

For the use only of a Registered Medical Practitioner or Hospital or Laboratory

# Favipiravir Tablets 400 mg



# ARAFLŮ 400

The CDSCO has issued an accelerated approval to manufacture and market Favipiravir for the treatment of mild to moderate COVID-19 disease under restricted

WARNINGS
Since early embryonic deaths and teratogenicity have been observed in animal studies for favipiravir, do not administer the drug to women known or suspected to be pregnant.

When administering favipiravir to women of child-bearing potential, confirm a negative pregnancy test result before starting the treatment. Explain fully the risks and instruct thoroughly to use most effective contraceptive methods with her partner during and for 7 days after the end of the treatment. If pregnancy is suspected during the treatment, instruct to discontinue the treatment immediately and to consult a doctor.

treatment, instruct to discontinue the treatment immediately and to consult a doctor.
Favipiravir is distributed in sperm. When administering the drug to male patients, explain fully the risks and instruct thoroughly to use most effective contraceptive methods in sexual intercourse during and for 7 days after the end of the treatment (men must wear a condom). In addition, instruct not to have sexual intercourse with

pregnant women.

Prior to the treatment, explain thoroughly the efficacy and risks (including the risk of exposure to fetus) to patients or their family members and written informed cons from each patient/ or his representative prior to administration of the drug shall be obtained by the prescriber.

Examine carefully the necessity of favipiravir before use.

### 1 NAME OF THE MEDICINAL PRODUCT

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### 3 PHARMACEUTICAL FORM

4 CLINICAL PARTICULARS

For the treatment of patients with mild to moderate COVID-19 disease

4.2 Posology and Method of Administration
The recommended dosage of favipiravir for adults is 1800 mg orally twice daily on 1<sup>st</sup> day followed by 800 mg orally twice daily, up to maximum of 14 days. Note: Use only as directed by a physician.

Use in the Elderty Since the elderty often have reduced physiological functions, favipiravir should be administered with care to them by monitoring their general conditions

Favipiravir has not been administered to children

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When administering favipiravir to women of child-bearing potential, confirm a negative pregnancy test result before starting the treatment. Explain fully the risks and instruct thoroughly to use most effective contraceptive methods with her partner during and for 7 days after the end of the treatment. If pregnancy is suspected during the treatment, instruct to discontinue the treatment immediately and to consult a doctor.

Favipiravir is distributed in sperm. When administering the drug to male patients, explain fully the risks and instruct thoroughly to use most effective contraceptive methods in sexual intercourse during and for 7 days after the end of the treatment (men must wear a condom). In addition, instruct not to have sexual intercourse with

pregnant women.
Prior to the treatment, explain thoroughly the efficacy and risks (including the risk of exposure to fetus) to patients or their family members Examine carefully the necessity of favipiravir before use.

Favipiravir should be administered with care in the following patients:Patients with history of abnormalities in metabolism of uric acid or having Gout, (Blood uric acid level may increase, and symptoms may get aggravated.)

Important Precautions
Although the causal relationship is unknown, psychoneurotic symptoms such as abnormal behavior after administration of anti-influenza virus agents including favipiravir 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.
Viral infection may be complicated or confused with bacterial infections. In case of bacterial infection or suspected to be bacterial infection, appropriate measures should

4.5 Interaction with other medicinal products and other forms of interaction
Favipiravir 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. Precautions for co-administration
Table 1 Favipiravir should be administered with care when co-administered with the following drugs

| Drugs                  | Signs, Symptoms, and<br>Treatment  | Mechanism and<br>Risk Factors  |
|------------------------|--|--|
| Pyrazinamide           | Blood uric acid level increases. When pyrazinamide 1.5g once daily and favipiravir 1400 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 favipiravir. | Reabsorption of uric acid in the renal tubule is additively enhanced.                    |
| Repaglinide            | Blood level of repaglinide may increase, and adverse reactions to repaglinide may occur.   | Inhibition of CYP2C8 increases blood level of repaglinide.                               |
| Theophylline           | Blood level of favipiravir may increase, and adverse reactions to favipiravir may occur.   | Interaction with XO may increase blood level of favipiravir.                             |
| Famcidovir<br>Sulindac | Efficacy of these drugs may be reduced.  | Inhibition of AO by favipiravir may decrease blood level of active forms of these drugs. |

Fertility
In animal toxicity 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. In fertility study in rats, effects on the testis and sperm and decreased fertility were observed in males and anestrus was observed in females at the high-dose.

Do not administer favipiravir to women known or suspected to be pregnant.

(Early embryonic deaths [rats] and teratogenicity [mouse, rat, rabbit and monkey] have been observed in animal studies with exposure levels similar to or lower than the clinical exposure.)

Do not administer to lactating women. (The major metabolite of favipiravir, a hydroxylated form, was found to be distributed in breast milk.)

The major undesirable effects observed in clinical studies with favipiravir used at different doses included: Increase of blood uric acid level (4.79%)

- Diarrhoea (4.79%)
- Decrease of neutrophil count (1.80%)
   Increase of AST (SGOT) (1.80%)
   Increase of ALT (SGPT) (1.60%)

|                                      | ≥ 1%   | 0.5 - < 1%                          | < 0.5%  |
|--------------------------------------|--|-------------------------------------|---|
| Hypersensitivity                     |  | Rash                                | Eczema, pruritus  |
| Hepatic                              | AST (GOT) increased,<br>ALT (GPT) increased,<br>y-GTP increased        |                                     | Blood ALP<br>increased, blood<br>bilirubin<br>increased   |
| Gastrointestinal                     | Diarrhoea (4.79%)  | Nausea, vomiting,<br>Abdominal pain | Abdominal discomfort,<br>duodenal ulcer, haematochezia,<br>gastritis  |
| Hematologic                          | Neutrophil count<br>decreased, white blood<br>cell count decreased     |                                     | White blood cell count increased,<br>reticulocyte count decreased,<br>monocyte increased  |
| Metabolic disorders                  | Blood uric acid increased (4.79%),<br>Blood triglycerides<br>increased | Glucose urine present               | Blood potassium<br>decreased  |
| Respiratory                          |  |                                     | Asthma, oropharyngeal pain, rhinitis, nasopharyngitis   |
| Others                               |  |                                     | Blood CK (CPK) increased, bloodurine<br>present, tonsil polyp,<br>pigmentation, dysgeusia, bruise,<br>vision blurred, eye pain, vertigo,<br>supraventricular<br>extrasystoles |
| *Adverse reactions observed dosage). | in Japanese clinical studies and the global phase                      | III clinical study (studies conduc  | ted with dose levels lower than the approval  |

B. 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.

bonormal behaviour (such as sudden movement or wandering) that could result in falls etc. may occur in patients infected with influenza, although the

In prospective, multicenter, comparative trial with 240 subjects, 37 incidences of antiviral-associated adverse effects (AE) were detected in the favipiravi

In prospective, multicenter, comparative trial with 240 subjects, 37 incidences of antiviral-associated adverse effects (AE) were detected in the favipiravir group (dose used: 1600 mg twice a day on first day; 600 mg twice a day first from second day up to a maximum of 10 days) and 28 incidences in the control group. All observed AE incidences were mild. Increased serum uric acid (3 (2.50%) vs 16 (13.79%), P=0.0014) were more common in patients of the favipiravir group. No statistical difference was observed for the frequency of abnormal liver function tests (LFT), psychiatric symptom reactions and digestive tract reactions (nausea, acid reflux, flatulence). Most of these adverse reactions disappeared by the time patients being discharged. Antiviral-associated adverse effects of favipiravir were mild and manageable. Chang C et al. (2020)

### Comparison of Anti-viral associated adverse effects

| Adverse effects               | Favipiravir group<br>(N=116) |                 | Control group<br>(N=120) |                 | P value |
|-------------------------------|------------------------------|-----------------|--------------------------|-----------------|---------|
|                               | Frequency                    | Cases,<br>n (%) | Frequency                | Cases,<br>n (%) |         |
| Total                         | 43                           | 37 (31.90)      | 33                       | 28 (23.33)      | 0.1410  |
| Abnormal LFT                  | 10                           | 10 (8.62)       | 12                       | 12 (10.00)      | 0.7156  |
| Raised serum uric acid        | 16                           | 16 (13.79)      | 3                        | 3 (2.50)        | 0.0014  |
| Psychiatric symptom reactions | 5                            | 5 (4.31)        | 1                        | 1 (0.83)        | 0.1149* |
| Digestive tract reactions     | 16                           | 16 (13,79)      | 17                       | 14 (11.67)      | 0,6239  |

day on first day; 600 mg twice a day from second day up to a maximum of 14 days) was four (11.43%), which was significantly fewer than the 25 adverse reactions (55.56%) in the control arm (P < 0.001). Two patients had diarrhea, one had a liver injury, and one had a poor diet in the favipiravir arm. Meanwhile, there were five patients with diarrhea, five with vomitting, six with nausea, four with rash, three with liver injury, and two with chest tightness and palpitations in the control arm. Cai Q et al

| Characteristic                 |                       | Treatment                      |         |
|--------------------------------|-----------------------|--------------------------------|---------|
|                                | Favipiravir<br>(N=35) | Lopinavir/ ritonavir<br>(N=45) | P value |
| Total no. of adverse reactions | 4 (11.43%)            | 25 (55.56%)                    | <0.001  |
| Diarrhea                       | 2 (5.71%)             | 5 (11.11%)                     | 0.46    |
| Vomiting                       | 0 (0%)                | 5 (11.11%)                     | 0.06    |
| Nausea                         | 0 (0%)                | 6 (13.33%)                     | 0.03    |
| Rash                           | 0 (0%)                | 4 (8.89%)                      | 0.13    |
| Liver and kidney injury        | 1 (2,86%)             | 3 (6.67%)                      | 0,63    |
| Others                         | 1 (2.86%)             | 2 (4.44%)                      | 1.00    |

Reporting of suspected adverse reactions If you experience any side effects, talk to your doctor or pharmacist or write to **drugsafety@biocon.com.** 

# 5. PHARMACOLOGICAL PROPERTIES 5.1 Pharmacodynamic properties Mechanism of action

Favipiravir is a prodrug that is metabolized in cells to the active form favipiravir-ribosyl triphosphate form (favipiravir RTP), which selectively inhibits RNA polymerase involved in viral replication. Inhibitory concentration (IC 50) of favipiravir RTP on human RNA polymerase II was 905 µmol/L.

In vitro antiviral activity
Favipiravir effectively inhibits SARS-CoV-2 infection in Vero E6 cells (half maximal effective concentration (EC 50) = 61.88 

µmol/L, half maximal cytotoxic concentration (CC50) > 400 

µmol/L, selectivity index (SI) > 6.46).

Therapeutic effect in animal models
In EBOV-infected mice models, lacking the type I IFN-alpha/beta receptor (IFNAR-/-), treatment with favipiravir 300 mg/kg/day initiated 6 days post infection induced rapid virus clearance, reduced biochemical parameters of disease severity, and prevented a lethal outcome in 100% of the animals.

No information about emergence of favipiravir-resistant viruses is available.

## Table 2 Comparison of time to relief for pyrexia, cough relief time and other secondary outcomes,

| Variables      | Time to rel       | lief for pyrexia | Cough relief time |               |  |
|----------------|-------------------|------------------|-------------------|---------------|--|
|                | Favipiravir group | Control group    | Favipiravir group | Control group |  |
| Total patients | (N = 71)          | (N = 74)         | (N = 78)          | (N = 73)      |  |
| Day 1          | 15 (21,13)        | 2 (2,70)         | 1 (1.28)          | 3 (4.11)      |  |
| Day 2          | 23 (32,39)        | 8 (10.81)        | 2 (2,56)          | 1 (1,37)      |  |



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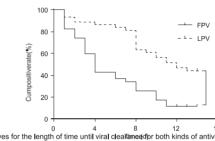


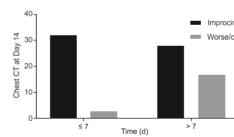
# ARAFL۰400

| Day 3   | 19 (26.76)        | 18 (24.32)             | 23 (29.49)                    | 7 (9.59)   |
|---|-------------------|------------------------|-------------------------------|------------|
| Day 4   | 10 (14.08)        | 15 (20.27)             | 20 (25.64)                    | 11 (15.07) |
| Day 5   | 1 (1.41)          | 16 (21,62)             | 10 (12.82)                    | 12 (16.44) |
| Day 6   |                   | 5 (6.76)               | 10 (12,82)                    | 10 (13.70) |
| Day 7   |                   | 3 (4.05)               | 3 (3.85)                      | 3 (4.11)   |
| Day 8   |                   |                        | 7 (8.97)                      | 6 (8,22)   |
| Day 9   |                   |                        | 1 (1,28)                      | 3 (4,11)   |
| Censored                                      |                   |                        | 1 (1.28)                      | 17 (23.29) |
| Log-rank P value < 0.0001                     |                   |                        | < 0.00                        | 01         |
|   |                   | Other secondary outcom | es                            |            |
| AOT or NMV*                                   | Favipiravir group | Control group          | Rate ratio (95% CI)           | P value    |
| Total patients                                | N= 116            | N= 120                 |                               |            |
| With auxiliary, n (%)                         | 21 (18,10)        | 27 (22,50)             | -0.0440<br>(-0.1464, -0.0585) | 0.4015     |
| Patients with hypertension<br>and/or diabetes | N = 42            | N = 35                 |                               |            |
| With auxiliary, n (%)                         | 9 (21.43)         | 10 (28.57)             | -0.0714<br>(-0.2658, 0.1230)  | 0.4691     |
| All-cause mortality                           | 0 (0,00)          | 0 (0.00)               | 1                             | 1          |
| Dyspnea after taking medicine, n (%)          | 4 (3,45)          | 14 (11.67)             | 1                             | 0.0174     |
| Respiratory failure, n (%)                    | 1 (0.86)          | 4 (3.33)               |                               | 0.3700*    |

In another open label study: favipiravir (FPV) has proven to be superior to lopinavir/ritonavir in treatment of COVID-19 positive patients. The results from a total of 80 patients indicated that favipriavir had more potent antiviral action than that of lopinavir (LPV)/ritonavir, A shorter viral clearance time was found for the favipiravir arm versus the control arm (median (interquartile range, IQR), 4 (2.5–9) days versus 11 (8–13) days, p < 0.001). The favipiravir arm also showed significant improvement in chest imaging compared with the control arm, with an improvement rate of 91.43% versus 62.22% (p = 0.004). Multivariable cox regression showed that favipiravir was independently associated with faster viral clearance. Cal Q et al (2020)

Viral response to the antiviral therapy
The Kaplan-Meier survival curves for the length of time until viral clearance for both kinds of antiviral therapy were presented in Figure below. The median time of viral clearance for the patients treated with favipiravir (FPV), designated as Group A, was estimated to be 4 d (IQR: 2.5–9), which was significantly shorter than the time for patients in the control group, designed as Group B, which was 11 d (IQR: 8–13) (P < 0.001)Cai Q et al (2020)





## Figure 2: Time of viral shedding and improving chest CT scan on Day 14 after treatment.

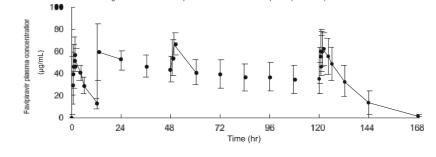
### Table 3 Results of primary analysis (ITT population) Study 2

|                        | Study I                |                       | Study 2                |                      |  |
|------------------------|------------------------|-----------------------|------------------------|----------------------|--|
|                        | Favipiravir<br>(N=301) | Placebo<br>(N=322)    | Favipiravir<br>(N=526) | Placebo<br>(N=169)   |  |
| Number of events       | 288                    | 306                   | 505                    | 163                  |  |
| Median [95% CI (hours) | 84.2<br>[77.1, 95.7]   | 98.6<br>[94.6, 107.1] | 77.8<br>[72.3, 82.5]   | 83.9<br>[76.0, 95.5] |  |
| p-value <sup>a</sup>   | 0.004                  |                       | 0.3                    | 03                   |  |

## αPeto-Peto-Prentice tes

Absorption
Blood Concentrations
Blood Concentrations
Blood Some spharmacokinetic 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).

| Dosage              |       | C <sub>max</sub> (µg/mL)# | AUC (µg · hr/mL)* | T <sub>max</sub> (hr)* | T <sub>1/2</sub> (hr)* |
|---------------------|-------|---------------------------|-------------------|------------------------|------------------------|
| 1600 mg/ 600 mg BID | Day 1 | 64.56 (17.2)              | 446.09 (28.1)     | 1.5 (0.75, 4)          | 4.8±1.1                |
|                     | Day 6 | 64,69 (24,1)              | 553,98 (31,2)     | 1,5 (0,75, 2)          | 5.6±2.3                |



Following multiple oral administration of favipiravir for 7 days 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.

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 1 days". Studies from healthy Japanese volunteers showed that the maximum plasma concentration of favipiravir occurred at 0.5 to 2 hours after oral administration, and then decreased rapidly with a short half-life time of 2–5.5 hours.

 $\frac{\textbf{Distribution}}{\textbf{The plasma protein binding of favipiravir was 54\% in humans.}} \textbf{The bound percentages of favipiravir to human serum albumin and $\alpha$ 1-acid glycoprotein were 65.0% and 6.5%, respectively.} \textbf{Favipiravir's apparent volume of distribution ranges from 15 to 20 L and is likely restricted to vascular and extra vascular fluids.}$ Metabolism
Favipiravir is mostly metabolized by aldehyde oxidase (AO), and partly 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.

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 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

Japan. When favipiravir was orally administered to subjects with mild and moderate liver function impairment (Child-Pugh classification A and B, 6 subjects each) at 1400 mg twice daily for 1 day followed by 800 mg twice daily for 4 days (1400 mg/800 mg BID), compared to healthy adult subjects, Cmax and AUC at day 5 were approximately 1.6 fold and 1.7 fold, respectively in subjects with mild liver function impairment, and 1.4 fold and 1.8 fold, respectively in subjects with moderate liver function impairment (Child-Pugh dassification 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), compaired to healthy adult subjects, C<sub>max</sub> and AUC at day 3 were approximately 2.1 fold and 6.3 fold,

# 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<br>drug and dosage | Favipiravir<br>dosage   |    | Time of<br>dosing | Parameter ratio for favipiravir (90% CI<br>(Co-administered/single administered |                   |  |
|-------------------------------------|---|----|-------------------|---|-------------------|--|
|                                     |   |    |                   | C <sub>max</sub>  | AUC               |  |
|                                     |   |    | Day 6             | 1.33 [1.19, 1.48]   | 1.27 [1.15, 1.40] |  |
| 1 to 9, 400mg once daily on Day 10  | 600mg once daily on Days 7 to 10  |    | Day 7             | 1.03 [0.92, 1.15]   | 1.17 [1.04, 1.31] |  |
|                                     | 600mg twice daily on Day 5,<br>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  | g once daily on Days 1400mg 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   | 1400mg/400mg on Day 1,  | 14 | Day 1             | 0.99 [0.92, 1.06]   | 0.99 [0.92, 1.07] |  |
| 1 and Day 5                         | 400mg twice daily on Days 2 to 4,<br>400mg once daily on Day 5  |    | Day 5             | 0.96 [0.89, 1.04]   | 1.04 [0.96, 1.12] |  |

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

| Co-administrated<br>drug and dosage                                      | Favipiravir<br>dosage  |                     | Time of<br>Dosing | Parameter ratio for co-administered drug [90%<br>(Co-administered/single administered) |                  |  |
|--|--|---------------------|-------------------|--|------------------|--|
|  |  |                     |                   | C <sub>max</sub>   | AUC              |  |
| Theophylline 400mg twice daily on Days                                   | 600mg twice daily on Day 6, 600mg<br>once daily on Days 7 to 10                                |                     | Day 7             | 0.93 [0.85,1.01]   | 0.92 [0.87,0.97] |  |
| 1 to 9, 400mg once daily on Day 10                                       |  |                     | Day 10            | 0.99 [0.94,1.04]   | 0.97 [0.91,1.03] |  |
| Oseltamivir 75mg twice daily on Days 1<br>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  | 1400mg twice daily on Day 1,   | 28 Day 1<br>Day 5   | Day 1             | 1.03 [0.93,1.14]   | 1.16 [1.08,1.25] |  |
| Day 1 and Day 5 ×  | 800mg twice daily on Days 2 to 4,<br>800mg once daily on Day 5                                 |                     | Day 5             | 1.08 [0.96,1.22]   | 1.14 [1.04,1.26] |  |
| Norethindrone/Ethinylestradiol   |  | Day 12 <sup>2</sup> | 1.23 [1.16,1.30]  | 1.47 [1.42,1.52]   |                  |  |
| Combination 1mg/0.035mg<br>once daily on Days 1 to Day 5 ×               | 800mg twice daily on Days 2 to 4,<br>800mg once daily on Day 5                                 |                     | Day 12**          | 1.48 [1.42,1.54]   | 1.43 [1.39,1.47] |  |
| Repaglinide 0.5mg once daily on Day<br>13 <sup>x</sup>                   | 1400mg twice daily on Day 1,<br>800mg twice daily on Days 2 to 4,<br>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                                      | 1400mg/400mg on Day 1,   | 14                  | Day 1             | 0.73 [0.67,0.81]   | 0.87 [0.78,0.97] |  |
| and Day 5  | 400mg twicedaily on Days 2 to 4,<br>400mg once daily on Day 5                                  | 1, Day 5            | Day 5             | 0.79 [0.71,0.88]   | 0.91 [0.82,1.01] |  |

5.3 Preclinical safety data
In pharmacokinetic study, 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. The toxicity profile of favipiravir was assessed in the repeat-dose oral toxicity studies in rats addogs up to 4-week duration and in monkeys in 2-week duration. At the no-observed—adverse-effect-levels [NOAEL] dose (rats, 32 mg/kg/day; dogs, 10 mg/kg/day; monkeys, 100 mg/kg/day) in these studies, the AUC in humans was approximately 0.75 to 0.87 times that in rats, approximately 0.21 to 0.24 times that in dogs, and approximately 0.15 to 0.87 times that in monkeys.

Favipiravir was non-genotoxic in various in vitro and in vivo studies. No carcinogenicity studies have been conducted and it not required as Favipiravir is indicated for a short period in clinical setting. In fertility study in rats, effects on the testis and spersy and decreased fertility were observed in measurements.

short period in clinical setting. In fertility study in rats, effects on the testis and sperm and decreased fertility were observed in males and anestrus was observed in females at the high-dose. In embryofetal developmental study, favipiravir was found to be teratogenic in all animal species (mouse, rat, rabbit and monkey) tested at systemic exposures equivalent to systemic exposure achieved in human at the proposed dosing regimen.

## 6. PHARMACEUTICAL PARTICULARS 6.1 List of excipients Excipients - L-Hydroxy propyl cellulose, Colloidal Silicon Dioxide, Crospovidone, Povidone K 30, Purified Water, Sodium Stearyl Fumarate, Opadry 03A540066 Yellow,

# **6.3 Special precautions for storage:** Store at a temperature not exceeding $30^{\circ}\text{C}$

 $\textbf{6.4 Nature and contents of container:} \ PVC/PVdC - Alu \ Blister \ Packaging$ 

# **6.5 Special precautions for disposal and other handling**Keep all medicines out of reach of children. Disposal and other handling, as per the local regulatory guidance

Marketed by: **Biocon Biologics India Limited**Biocon House, Semicon Park, Electronics City, Phase - II, Bengaluru - 560 100, India 
© - Registered trademark.

The data represented in this prescribing information are based on publicly available information/ Manufacturer\* Leafleft generated on September 2020 \*Reference: https://bit.ly/2ZzPkhn