AVIGAN Tablets 200mg
Favipiravir

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 sperm1. 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

Note: Use only as directed by a physician.

DESCRIPTION

<table>
<thead>
<tr>
<th>Brand name</th>
<th>AVIGAN Tablets 200mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredient/content (Content per tablet)</td>
<td>Favipiravir 200mg</td>
</tr>
<tr>
<td>Inactive ingredient</td>
<td>Povidone, colloidal silicon dioxide, low-substituted hydroxypropyl cellulose, crospovidone, sodium stearyl fumarate, hypromellose, titanium dioxide, talc, yellow ferric oxide</td>
</tr>
<tr>
<td>Color/dosage form</td>
<td>Light-yellow, film-coated tablet</td>
</tr>
<tr>
<td>Appearance</td>
<td></td>
</tr>
</tbody>
</table>
| Size (mm) | 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”).
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 (See “PHARMACOKINETICS” and “CLINICAL STUDIES”).

(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 (See “Clinically significant adverse reactions”). 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.

(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

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.)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Signs, Symptoms, and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrazinamide</td>
<td>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.</td>
<td>Reabsorption of uric acid in the renal tubule is additively enhanced.</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Blood level of repaglinide may increase, and adverse reactions to repaglinide may occur.</td>
<td>Inhibition of CYP2C8 increases blood level of repaglinide.</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Blood level of AVIGAN may increase, and adverse reactions to AVIGAN may occur.</td>
<td>Interaction with XO may increase blood level of AVIGAN.</td>
</tr>
<tr>
<td>Famiclovir Sulindac</td>
<td>Efficacy of these drugs may be reduced.</td>
<td>Inhibition of AO by AVIGAN may decrease blood level of active forms of these drugs.</td>
</tr>
</tbody>
</table>

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

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 “2. Important Precautions”).

(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.

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, deliria, hallucination, delusion, convulsion, etc.)

8. Collitis haemorrhagic
(3) Other adverse reactions

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

<table>
<thead>
<tr>
<th>Hypersensitivity</th>
<th>≥ 1%</th>
<th>0.5% - &lt;1%</th>
<th>&lt; 0.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>Eczema, pruritus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>AST (GOT) increased, ALT (GPT) increased, γ-GTP increased</td>
<td>Blood ALP increased, blood bilirubin increased</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhoea (4.79%)</td>
<td>Nausea, vomiting, abdominal pain</td>
<td>Abdominal discomfort, duodenal ulcer, haematochezia, gastritis</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>Decreased, white blood cell count decreased</td>
<td>White blood cell count increased, reticulocyte count decreased, monocyte increased</td>
<td></td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>Blood uric acid increased (4.79%), blood triglycerides increased</td>
<td>Glucose urine present</td>
<td>Blood potassium decreased</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Asthma, oropharyngeal pain, rhinitis, nasopharyngitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Blood CK (CPK) increased, blood urea present, tensil polyp, pigmentation, dysgeusia, bruise, vision blurred, eye pain, vertigo, supraventricular extrasystoles</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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
(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
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
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).

<table>
<thead>
<tr>
<th>Dosage</th>
<th>C_{max} Note 2 (μg/mL)</th>
<th>AUC_{0-24} Note 2, 3 (μg·hr/mL)</th>
<th>T_{max} Note 4 (hr)</th>
<th>T_{1/2} Note 5 (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1600 mg/600 mg BID</td>
<td>Day 1: 64.56 (17.2)</td>
<td>446.09 (28.1)</td>
<td>1.5 (0.75, 4)</td>
<td>4.8±1.1</td>
</tr>
<tr>
<td>Day 6: 64.69 (24.1)</td>
<td>553.98 (31.2)</td>
<td>1.5 (0.75, 2)</td>
<td>5.6±2.3</td>
<td></td>
</tr>
</tbody>
</table>

Note 2 Geometric mean (CV%)
Note 3 Day 1: AUC_{0-24}, Day 6: AUC_{0-24}
Note 4 Median (minimum, maximum)
Note 5 Mean±SD

![Figure 1: Time course of plasma concentration of favipiravir (mean±SD)](image)

Following multiple oral administration of favipiravir for 7 days Note 6 to an healthy adult who appeared to have little AO activity, the estimated AUC of unchanged drug was 1452.73 μg·hr/mL on Day 1 and 1324.09 μg·hr/mL on Day 7 Note 7.

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) Note 7, 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 data12
When a single dose of 14C-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. Metabolism3
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. Excretion11
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 Note 5 with 6 healthy adults, cumulative urinary excretion ratio of the unchanged drug and the hydroxylated form was 0.8% and 55.1%, 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 impairment2
(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) Note 9, 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) Note 9, compared to healthy adult subjects, Cmax 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 Interactions14
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 X0, 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

<table>
<thead>
<tr>
<th>Co-administered drug and dosage</th>
<th>Favipiravir dosage</th>
<th>n</th>
<th>Time of dosing</th>
<th>Parameter ratio for favipiravir (90% CI) (Co-administered/single administered)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide1 200mg twice daily on Days 1 to 9, 200mg once daily on Day 10</td>
<td>600mg twice daily on Day 6, 600mg once daily on Days 7 to 10</td>
<td>10</td>
<td>Day 6</td>
<td>1.33 [1.19, 1.48]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 7</td>
<td>1.03 [0.92, 1.15]</td>
</tr>
<tr>
<td>Oseitamivir13 75mg twice daily on Days 1 to 5, 75mg once daily on Day 6</td>
<td>600mg twice daily on Day 5, 600mg once daily on Day 6</td>
<td>10</td>
<td>Day 6</td>
<td>0.98 [0.87, 1.10]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 1</td>
<td>1.00 [0.96, 1.04]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 3</td>
<td>0.90 [0.81, 0.99]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 5</td>
<td>0.96 [0.89, 1.04]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 7</td>
<td>0.99 [0.92, 1.06]</td>
</tr>
</tbody>
</table>

Note 10 Results in non-Japanese
Effects of favipiravir on pharmacokinetics of co-administered drugs

<table>
<thead>
<tr>
<th>Co-administered drug and dosage</th>
<th>Favipiravir dosage</th>
<th>n</th>
<th>Time of dosing</th>
<th>Parameter ratio for co-administered drug (90% CI) (Co-administered/single administered)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline3 200mg twice daily on Days 1 to 9, 200mg once daily on Day 10</td>
<td>600mg twice daily on Day 6, 600mg once daily on Days 7 to 10</td>
<td>10</td>
<td>Day 7</td>
<td>0.93 [0.85, 1.01]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 10</td>
<td>0.99 [0.94, 1.04]</td>
</tr>
<tr>
<td>Oseitamivir13 75mg twice daily on Days 1 to 5, 75mg once daily on Day 6</td>
<td>600mg twice daily on Day 5, 600mg once daily on Day 6</td>
<td>10</td>
<td>Day 6</td>
<td>1.10 [1.06, 1.13]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 1</td>
<td>1.03 [0.93, 1.14]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 5</td>
<td>1.08 [0.96, 1.22]</td>
</tr>
</tbody>
</table>
Clinical Studies

Results in non-Japanese

A placebo-controlled phase 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) (Note 14). With regards to the primary endpoint (Note 15), 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).

Results of primary analysis (ITTI population)

<table>
<thead>
<tr>
<th>Study1</th>
<th>Study2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favipiravir (N=301)</td>
<td>Placebo (N=322)</td>
</tr>
<tr>
<td>Number of events</td>
<td>288</td>
</tr>
<tr>
<td>Median [95% CI] (hours)</td>
<td>84.2 [71.0, 91.0]</td>
</tr>
<tr>
<td>p-Value (log-rank)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

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). 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 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 21 The approved dosage of favipiravir is “1600 mg orally twice daily for 1 day followed by 800 mg orally twice daily for 4 days.”

Note 22 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.

PHARMACOLOGY

1. In vitro antiviral activity

Favipiravir showed antiviral activity against type A and type B influenza virus laboratory strains with an EC50 of 0.014–0.55 μg/mL.

The EC50 against seasonal type A and type B influenza viruses including strains resistant to adamantane (amantadine and rimantadine), oseltamivir or zanamivir was 0.03–0.94 and 0.09–0.83 μg/mL, respectively.

The EC50 against type A influenza viruses (including strains resistant to adamantane, oseltamivir or zanamivir) such as swine-origin type A and avian-origin type A including highly-pathogenic strains (including H5N1 and H7N9) was 0.06–3.53 μg/mL.

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

2. Therapeutic effect in animal models

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

In mouse infection models inoculated with influenza viruses A (H3N2) or A (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

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 α, β and γ, favipiravir RTP (1000 μmol/L) showed no inhibitory effect on α, 9.1–13.5% inhibitory effect on β and 11.7–41.2% inhibitory effect on γ. Inhibitory concentration (IC50) of favipiravir RTP on human RNA polymerase II was 905 μmol/L.

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. 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_{8}H_{7}F_{2}N_{2}O_{4}
Molecular weight: 157.10
Description: Favipiravir is a white-light yellow powder. It is sparingly solubile in acetoneitrile and methanol, slightly soluble in water and ethanol (99.5).

Melting point: 187–193°C

CONDITIONS FOR APPROVAL

1. Develop and appropriately implement a risk management plan.
2. Conduct appropriate post marketing surveillance in order to develop additional data regarding the efficacy and safety of favipiravir.
3. Do not market the drug unless the MHLW requests.
4. Implement strict distribution management and thorough safety measures when marketing favipiravir so that the drug will not be used for seasonal influenza.
5. Take strict and proper measures so that the drug is administered only to patients who are considered appropriate to take the drug, have been informed in advance about the efficacy and risk in writing, and they or their family member 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)
15. In-house document (Antiviral activity and cross resistance)
18. In-house document (Therapeutic effect/mice)
19. In-house document (Therapeutic effect/immune-deficient mice)

REQUEST FOR LITERATURE SHOULD BE MADE TO:
Please request for the in-house documents cited in the REFERENCES to the following company:
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