To be sold on the prescription of Medical Specialist.

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Favipiravir Tablets 200 mg

Biocon Biologics

ARAFLU® 200 आराफ्लू २००

WARNING

In the experiments with animals, this drug has been proved to be lethal to early embryo as well as to cause teratogenicity and, hence, cannot be administered to a pregnant woman or a woman who may pregnant (see **Contraindications**). If the drug is to be administered to a woman with a possibility of becoming pregnant, a pregnancy test should be done before starting the drug to confirm negative pregnancy before starting the drug. In addition, the risks should be fully explained and guidance should be given (to the female patient), including her partner, to ensure implementation of extremely effective contraceptive methods during the administration period and for 7 days after the completion of the administration (see **Contraindications**). Furthermore, if pregnancy is suspected during the administration period of this product, administration should be discontinued immediately and the patient should be instructed to contact a physician. The drug migrates into the semen. Therefore, when administering to male patients, make sure to fully explain the risks and instruct them to use extremely effective contraceptive methods during sexual intercourse, during the administration period and up to 7 days after the completion of the administration of the drug (men must wear condoms). Also, advise them against having sexual intercourse with partners/women who are pregnant or may possibly become pregnant during this period. Prior to starting the treatment, patients or their families should be fully explained about the efficacy and risks (including risk of foetal exposure) and this should be documented. When administering this drug, the necessity of this drug should be carefully considered. Drug to be used with caution in the patients with history of abnormalities in the metabolism of uric acid or having gout.

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains:
Favipiravir.....200mg
Excipients.....q.s.
Colours: Yellow Oxide of Iron & Titanium Dioxide IP

DOSAGE FORM AND STRENGTH
Oral, film-coated tablet of 200 mg

CLINICAL PARTICULARS
Therapeutic Indications

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

Posology and Method of Administration

The recommended dosage is as follows:
Day 1: 1,800 mg, twice daily
Day 2 onwards: 800 mg, twice daily, up to a maximum of 14 days Note: Use only as directed by the Physician
The administration should be started promptly after suspected or laboratory confirmation of SARS CoV-2 infection in adults with mild to moderate disease.

Use in Elderly: Since the elderly often have reduce physiological function, favipiravir should be administered with care to them by monitoring their general condition

Use in Children: Favipiravir has not been administered to children

Contraindications
- A pregnant or lactating woman or a woman who may be pregnant (early embryonic lethality and teratogenicity observed in animal experiments)
- Patients with a history of hypersensitivity to the components of this drug
- Patients with severe hepatic impairment
- Patients with severe renal impairment

Special Warnings and Precautions for Use
Warnings
Favipiravir has been proved to be lethal to early embryo as well as to cause teratogenicity in animal studies and, hence, cannot be administered to a pregnant woman or a woman who may pregnant.

If the drug is to be administered to a woman with a possibility of becoming pregnant, a pregnancy test should be done before starting the drug to confirm negative pregnancy before starting the drug. In addition, the risks should be fully explained and guidance should be given (to the female patient) accompanied by the partner to ensure implementation of extremely effective contraceptive methods during the administration period and for 7 days after the completion of the administration. Furthermore, if pregnancy is suspected during the administration period of this product, administration should be discontinued immediately and the patient should be instructed to contact a physician.

The drug migrates into the semen. Therefore, when administering to male patients, make sure to fully explain the risks and instruct to use extremely effective contraceptive methods during sexual intercourse during the administration period and up to 7 days after the completion of the administration of the drug (men must wear condoms). Also, advise them against having sexual intercourse with partners/women who are pregnant or may possibly become pregnant during this period.
Prior to starting the treatment, patients or their families should be fully explained about the efficacy and risks (including risk of foetal exposure) and this should be documented.

When administering this drug, the necessity of this drug should be carefully considered.

Precautions
Patients with gout or a history of gout and patients with hyperuricaemia (there is a concern of increase in blood uric acid levels and worsening of symptoms). The drug should be used with caution in the patients with history of abnormalities in the metabolism of uric acid or having gout.

The approved dosage and administration are estimated based on the results of placebo-controlled Phase I/II studies in influenza-virus infected patients and pharmacokinetic data in Japan and other countries. In a clinical study conducted outside Japan to examine the pharmacokinetics of patients with liver dysfunction, plasma concentrations of the drug increased in patients with liver dysfunction.

Although the causal relationship is unknown, psychoneurotic symptoms such as abnormal behaviour 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 behaviour such as fall, patients/their family should be instructed that, after the start of treatment with anti-influenza virus agents, (i) abnormal behaviour may develop, 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.

Bacterial infections can be associated with influenza virus infection or can be confused with flu-like symptoms. In case of a bacterial infection and if a bacterial infection is suspected, take appropriate measures such as administration of antibacterial agents.

Drug Interactions
Favipiravir is not metabolised by cytochrome P450 (CYP), it is mainly metabolised by aldehyde oxidase (AO), and partly by xanthine oxidase (XO). Furthermore, it inhibits AO and CYP2C8, but has no CYP-inducing effect.

Precautions (When Used in Combination)

Drug Name	Clinical Symptoms and Measures	Mechanism and Risk Factors
Pyrazinamide	Increase in blood uric acid levels. When pyrazinamide 1.5 g once a day was administered alone and then administered along with favipiravir 1,200/400 mg twice daily, the blood uric acid level was 11.6 and 13.9 mg/dL, respectively.	Additively promotes reabsorption of uric acid in renal tubules.
Repaglinide	There may be an increase in blood levels of repaglinide, and side effects of repaglinide may occur.	Inhibition of CYP2C8 increases repaglinide blood levels.
Theophylline	There may be an increase in blood concentration of favipiravir, and side effects of favipiravir may occur.	XO-mediated interaction may increase the blood concentration of favipiravir.
Famciclovir Sulindac	The efficacy of these drugs may be diminished.	It is considered that the inhibition of AO by this drug may decrease the blood concentration of activated forms of these drugs.

AO, aldehyde oxidase; XO, xanthine oxidase

Use in Special Populations
Pregnant Women
Favipiravir should not be administered to a pregnant woman or a woman who may be pregnant. In animal studies, early embryonic lethality (rat) and teratogenicity (monkey, mouse, rat, and rabbit) were observed at doses similar to or lower than the clinical trial exposure level.

Lactating Women
If administered to a nursing mother, stop the breastfeeding. It has been observed that the hydroxylated product, the main metabolite of this drug, migrates into breast milk.

Paediatric Patients
There is no administration experience in children.

Geriatric Patients
In general, since the physiological functions are often reduced in the elderly, the administration should be done while observing the patient's condition.

Effects on Ability to Drive and Use Machines
In the case of side effects such as abnormal behaviour or psychiatric symptoms, the patient's ability to concentrate and to react properly may be impaired. In such cases, patients should refrain from driving cars and using machines

Undesirable Effects
In a Japanese clinical study in Influenza and a global joint Phase III study (a study conducted at a dose lower than the approved dosage and administration), 100 out of the 501 patients evaluated for safety (19.96%) showed adverse reactions (including abnormal laboratory test values).

The main side effects were blood uric acid increased in 24 cases (4.79%), diarrhoea in 24 cases (4.79%), neutrophil count decreased in 9 cases (1.80%), AST (GOT) increased in 9 cases (1.80%), ALT (GPT) increased in 8 cases (1.60%).

1. Significant Side Effects
Abnormal Behaviour (Frequency Unknown): The causal relationship is unknown but when influenza occurs, abnormal behaviour (sudden running, wandering, etc.) that may lead to falling, etc., may occur.

2. Serious Side Effects (Similar Drugs)
Since the following serious side effects have been reported with other anti-influenza virus drugs, the patient should be carefully monitored and if any abnormalities are found, discontinue administration and take appropriate measures.

- Shock, anaphylaxis
- Pneumonia
- Fulminant hepatitis, liver dysfunction, jaundice
- Toxic epidermal necrolysis (TEN) syndrome, Stevens-Johnson syndrome
- Acute kidney injury
- Leucopaenia, neutropaenia, thrombocytopaenia.
- Psychiatric symptoms (disturbance of consciousness, delirium, hallucinations, delusions, convulsions, etc.)
- Haemorrhagic colitis

3. Other Adverse Effects
If any of the following adverse reactions occur, take appropriate measures according to the symptoms.

Type	1% or more	0.5 to 1%	Less than 0.5%
Hypersensitivity		Rash	Eczema, pruritus
Liver	Increase in AST (sGOT), Increase in ALT (sGPT), Increase in gamma-GTP		Increase in blood ALP, increase in blood bilirubin
Digestive organs	Diarrhoea (4.79%)	Nausea, vomiting, abdominal pain	Abdominal discomfort, duodenal ulcer, excretion of bloody stool, gastritis
Blood	Reduction in neutrophil count, reduction in leucocyte count		Increase in leucocyte count, reduction in reticulocyte count, increase in monocyte count
Metabolic Disorders	Increase in blood uric acid (4,79%), increase in blood triglycerides	Urinary glucose positive	Decrease in blood potassium
Respiratory			Asthma, oropharyngeal pain, rhinitis, nasopharyngitis
Other			Increase in blood CK (CPK), urine blood positive, tonsillar polyp, pigmentation, dysgeusia, contusion, blurred vision, eye pain, vertigo, supraventricular extrasystole

AST (sGOT), aspartate aminotransferase (serum glutamic oxaloacetic transaminase); ALT (sGPT), alanine aminotransferase (serum glutamic pyruvic transaminase); γ-GTP, glutamyl transpeptidase; CK (CPK), creatine kinase (creatine phosphokinase); ALP, alkaline phosphatase

Reporting of Side Effects
If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@biocon.com

Overdose
No data available.

PHARMACOLOGICAL PROPERTIES
Mechanism of Action
Favipiravir is metabolised in cells to a ribosyl triphosphate (favipiravir RTP), which selectively inhibits RNA polymerase involved in influenza virus replication. For human DNA polymerases alpha, beta and gamma, favipiravir RTP (1,000 μmol/L) has no inhibitory effect on alpha, and it showed an inhibitory effect of 9.1 to 13.5% against beta and 11.7 to 41.2% against gamma (human DNA polymerase). The inhibitory concentration (IC_x value) of favipiravir RTP on human RNA polymerase II was 905 μmol/L.

Pharmacodynamic Properties
In vitro Antiviral Activity
In vitro, the 50% effective concentration (EC50) of favipiravir against SARS-CoV-2 was 61.88 μM/L in Vero E6 cells indicating that higher concentrations than the dose used in influenza may be required. Further, half cytotoxic Concentration CC50 > 400 μM and selectivity index SI > 6.46 were required to reduce the viral infection

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

Pharmacokinetic Properties
Blood Concentration
When favipiravir was administered orally in 8 healthy adults at 1,600 mg twice daily on day 1, 600 mg twice a day from the day 2 to day 5 and 600 mg once on day 6 (1,600 mg/600 mg BID), the pharmacokinetic parameters were as follows:

Administration method		C_{max}[a] (μg/mL)	AUC[a,b] (μg.hr/mL)	T_{ss}[c] (hr)	$t_{1/2}$[d] (hr)
1,600 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

[a]Geometric mean [coefficient of variance%].
[b]AUC on day 1 is AUC_{0-12hr} and AUC on day 6 is AUC,
[c]Median value [minimum value, maximum value].
[d]Mean +/- standard deviation

Furthermore, when favipiravir was orally administered for 7 days to a healthy adult patient considered to have almost no AO activity, the estimated AUC of unchanged drug on day 1 and day 7 of administration was 1,452.73 μg·hr/mL and 1,324.09 μg·hr/mL, respectively.

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ARAFLU® 200 आराफ्लू २००

Note: On day 1, first dose was 1,200 mg, second dose was 400 mg; from day 2 to day 6, 400 mg twice a day; and on day 7, 400 mg once was administered. The approved dosage and administration regimen for this product is oral administration of 1,800 mg twice a day on day 1 and 800 mg twice a day from day 2 upto day 14.

Distribution
On oral administration (1,200 mg/800 mg BID) of favipiravir to 20 healthy adult males at a dose of 1,200 mg twice a day on day 1 and 800 mg twice a day from day 2 to day 5, the semen concentrations (geometric mean) of the drug were 18.341 μg/mL and 0.053 μg/mL on day 3 of administration and on day 2 after the end of administration, respectively; on day 7 after the end of treatment, the dose was below the lower limit of quantification (0,02 μg/mL) in all subjects. The semen/plasma concentration ratio (mean value) was 0.53 and 0.45 on day 3 of administration and on day 2 after administration, respectively

Note: The approved dosage and administration regimen for this product is oral administration of 1,800 mg twice a day on day 1, and 800 mg twice a day from day 2 upto day 14.The binding ratio of favipiravir to human serum protein was 53.4 to 54.4% at a concentration of 0.3 to 30 μg/mL (*in vitro*, centrifugal ultrafiltration).

Metabolism
This drug is not metabolised by CYP450,but mainly metabolised by AO and partly by XO to a hydroxylated form. The metabolism of this drug was studied in human liver cytosol. Hydroxide formation was 3.98 to 47.6 pmol/mg protein/min, and AO activity showed a maximum of 12-fold difference between individuals. Glucuronic acid conjugates were also found in human plasma and urine as metabolites other than the hydroxylated form.

Elimination
Favipiravir is mainly excreted in the urine as a hydroxylated form and unchanged form was in very little quantity. After oral administration of this drug to 6 healthy adults for 7 days, the cumulative urinary excretion rate of the unchanged form and the hydroxylated form until 48 hours after the last dose was 0.8% and 53.1%, respectively.

Note: On day 1, first dose was 1,200 mg, second dose was 400 mg; from day 2 to day 6, 400 mg twice a day; and on day 7, 400 mg once was administered. The approved dosage and administration regimen for this product is *oral administration of 1,800 mg twice a day on day 1 and 800 mg twice a day from day 2 upto day 14*.

Special Populations
Patients with Hepatic Impairment
In patients with mild and moderate hepatic impairment (Child-Pugh Classes A and B, 6 patients each), favipiravir was administered orally at 1,200 mg twice a day on day 1, and on days 2 to 5, 800 mg twice daily (1,200 mg/800 mg BID). The C_{max} and AUC on day 5 of administration were lower in patients with mild hepatic impairment than in healthy adults given the same dosage regimen and usage. They were about 1.6 and 1.7 times lower, respectively, and about 1.4 and 1.8 times lower, respectively, for patients with moderate hepatic impairment.

In patients with severe hepatic impairment (Child-Pugh Class C, 4 patients), favipiravir was administered orally at 800 mg twice a day on day 1, 400 mg twice a day from day 2 to day 3 (800 mg/400 mg BID). The C_{max} and AUC on day 3 of administration were approximately 2.1 times and approximately 6.3 times lower, respectively, compared to when administered to healthy adults with the same dosage and administration. Favipiravir is contraindicated in patients with severe hepatic impairment.

Note: The approved dosage and administration regimen for this product is *oral administration of 1,800 mg twice a day on day 1 and 800 mg twice a day from day 2 upto day 14*.

Drug Interactions
In vitro: Favipiravir irreversibly inhibited AO activity in a dose- and time-dependent manner and CYP2C8 in a dose-dependent manner. On the other hand, the inhibitory effect of this drug on XO was not observed, and the inhibitory effect on CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 was weak. The inhibitory effect of the metabolite of this drug, hydroxylated form, on CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 was weak.

Inductive effect of favipiravir on CYP was not seen.
Clinical Drug–Drug Interaction Study
Effect of Concomitant Drugs on the Pharmacokinetics of favipiravir

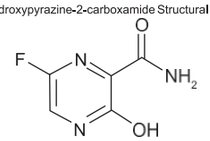
Concomitant drugs and dosage	Dosage of favipiravir	No. of cases	Period of administration	Ratio of pharmacokinetic parameters of this drug [90% confidence interval] (combination/single administration)	
				C_{max}	AUC
Theophylline 200 mg twice daily on days 1 to 9; 200 mg once on day 10	600 mg twice daily on day 6; 600 mg once daily on days 7 to 10	10	day 6	1,33 [1.19,1.48]	1,27 [1.15, 1.40]
			day 7	1.03 [0.92, 1.15]	1.17 [1.04, 1.31]
Oseltamivir 75 mg twice daily on days 1 to 5; 75 mg once on day 6	600 mg twice daily on day 5; 600 mg once on day 6	10	day 6	0.98 [0.87, 1.10]	1.01 [0.91, 1.11]
Raloxifene 60 mg once daily on days 1 to 3	1,200 mg twice daily on day 1; 800 mg twice daily on day 2; 800 mg once 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 5 mg once daily on day 1 and day 5	1,200 mg (first dose) and 400 mg (second dose) on day 1; 400 mg twice daily on days 2 to 4; 400 mg once on day 5	14	day 1	0,99 [0.92, 1.06]	0,99 [0.92, 1.07]
			day 5	0,96 [0.89, 1.04]	1.04 [0.96, 1.12]
Repaglinide 0.5 mg once on day 13	1,200 mg twice daily on day 1; 800 mg twice daily on days 2 to 4; 800 mg once on day 5	17	day 13	1,28 [1.16, 1.41]	1.52 [1.37, 1.68]
Hydralazine 5 mg once daily on day 1 and day 5 -	1,200 mg (first dose) and 400 mg (second dose) on day 1; 400 mg twice daily on days 2 to 4; 400 mg once on day 5	14	day 1	0,73 [0.67, 0.81]	0,87 [0.78, 0.97]
			day 5	0,79 [0.71, 0.88]	0,91 [0.82, 1.01]

Effect of Favipiravir on the Pharmacokinetics of Concomitant Drugs

Concomitant drugs and dosage	Dosage of this favipiravir	No. of cases	Period of administration	Ratio of pharmacokinetic parameters of concomitant drugs [90% confidence interval] (combination/single administration)	
				C_{max}	AUC
Theophylline 200 mg twice daily on days 1 to 9; 200 mg once on day 10	600 mg twice daily on day 6; 600 mg once daily on days 7 to 10	10	day 7	0.93 [0.85, 1.01]	0.92 [0.87, 0.97]
			day 10	0.99 [0.94, 1.04]	0.97 [0.91, 1.03]
Oseltamivir 75 mg twice daily on days 1 to 5; 75 mg once on day 6	600 mg twice daily on day 5; 600 mg once on day 6	10	day 6	1.10 [1.06, 1.1 5]	1.14 [1.10, 1.18]
Acetaminophen 650 mg once daily on day 1 and day 5	1,200 mg twice daily on day 1; 800 mg twice daily on days 2 to 4; 800 mg once on day 5	28	day 1	1.03 [0.93, 1.14]	1.16 [1.08, 1.25]
			day 5	1.08 [0.96, 1.22]	1.14 [1.04, 1.26]
Norethindrone/ ethinyl oestradiol combination: 1 mg/0.035 mg once daily on days 1 to 5	1,200 mg twice daily on day 1; 800 mg twice daily on days 2 to 4; 800 mg once on day 5	25	day 12	1.23 [1.16, 1.30]	1.47 [1.42, 1.52]
			day 12	1.48 [1.42, 1.54]	1.43 [1.39, 1.47]

NON-CLINICAL PROPERTIES
Animal Toxicology or Pharmacology
In mouse infection models of influenza viruses A (H7N9), A (H1N1) pdm09 or A (H3N2), decrease of virus titres in lung tissues was reported with a 5-day oral administration of favipiravir at a dose of ≤60 mg/kg/day.
In mouse infection models of influenza viruses A (H3N2) or A (H5N1), a therapeutic effect was observed with a 5-day oral administration of favipiravir at a dose of 30 mg/kg/day.
In a SCID mouse infection model of influenza virus A (H3N2), a therapeutic effect was observed with a 14-day oral administration of favipiravir at a dose of 30 mg/kg/day.

DESCRIPTION
Chemical name: 6-fluoro-3-hydroxypyrazine-2-carboxamide Structural formula:



Molecular formula: $C_5H_4FN_3O_2$ Molecular weight: 157.10
Properties: White to pale yellow powder. Sparingly soluble in acetonitrile or methanol and slightly soluble in water or ethanol (99.5).
Melting point: 187°- 193°C

PHARMACEUTICAL PARTICULARS
Incompatibilities
Not applicable.

Shelf-life: Refer carton/strip

Packaging Information ARAFLU®: Pack of 10 x 10 Tablets

Storage and Handling Instructions
Store at a temperature not exceeding 30°C.
Keep out of reach of children.

PATIENT COUNSELLING INFORMATION
1. What is ARAFLU®?
ARAFLU® tablets are a prescription medicine used to treat mild to moderate COVID 19. This drug does not treat bacterial infections.
It should not be used in children.

2. Who should not take ARAFLU®?
Do not take **ARAFLU®** tablets if you are allergic to favipiravir or any other ingredient of this tablet.

You should not be taking **ARAFLU®** if you are suffering from severe hepatic impairment (liver failure) or severe renal impairment (kidney failure).
If you are pregnant or lactating/nursing or may be pregnant you should not take **ARAFLU®**.
Guidance should be given (to the female patient) as well as her partner to ensure implementation of extremely effective contraceptive methods during the administration period and for 7 days after the completion of the administration.

3. What precautions should I follow when taking ARAFLU®?
The drug migrates into the semen. Male patients must wear a condom during sexual intercourse during the administration period and up to 7 days after the completion of the administration of the drug.
Female patients must avoid breastfeeding while using this drug.

4. What should I tell my healthcare provider before taking ARAFLU®?
Before you take **ARAFLU®** tablets, tell your healthcare provider if
- you have gout;
- you have any other medical condition;
- you are pregnant or planning to become pregnant; and/or
- you are breastfeeding or planning to breastfeed.
- you have kidney disease
- you have liver disease

Tell your healthcare provider about all the medicines you take, including prescription or over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

5. How should I take ARAFLU®?
Take **ARAFLU®** tablets exactly as your healthcare provider tells you to.

6. What are the possible side effects of ARAFLU®?
The most common side effects of **ARAFLU®** tablets include increase in uric acid levels in the blood, diarrhoea, decrease in white blood cells count, and increase in liver enzymes.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of **ARAFLU®** tablets. Call your doctor for medical advice about side effects.

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

7. How should I store ARAFLU®?
Store at a temperature not exceeding 30°C.
Keep **ARAFLU®** tablets and all medicines out of the reach of children.

8. General information about the safe and effective use of ARAFLU®
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use **ARAFLU®** tablets for a condition for which it was not prescribed. Do not give **ARAFLU®** tablets to other people, even if they have the same symptoms you have. It may harm them.
If you would like more information, talk with your healthcare provider.

Manufactured by:
Optimus Pharma Private Limited,
Plot No. : 73/B, 73/B/2, EPIP, Pashamylaram (V), Patancheru (M), Sangareddy District - 502 307, Telangana State, India.

Marketed by :
Biocon Biologics India Limited
Biocon House, Semicon Park, Electronics City, Phase - II, Bengaluru - 560 100, India.
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DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
22/SRD/TS/2017/F/G dated 23.07.2020

DATE OF REVISION
09-09-2020

The data represented in this prescribing information are based on publicly available information/ Manufacturer*

*Reference: https://bit.ly/2ZzPkhn

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