In Mild to Moderate COVID-19 Patients

ACTAVIR™
Favipiravir 200 mg Tablets
Makes the Difference

PRODUCT MONOGRAPH
In Mild to Moderate COVID-19 Patients

RECOMMENDED DOSAGE:

1800 mg orally twice daily on day 1 and 800 mg orally twice daily from Day 2 upto maximum 14 days along with supportive care

Per Patient Dosage

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2-14</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1800 mg BID</td>
<td>800 mg BID</td>
</tr>
<tr>
<td>Morning</td>
<td>200 mg x 9 Tabs</td>
<td>200 mg x 4 Tabs each day</td>
</tr>
<tr>
<td>Evening</td>
<td>200 mg x 9 Tabs</td>
<td>200 mg x 4 Tabs each day</td>
</tr>
</tbody>
</table>

Favipiravir 200 mg Tablets

ACTAVIR™

Makes the Difference

Favipiravir Tablets 200 mg

1 x 10 Tablets

*For Restricted Emergency use

Approved By DCGI
Dear Doctor,

Greetings from Micro Labs Ltd!!

COVID-19 pandemic has affected a significant number of people in India with wide range of signs and symptoms ranging from mild to severe infection and has led to significant mortality.

Global burden of the COVID-19 pandemic has pushed the scientific domain into finding various avenues to fight the virus, and in this effort Micro Labs Ltd. is committed in providing the best possible therapy with its global outreach so that every patient is benefitted during these times.

Favipiravir a broad range anti-viral, has recently been approved for mild to moderate COVID-19 in India, and we are happy to present the monograph of the Actavir (favipiravir) with all information for your kind reference.

Should you require any further information or for any feedback please write to us at medicalservices@microlabs.in.

Best regards

Dr. Manjula Suresh MBBS, MD, FAGE
Sr. Vice President - Medical Services,
Micro Labs Limited | 31, Race Course Road | Bangalore 560 001
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COVID-19

The coronavirus (CoV) have become the major pathogens of emerging respiratory disease outbreaks. They are a large family of single-stranded RNA viruses (+ssRNA) that can be isolated in different animal species. CoVs are positive-stranded RNA viruses with a crown-like appearance under an electron microscope (coronam is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. For reasons yet to be explained, these viruses can cross species barriers and can cause, in humans, illness ranging from the common cold to more severe diseases such as MERS and SARS.

Transmission:
Infection with SARS-CoV-2 primarily causes respiratory illness ranging from mild disease to severe disease and death, and some people infected with the virus never develop symptoms.

The following are the different modes of transmission:

- Contact and droplet transmission
- Airborne transmission
- Fomite transmission

Viral Replication
Incubation period

- Incubation period of SARS-CoV-2 is 2 to 14 days
- 97.5% of persons with COVID-19 who develop symptoms will do so within 11.5 days of SARS-CoV-2 infection

Disease progression and viral load

- Virus shedding is highest in the early course of disease
- Virus shedding can occur 24-48 hours prior to symptom onset
- Virus can be isolated from the stool but there is no epidemiologic evidence of feco-oral transmission
- Virus shedding usually continues for 7-12 days in mild/moderate cases, and for more than 2 weeks in severe cases

Favipiravir

Favipiravir is a pyrazine carboxamide derivative (6-fluoro-3-hydroxy-2-pyrazinecarboxamide). It is a broad-spectrum antiviral drug - effective against various subtypes and strains of influenza and other RNA viruses. Favipiravir is a repurposed drug for COVID-19.
Pharmacokinetic properties

- **Absorption** - Quick oral absorption, $t_{1/2} = 2.5$ to 5 hrs, $T_{max} = 2$ hours, bioavailability 98%
- **Distribution** - Plasma protein binding = 54%, $V_d$: 15-20 liters
- **Metabolism** - Not metabolised by cytochrome P-450 (CYP), mostly metabolised by aldehyde oxidase (AO), and partly metabolized to a hydroxylated form by xanthine oxidase (XO)
- **Excretion** - As hydroxylated form into urine

![Chemical Structure]

**Mechanism of action**

- Favipiravir is incorporated into cells and converted to favipiravir ribofuranosyl-5-triphosphate (Favipiravir - RTP)
- The Triphosphate form, Favipiravir - RTP, inhibits the activity of RNA dependent RNA polymerase (RdRp) of RNA viruses
RdRp is responsible for the replication of viral RNA to create more copies of Virus
Thus by inhibiting RdRp, Favipiravir inhibits viral replication

**Dosage**

<table>
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<tr>
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<th>Day 1</th>
<th>Day 2 to max 14 days</th>
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<tr>
<td><strong>Total daily dose</strong></td>
<td>1800 mg bid</td>
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**Favipiravir - Clinical Evidences**

**Clinical Study 1**

An open-label control study on Favipiravir for the treatment of laboratory confirmed COVID-19 patients

**Methods:**

- Favipiravir (FPV) versus Lopinavir (LPV)/ritonavir (RTV) for the treatment of COVID-19.
- FPV arm: n=35; FPV (Day 1: 1600 mg twice daily; Days 2-14: 600 mg twice daily) plus interferon (IFN)-α by aerosol inhalation (5 million U twice daily)
- Control arm: n=45; LPV/RTV (Days 1–14: 400 mg/100 mg twice daily) plus IFN-α by aerosol inhalation (5 million U twice daily)

**Results:**

- A shorter viral clearance time was found for the FPV arm versus the control arm.
- The FPV arm also showed significant improvement in chest imaging compared with the control arm [91.43% versus 62.22% (P= 0.004)]
- FPV arm also showed a significantly higher improvement rate in chest imaging.
- Multivariable Cox regression showed that FPV was independently associated with faster viral clearance.
- In addition, fewer adverse events were found in the FPV arm than in the control arm.

Kaplan-Meier survival curves for the length of time until viral clearance for both kinds of antiviral therapy (P <0.001).
FPV showed better therapeutic responses on COVID-19 in terms of disease progression and viral clearance.

![Graph showing time of viral shedding and improving chest CT scan on Day 14 after treatment.](image)

Clinical Study 2

Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial

**Methods:**
- Prospective, randomized, controlled, open-label multicenter trial involving adult patients with COVID-19.
- Patients were randomly assigned in a 1:1 ratio to receive conventional therapy plus Umifenovir (Arbidol) (200mg×3/day) or Favipiravir (1600mg×2/first day followed by 600mg×2/day) for 10 days.
- The primary outcome was clinical recovery rate of Day 7.
- Latency to relief for pyrexia and cough, the rate of auxiliary oxygen therapy (AOT) or noninvasive mechanical ventilation (NMV) were the secondary outcomes.
- Safety data were collected for 17 days.

**Results**
- 240 enrolled COVID-19 patients underwent randomization; 120 patients were assigned to receive Favipiravir (116 assessed), and 120 to receive Arbidol (120 assessed).
- Clinical recovery rate of Day 7 does not significantly differ between Favipiravir group (71/116) and Arbidol group (62/120) (P=0.1396, difference of recovery rate: 0.0954; 95% CI: -0.0305 to 0.2213).
- Favipiravir led to shorter latencies to relief for both pyrexia (difference: 1.70 days, P<0.0001) and cough (difference: 1.75 days, P<0.0001).
- No difference was observed of AOT or NMV rate (both P>0.05). The most frequently observed Favipiravir-associated adverse event was raised serum uric acid (16/116, OR: 5.52, P=0.0014).
No difference was observed of AOT or NMV rate (both P>0.05). The most frequently observed Favipiravir-associated adverse event was raised serum uric acid (16/116, OR: 5.52, P=0.0014).
**Contraindication**
- Women known or suspected to be pregnant (Early embryonic deaths and teratogenicity have been observed in animal studies)
- Hypersensitivity to the active substance or to any of the excipients
- Lactating women
- Severe hepatic impairment
- Severe renal impairment

**Warnings**
Possible contraindications/warnings for the use of Favipiravir:

- 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 the most effective contraceptive methods with her partner during and for 7 days after 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 the most effective contraceptive methods for sexual intercourse during and for 7 days after 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 the foetus) to patients or their family members.
Undesirable effects

- The major undesirable effects observed in clinical studies with Favipiravir includes increase of blood uric acid level, diarrhoea, decrease of neutrophil count, increase of AST (SGOT) and ALT (SGPT), and psychiatric symptoms.

- In patients with gout or a history of gout, and in patients with hyperuricaemia, blood uric acid level may increase, and symptoms may be aggravated after Favipiravir administration.

Abridged prescribing information

**Active ingredient:** Favipiravir 200 mg. Indication: For the treatment of adults in mild to moderate COVID-19 disease under restricted emergency use.

**Dosage and Administration:** The recommended dosage of favipiravir for adults is 1800 mg orally twice daily on 1st day followed by 800 mg orally twice daily, up to maximum of 14 days.

**Contraindications:** Women known or suspected to be pregnant (Early embryonic deaths and teratogenicity have been observed in animal studies), lactating women, severe renal and hepatic impairment. Hypersensitivity to the active substances or to any of the excipients.

**Warnings:** 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 and written informed consent from each patient/ or his/her representative prior to administration of the drug shall be obtained by the prescriber.

**Precautions:** Caution in patients with history of abnormalities in metabolism of uric acid or having Gout. Psychoneurotic symptoms such as abnormal behavior after administration of anti-influenza virus agents including favipiravir have been reported.

**Drug interactions:** Favipiravir 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 of Pyrazinamide, Repaglinide, Famciclovir, Sulindac.

**Pregnancy & Lactation:** Contraindicated in pregnant and lactating women.

**Adverse Events:** The major undesirable effects observed in clinical studies with favipiravir used at different doses included: Increase of blood uric acid level, diarrhoea, decrease of neutrophil count, increase of AST (SGOT), increase of ALT (SGPT), psychiatric symptoms. 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: Shock, anaphylaxis, Pneumonia, Hepatitis fulminant, Hepatic dysfunction, Jaundice, Toxic epidermal necrolysis (TEN), Oculo-muco-cutaneous syndrome (Stevens-Johnson syndrome), Acute renal failure, White blood cell count decreased, Neutrophil count decreased, Platelet count decreased.
Summary

- Favipiravir is a broad-spectrum antiviral drug - effective against various subtypes and strains of influenza and other RNA viruses currently approved for the treatment of mild to moderate COVID-19.
- Given orally, favipiravir has a good bioavailability and absorption.
- DCGI has approved the drug for restricted emergency use in mild to moderate COVID-19 patients.
- Favipiravir acts by inhibiting RdRp, and therefore inhibiting the viral replication.
- There are currently evidences show that it has shorter viral clearance time and several ongoing trials are evaluating its effectiveness and safety.
- Contraindicated in Women known or suspected to be pregnant, lactating women, severe renal and hepatic impairment. Hypersensitivity to the active substances or to any of the excipients.
- Explain thoroughly the efficacy and risks to patients or their family members and written informed consent from each patient/ or his/her representative prior to administration of the drug shall be obtained by the prescriber.

References

5. International brand prescriber information