknown for both)

#### 11.1.3 Pneumonia (frequency unknown)

#### 11.1.4 Hepatitis fulminant (frequency unknown), hepatic impairment (0.2%), jaundice (frequency unknown) [See 8.1.]

#### 11.1.5 Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome) (frequency unknown for both)

#### 11.1.6 Acute kidney injury (frequency unknown)

#### 11.1.7 White blood cell count decreased, neutrophil count decreased, platelet count decreased (frequency unknown for all)

#### 11.1.8 Convulsion (0.2%), neurological and psychiatric symptoms (consciousness disturbed, delirium, hallucination, delusion, etc.) (frequency unknown)

#### 11.1.9 Colitis haemorrhagic (frequency unknown)

### 11.2 Other Adverse Reactions

| Type                | ≥ 1%   | 0.5 - < 1%                       | < 0.5%  | Frequency unknown |
|---------------------|--|----------------------------------|---|-------------------|
| Hypersensitivity    | Rash   | -                                | Eczema, pruritus, erythema  | -                 |
| Hepatic             | AST increased, ALT increased, γ-GTP increased                                    | -                                | Blood ALP increased, blood bilirubin increased  | -                 |
| Renal               | -  | Glucose urine present            | Blood urine present   | -                 |
| Gastrointestinal    | Diarrhoea (4.5%)   | Nausea, abdominal pain, vomiting | Abdominal discomfort, gastritis, duodenal ulcer, haematochezia, stomatitis                          | -                 |
| Hematologic         | Neutrophil count decreased, white blood cell count decreased                     | -                                | White blood cell count increased, reticulocyte count decreased, monocyte increased, lymphadenopathy | -                 |
| Metabolic disorders | Blood uric acid increased (7.0%) <sup>Note</sup> , blood triglycerides increased | -                                | Gout <sup>Note</sup> , blood potassium decreased  | -                 |
| Respiratory         | -  | -                                | Asthma, oropharyngeal pain, rhinitis, nasopharyngitis, pneumonia aspiration                         | -                 |

| Type   | ≥ 1% | 0.5 - < 1% | < 0.5%  | Frequency unknown |
|--------|------|------------|---|-------------------|
| Others | -    | -          | Dysgeusia, blood CK increased, electrocardiogram QT prolonged, tonsil polyp, cellulitis, vision blurred, eye pain, vertigo, supraventricular extrasystoles, ventricular extrasystoles, electrocardiogram ST-T segment abnormal, electrocardiogram T wave inversion, pigmentation, myalgia, bruise | Fever             |

Note) [See 9.1.1.]

## 14. PRECAUTIONS CONCERNING USE

### 14.1 Precautions Concerning the Dispensing of the Drug

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. If the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.

## 15. OTHER PRECAUTIONS

### 15.2 Information Based on Nonclinical Studies

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<sup>7)8)</sup>.

## 16. PHARMACOKINETICS

### 16.1 Blood Level

#### 16.1.1 Repeated doses (1600 mg/600 mg BID)

The following table and Figure 1 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). [See 7.2.]

| Pharmacokinetic parameters of favipiravir |       |   |  |  |   |   |
|---|-------|---|--|--|---|---|
| Dosage                                    |       | n | C <sub>max</sub> <sup>Note 1)</sup><br>(μg/mL) | AUC <sup>Note 1) Note 2)</sup><br>(μg·hr/mL) | T <sub>max</sub> <sup>Note 3)</sup><br>(hr) | t <sub>1/2</sub> <sup>Note 4)</sup><br>(hr) |
| 1600 mg/<br>600 mg<br>BID                 | Day 1 | 8 | 64.56<br>[17.2]                                | 446.09<br>[28.1]                             | 1.5<br>[0.75, 4]                            | 4.8±1.1                                     |
|   | Day 6 | 8 | 64.69<br>[24.1]                                | 553.98<br>[31.2]                             | 1.5<br>[0.75, 2]                            | 5.6±2.3                                     |

Note 1) Geometric mean [CV%]

Note 2) Day 1: AUC<sub>0-∞</sub>, Day 6: AUC<sub>τ</sub>

Note 3) Median [minimum, maximum]

Note 4) Mean ± SD

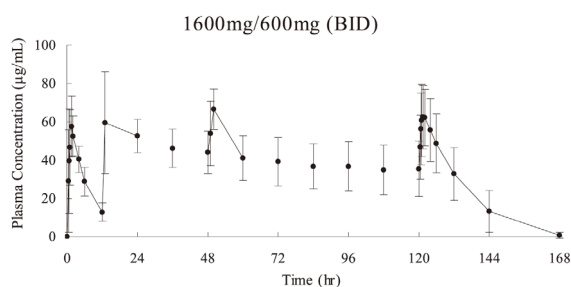


Figure 1. Time course of plasma concentration of favipiravir (mean±SD)

### 16.1.2 Repeated doses (1800 mg/800 mg BID)

The following table and Figure 2 shows pharmacokinetic parameters of favipiravir after an oral administration in 8 healthy adults at 1800 mg twice daily for 1 day, then 800 mg twice daily for 20 day followed by 800 mg once daily for 1 day (1800 mg/800 mg BID)<sup>9)</sup>.

| Dosage                    |        | n                    | C <sub>max</sub> <sup>Note 5)</sup><br>(µg/mL) | AUC <sub>inf</sub> <sup>Note 5)</sup> Note 6)<br>(µg·hr/mL) | T <sub>max</sub> <sup>Note 7)</sup><br>(hr) | t <sub>1/2</sub> <sup>Note 8)</sup><br>(hr) |
|---------------------------|--------|----------------------|--|---|---|---|
| 1800 mg/<br>800 mg<br>BID | Day 1  | 8 <sup>Note 9)</sup> | 65.06<br>[22.7]                                | 724.56<br>[47.1]  | 1.5<br>[1, 4]                               | 7.5±2.7                                     |
|                           | Day 12 | 7                    | 104.08<br>[21.3]                               | 966.41<br>[23.9]  | 1.5<br>[0.5, 2]                             | 17.6±7.4                                    |
|                           | Day 22 | 7                    | 100.39<br>[21.3]                               | 932.44<br>[24.6]  | 1.5<br>[0.75, 2]                            | 8.1±2.6                                     |

Note 5) Geometric mean [CV%]

Note 6) Day 1: AUC<sub>inf</sub>, Day 12 and 22: AUC<sub>r</sub>

Note 7) Median [minimum, maximum]

Note 8) Mean ± SD

Note 9) AUC, t<sub>1/2</sub> of 1 case in which the elimination phase of Favipiravir on day 1 was not clear was not calculated.

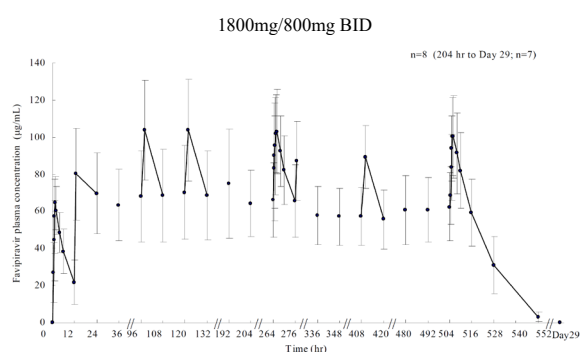


Figure 2. Time course of plasma concentration of favipiravir (mean±SD)

### 16.1.3 Individuals considered to have low aldehyde oxidase activity

Following multiple oral administration of favipiravir for 7 days [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]<sup>Note 10)</sup> to a healthy adult who appeared to have little aldehyde oxidase (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<sup>10)</sup>.

### 16.2 Absorption

#### 16.2.1 Effect of food

When 1200 mg of favipiravir was orally administered to 15 healthy adults as a single dose in a fasting state and a postprandial state by a crossover method<sup>Note 10)</sup>, the geometric mean ratios [90% confidence interval] of C<sub>max</sub> and AUC of favipiravir for postprandial state to those in a fasting state were 0.908 [0.826, 0.998] and 0.963 [0.888, 1.044], respectively, and the 90% confidence intervals of the ratios were within the predetermined range (0.80 to 1.25)<sup>11)</sup>.

### 16.3 Distribution

#### 16.3.1 Distribution in semen

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 10)</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 finishing 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<sup>12)</sup>. 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 finishing the treatment (results from non-Japanese).

#### 16.3.2 Serum protein binding ratio

The human serum protein binding ratio was 53.4 to 54.4% (*in vitro*, centrifugal ultrafiltration) at 0.3 to 30 µg/mL.

#### 16.3.3 Animal data

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. 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<sup>13)</sup>.

### 16.4 Metabolism

Favipiravir was not metabolized by cytochrome P-450 (CYP), mostly metabolized by AO, and partly metabolized to a hydroxylated form by xanthine oxidase (XO). In studies using human liver microsomes, formation of the hydroxylated form ranged from 3.98 to 47.6 pmol/mg protein/min, with an inter-individual variation of AO activity by 12 times at maximum<sup>4)</sup>. A glucuronate conjugate was observed in human plasma and urine as a metabolite other than the hydroxylated form. [See 10.]

### 16.5 Excretion

Favipiravir was mainly excreted as a hydroxylated form into urine, and little amount of the unchanged drug was observed. In an oral 7 day multiple dose study [1200 mg + 400 mg for 1 day, then 400 mg twice daily for 4 days followed by 400 mg once daily for 1 day]<sup>Note 10)</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<sup>10)</sup>.

### 16.6 Patients with Specific Backgrounds

#### 16.6.1 Patients with Hepatic Impairment

When favipiravir was orally administered to subjects with mild and moderate hepatic 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 10)</sup>, compared to healthy adult subjects, C<sub>max</sub> and AUC at Day 5 were approximately 1.6-fold and 1.7-fold each, in subjects with mild hepatic impairment, and 1.4-fold and 1.8-fold each, in subjects with moderate hepatic impairment.

When favipiravir was orally administered to subjects with severe hepatic 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 10)</sup>, compared to healthy adult subjects, C<sub>max</sub> and AUC at Day 3 were approximately 2.1-fold and 6.3-fold each (results from non-Japanese)<sup>14)</sup>. [See 9.3.1 and 9.3.2.]

#### 16.6.2 Patients with Renal Impairment

When a single oral dose of favipiravir 1800 mg<sup>Note 10)</sup> was administered to subjects with mild, moderate, and severe renal impairment (CL<sub>cr</sub>: 60 to 89 mL/min, 30 to 59 mL/min, and < 30 mL/min, 4 subjects each not on dialysis), compared to those in healthy adult subjects who received a single oral dose of favipiravir 1800 mg, the C<sub>max</sub> and AUC<sub>inf</sub> were approximately 1.0-fold and 1.2-fold each, in subjects with mild renal impairment, approximately 0.9-fold in both subjects with moderate renal impairment, and approximately 1.0-fold and 1.2-fold each, in subjects with severe renal impairment.

Compared to healthy adult subjects who received a single oral dose of favipiravir 1800 mg, the C<sub>max</sub> and AUC<sub>inf</sub> of the hydroxylated form, which is a metabolite of favipiravir, were approximately 1.1-fold and 1.2-fold each, in subjects with mild renal impairment, approximately 1.6-fold and 2.2-fold each, in subjects with moderate renal impairment, and approximately 2.5-fold and 6.5-fold each, in subjects with severe renal impairment (results from non-Japanese)<sup>15)</sup>.

Note 10) The approved dosage of favipiravir is “1600 mg orally twice daily for 1 day followed by 600mg orally twice daily for 4 days” and “1800 mg orally twice daily for 1 day followed by 800mg orally twice daily for 9 days”.

### 16.7 Drug-Drug Interaction

#### 16.7.1 Nonclinical drug-drug interaction studies

Favipiravir irreversibly inhibited AO activity<sup>4)</sup>. It also inhibited CYP2C8, CYP3A, OAT1, OAT3, MATE1 and MATE2-K. [See 10.]

### 16.7.2 Clinical drug-drug interaction studies

The results of clinical drug-drug interaction studies are provided in the following tables. [See 10.2.]

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) |                     |
|---|--|----|----------------|--|---------------------|
|   |  |    |                | C <sub>max</sub>   | AUC                 |
| Theophylline <sup>(6)</sup><br>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<br>[1.19,1.48]  | 1.27<br>[1.15,1.40] |
|   |  |    | Day 7          | 1.03<br>[0.92,1.15]  | 1.17<br>[1.04,1.31] |
| Oseltamivir <sup>(6)</sup><br>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<br>[0.87,1.10]  | 1.01<br>[0.91,1.11] |
| Raloxifene<br>60mg once daily on Days 1 to 3 <sup>(Note 11)</sup>                           | 1200mg twice daily on Day 1, 800mg twice daily on Day 2, 800mg once daily on Day 3 | 17 | Day 1          | 1.00<br>[0.90,1.10]  | 1.03<br>[0.95,1.12] |
|   |  |    | Day 3          | 0.90<br>[0.81,0.99]  | 0.85<br>[0.79,0.93] |
| Hydralazine<br>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<br>[0.92,1.06]  | 0.99<br>[0.92,1.07] |
|   |  |    | Day 5          | 0.96<br>[0.89,1.04]  | 1.04<br>[0.96,1.12] |

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>(6)</sup><br>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<br>[0.85,1.01]   | 0.92<br>[0.87,0.97] |
|  |  |    | Day 10                      | 0.99<br>[0.94,1.04]   | 0.97<br>[0.91,1.03] |
| Oseltamivir <sup>(6)</sup><br>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<br>[1.06,1.15]   | 1.14<br>[1.10,1.18] |
| Acetaminophen<br>650 mg 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, and 800mg once daily on Day 5 | 28 | Day 1                       | 1.03<br>[0.93,1.14]   | 1.16<br>[1.08,1.25] |
|  |  |    | Day 5                       | 1.08<br>[0.96,1.22]   | 1.14<br>[1.04,1.26] |
| Norethindrone/<br>ethinylestradiol combination<br>1 mg/0.035 mg once daily on Days 1 to 5 <sup>(Note 11)</sup> | 1200mg twice daily on Day 1, 800mg twice daily on Days 2 to 4, and 800mg once daily on Day 5 | 25 | Day 12 <sup>(Note 12)</sup> | 1.23<br>[1.16,1.30]   | 1.47<br>[1.42,1.52] |
|  |  |    | Day 12 <sup>(Note 13)</sup> | 1.48<br>[1.42,1.54]   | 1.43<br>[1.39,1.47] |
| Repaglinide<br>0.5mg once daily on Day 13 <sup>(Note 11)</sup>   | 1200mg twice daily on Day 1, 800mg twice daily on Days 2 to 4, and 800mg once daily on Day 5 | 17 | Day 13                      | 1.28<br>[1.16,1.41]   | 1.52<br>[1.37,1.68] |
| Hydralazine<br>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<br>[0.67,0.81]   | 0.87<br>[0.78,0.97] |
|  |  |    | Day 5                       | 0.79<br>[0.71,0.88]   | 0.91<br>[0.82,1.01] |
| Triazolam<br>0.25mg once daily on Day 1 and Day 4  | 1800mg twice daily on Days 3, 800mg twice daily on Day 4                                     | 12 | Day 4                       | 1.12<br>[0.89,1.42]   | 1.01<br>[0.91,1.11] |
| Metformin<br>250mg once daily on Day 1 and Day 4   | 1800mg twice daily on Days 3, 800mg twice daily on Day 4                                     | 12 | Day 4                       | 0.96<br>[0.87,1.07]   | 1.01<br>[0.94,1.09] |

Note 11) Results from non-Japanese

Note 12) Norethindrone

Note 13) Ethinylestradiol

## 17. CLINICAL STUDIES

### 17.1 Clinical Studies for Efficacy and Safety

〈Novel or re-emerging influenza virus infections〉

#### 17.1.1 Overseas phase I/II study

A placebo-controlled phase I/II study in type A or type B influenza patients (adults) 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 2400 mg + 600 mg + 600 mg for 1 day followed by 600 mg three times daily for 4 days)<sup>(Note 1)</sup>. With regards to the primary endpoint<sup>(Note 2)</sup>, favipiravir 1800 mg/800 mg BID (101 patients) demonstrated statistically 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 statistically significant difference ( $p=0.414$ , Gehan-Wilcoxon test). No adverse reactions were observed in the favipiravir group. [See 7.2.]

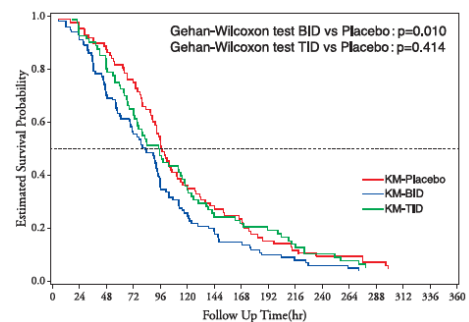


Figure 1. Time to alleviation of influenza symptoms

#### 17.1.2 Overseas phase III study (Study 1)

A placebo-controlled phase III study in type A or type B influenza patients (adults) [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 1)</sup> with the primary endpoint: the time required to alleviate primary influenza symptoms<sup>(Note 3)</sup>, was conducted. The results are provided in the following table and figure.

Results of primary analysis (ITTI population)

|                                   | Favipiravir (N=301) | Placebo (N=322)      |
|-----------------------------------|---------------------|----------------------|
| Number of events                  | 288                 | 306                  |
| Median [95% CI] (hours)           | 84.2<br>[77.1,95.7] | 98.6<br>[94.6,107.1] |
| p-value (Peto-Peto-Prentice test) | 0.004               |                      |

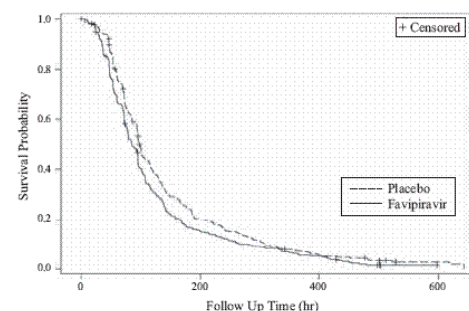


Figure 2. Kaplan-Meier Plot with regard to primary endpoint<sup>(Note 3)</sup> (ITTI population)

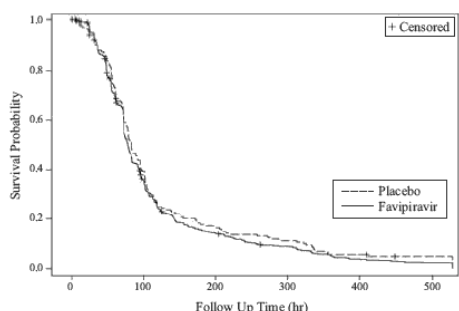
The frequency of adverse reactions was 7.9% (34/428 patients) in the favipiravir group, and the most common adverse reaction was dizziness occurring in 1.2% (5/428 patients).

#### 17.1.3 Overseas phase III study (Study 2)

A placebo-controlled phase III study in type A or type B influenza patients (adults) [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 1)</sup> with the primary endpoint: the time required to alleviate primary influenza symptoms<sup>(Note 3)</sup>, was conducted. The results are provided in the following table and figure.

Results of primary analysis (ITTI population)

|                                      | Favipiravir<br>(N=526) | Placebo<br>(N=169)  |
|--------------------------------------|------------------------|---------------------|
| Number of events                     | 505                    | 163                 |
| Median [95% CI]<br>(hours)           | 77.8<br>[72.3,82.5]    | 83.9<br>[76.0,95.5] |
| p-value<br>(Peto-Peto-Prentice test) | 0.303                  |                     |

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

The frequency of adverse reactions was 10.2% (88/861 patients) in the favipiravir group, and the most common adverse reactions were blood triglycerides increased occurring in 2.0% (17/861 patients), nausea occurring in 1.5% (13/861 patients), and diarrhoea occurring in 1.3% (11/861 patients).

#### 17.1.4 Global phase III clinical study (reference)

A global phase III clinical study of favipiravir [1200 mg + 400 mg for 1 day followed by 400 mg twice daily for 4 days] <sup>Note 1)</sup> versus oseltamivir phosphate (75 mg twice daily for 5 days) was conducted in patients with type A or type B influenza (adults) [757 patients (540 patients in Japan, 78 patients in Korea, and 139 patients in Taiwan)]. The median time [95% CI] to alleviation of primary influenza symptoms <sup>Note 4)</sup> was 63.1 hours [55.5, 70.4] for the favipiravir group (377 patients) and 51.2 hours [45.9, 57.6] for the 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).

The frequency of adverse reactions was 19.8% (75/378 patients) in the favipiravir group. The most common adverse reactions were blood uric acid increased occurring in 5.6% (21/378 patients), diarrhoea occurring in 4.2% (16/378 patients), and blood triglycerides increased occurring in 1.9% (7/378 patients).

#### 17.1.5 Overseas phase II study (reference)

A placebo-controlled phase II study of favipiravir was conducted in patients with type A or type B influenza (adults) [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 1)</sup>. The median time [95% CI] to alleviation of primary influenza symptoms <sup>Note 5)</sup> was 100.4 hours [82.4, 119.8] for the favipiravir 1000 mg/400 mg BID group (88 patients), 86.5 hours [79.2, 102.1] for the favipiravir 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 both of the favipiravir group and the 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).

The frequency of adverse reactions was 18.9% (25/132 patients) in the favipiravir 1000 mg/400 mg BID group and 19.6% (37/189 patients) in the favipiravir 1200 mg/800 mg BID group. The most common adverse reactions in the favipiravir 1000 mg/400 mg BID group were diarrhoea occurring in 2.3% (3/132 patients) and blood uric acid increased occurring in 2.3% (3/132 patients) and in the favipiravir 1200 mg/800 mg BID group diarrhoea occurring in 3.2% (6/189 patients) and blood uric acid increased occurring in 3.2% (6/189 patients).

<sup>Note 1)</sup> The approved dosage of favipiravir for novel or re-emerging influenza virus infections is "1600 mg orally twice daily for 1 day followed by 600 mg orally twice daily for 4 days".

<sup>Note 2)</sup> Time required to alleviate 6 primary influenza symptoms (cough, sore throat, headache, nasal congestion, body aches and pains, fatigue [tiredness]) and body temperature

<sup>Note 3)</sup> 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.

<sup>Note 4)</sup> 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.

<sup>Note 5)</sup> 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 ≥65 years old.

### 〈SFTS virus infections〉

#### 17.1.6 Phase III study in Japan

A phase III study of favipiravir in Japan was conducted in patients with severe fever with thrombocytopenia syndrome (SFTS) [oral administration of favipiravir 1800 mg twice daily for 1 day followed by 800 mg twice daily for 9 days]. The cumulative incidence of fatality from the primary endpoint of drug treatment to Day 28 in the primary efficacy population (mITTE) <sup>Note 6)</sup> was 15.8% (3/19 patients) [95% CI: 3.4, 39.6%], which exceeded the pre-specified threshold for fatality (12.5%) <sup>Note 7)</sup> point estimate. The frequency of adverse reactions was 70.0% (21/30 patients). The most common adverse reactions were hyperuricaemia occurring in 23.3% (7/30 patients), blood uric acid increased occurring in 20.0% (6/30 patients), hypertriglyceridaemia occurring in 10.0% (3/30 patients), rash occurring in 6.7% (2/30 patients), electrocardiogram QT prolonged occurring in 6.7% (2/30 patients).

<sup>Note 6)</sup> SFTS viruses were detected in RT-PCR tests performed at the National Institute of Infectious Diseases, and drug was started within 5 days (within 144 hours) after symptomatic onset (modified intention-to-treat evaluable).

<sup>Note 7)</sup> Cumulative case fatality rates from the National Institute of Infectious Diseases Survey on Infectious Diseases between January 2015 and September 2017 (excluding 10 patients who received drug in physician-initiated clinical studies conducted in 2016).

## 18. PHARMACOLOGY

### 18.1 Mechanism of Action

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 and severe fever with thrombocytopenia syndrome (SFTS) viral replication <sup>17)18)</sup>. With regards to the activity against human DNA polymerases  $\alpha$ ,  $\beta$  and  $\gamma$ , favipiravir RTP (1000  $\mu\text{mol/L}$ ) showed no inhibitory effect on  $\alpha$ , 9.1 to 13.5% inhibitory effect on  $\beta$  and 11.7 to 41.2% inhibitory effect on  $\gamma$ . Inhibitory concentration ( $\text{IC}_{50}$ ) of favipiravir RTP on human RNA polymerase II was 905  $\mu\text{mol/L}$  <sup>19)</sup>.

### 18.2 In vitro antiviral activity

Favipiravir showed antiviral activity against type A and type B influenza virus laboratory strains with an  $\text{EC}_{50}$  of 0.014 to 0.55  $\mu\text{g/mL}$ .

The  $\text{EC}_{50}$  against seasonal type A and type B influenza viruses including strains resistant to adamantane (amantadine and rimantadine), oseltamivir or zanamivir was 0.03 to 0.94 and 0.09 to 0.83  $\mu\text{g/mL}$ , respectively.

The  $\text{EC}_{50}$  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 to 3.53  $\mu\text{g/mL}$ .

The  $\text{EC}_{50}$  against type A and type B influenza viruses resistant to adamantane, oseltamivir and zanamivir was 0.09 to 0.47  $\mu\text{g/mL}$ , and no cross resistance was observed <sup>19)20)</sup>.

Favipiravir showed antiviral activity against various clinical isolates of SFTS viruses (J1 type, J2 type, J3 type, C3 type, C4 type and C5 type) with an  $\text{EC}_{90}$  of 14.83 to 38.73  $\mu\text{mol/L}$  (2.33 to 6.08  $\mu\text{g/mL}$ ) and an  $\text{EC}_{99}$  of 48.20 to 79.40  $\mu\text{mol/L}$  (7.57 to 12.47  $\mu\text{g/mL}$ ).



### 18.3 Therapeutic effect in animal models

In mouse infection models inoculated with influenza viruses A (H7N9), A (H1N1) pdm09 or A (H3N2), decrease of virus titers in lung tissues was observed by a 5-day oral administration of favipiravir with a dose of  $\leq 60$  mg/kg/day<sup>21)22)23)</sup>.

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<sup>19)23)</sup>.

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<sup>24)</sup>.

In mouse infection models inoculated with SFTS viruses, therapeutic effect based on survival rate and body weight change and decrease of the blood viral RNA level was observed by a 5-day oral administration of favipiravir with a dose of 120 mg/kg/day and 200 mg/kg/day<sup>25)</sup>.

### 18.4 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<sup>19)</sup>. In clinical studies including the global phase III study, information about emergence of favipiravir-resistant influenza viruses has not been obtained.

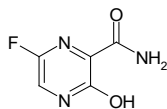
No change of susceptibility of SFTS viruses to favipiravir was observed after 10 passages in the presence of favipiravir, and no resistant viruses have been selected. In the domestic phase III study, information about emergence of favipiravir-resistant SFTS viruses has not been obtained.

## 19. PHYSICOCHEMICAL PROPERTIES

Nonproprietary name: Favipiravir

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

Structural 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 to 193°C

## 21. APPROVAL CONDITIONS

### (Common indication)

21.1 Develop and appropriately implement a risk management plan.

21.2 Strict distribution control and appropriate safety measures should be implemented to ensure that drug is used only for indications approved (for novel or re-emerging influenza virus infections in which other anti-influenza virus agents are not effective or insufficiently effective, only if the MHLW decides that it will be used to control the infection).

### (Novel or re-emerging influenza virus infections)

21.3 Conduct appropriate post marketing surveillance in order to develop additional data regarding the efficacy and safety of favipiravir.

### (SFTS virus infections)

21.4 Since only an extremely limited number of Japanese patients participated in clinical studies of the product, the applicant is required to conduct a use-results survey covering all Japanese patients treated with the product after the market launch until data from a certain number of patients have been gathered, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

21.5 Take steps required for marketing to ensure that the product is prescribed and used only by physicians who are adequately knowledgeable and experienced in the use of this product for drug SFTS virus infections.

## 22. PACKAGING

90 tablets [10 tablets (PTP) × 9]

100 tablets [10 tablets (PTP) × 10]

## 23. REFERENCES

- 1) In-house document: Reproductive and developmental toxicity study in rats (Date of approval: March 24, 2014; CTD2.6.6.6.1, 2.6.6.6.2)
- 2) In-house document: Reproductive and developmental toxicity study in mice, etc. (Date of approval: March 24, 2014; CTD2.6.6.6.6)

- 3) In-house document: Toxicity study in juvenile dogs, etc. (Date of approval: March 24, 2014; CTD2.6.6.9.4.3)
- 4) In-house document: Metabolism (Date of approval: March 24, 2014; CTD2.6.4.5.3, 2.6.4.7)
- 5) In-house document: Drug-drug interactions (Date of approval: March 24, 2014; CTD2.6.4.7, 2.6.4.8)
- 6) In-house document: Theophylline combination study (Date of approval: March 24, 2014; CTD2.7.6.6.1)
- 7) In-house document: Toxicity study in dogs (Date of approval: March 24, 2014; CTD2.6.6.3.3)
- 8) In-house document: Testicular toxicity study in mice, etc. (Date of approval: March 24, 2014; CTD2.6.6.9.4.2)
- 9) In-house document: 22-day repeated dose study
- 10) In-house document: High-dose repeated dose study (Date of approval: March 24, 2014; CTD2.7.6.4.5)
- 11) In-house document: Study on effects of food (Date of approval: March 24, 2014; CTD2.7.6.1.2)
- 12) In-house document: Testicular migration study (Date of approval: March 24, 2014; CTD2.7.6.7.3)
- 13) In-house document: *In vivo* kinetics in animals (Date of approval: March 24, 2014; CTD2.6.4.4)
- 14) In-house document: Pharmacokinetics in patients with hepatic impairment
- 15) In-house document: Pharmacokinetics in patients with renal impairment
- 16) In-house document: Oseltamivir combination study (Date of approval: March 24, 2014; CTD2.7.6.6.2)
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- 18) Yamada H, et al.: Viruses. 2021; 13 (6) : 1061-1073
- 19) Takahashi K, et al.: Jpn J Med Pharm Sci. 2011; 66: 429-441
- 20) In-house document: Antiviral activity and cross-resistance (Date of approval: March 24, 2014; CTD2.6.2.2.1)
- 21) Ito Y, et al.: Nature. 2009; 460: 1021-1025
- 22) Watanabe T, et al.: Nature. 2013; 501: 551-555
- 23) In-house document: Therapeutic effect in mice (Date of approval: March 24, 2014; CTD2.6.2.2.2)
- 24) In-house document: Therapeutic effect in immunodeficient mice (Date of approval: March 24, 2014; CTD2.6.2.2.2.6)
- 25) Tani H, et al.: PLoS One. 2018; 13 (10) : e0206416

## 24. REFERENCE REQUEST AND CONTACT INFORMATION

Product Information Center

FUJIFILM Toyama Chemical Co., Ltd.

14-1, Kyobashi 2-chome, Chuo-ku, Tokyo 104-0031, Japan

Toll-Free: 0120-502-620

## 25. PRECAUTION CONCERNING HEALTH INSURANCE BENEFITS

AVIGAN is not listed in the National Health Insurance drug price list.

## 26. MARKETING AUTHORIZATION HOLDER, etc.

### 26.1 Marketing Authorization Holder

FUJIFILM Toyama Chemical Co., Ltd.

14-1, Kyobashi 2-chome, Chuo-ku, Tokyo 104-0031, Japan