Molnupiravir Capsules 200 mg

Molulow 200 मोलुलो २००

The product is manufactured under a license from the Medicines Patent Pool;

any other use, beyond the Field, is not authorized

The product is "**NOT FOR RESALE**" outside of the initial country of sale.

For the treatment of COVID-19 caused by SARS-CoV-2

To be sold by retail only under prescription of medical specialists

PRESCRIBING INFORMATION

1. GENERIC NAME

Molnupiravir Capsules 200 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Molnupiravir Capsules 200 mg:
Each hard gelatin capsule contains
Molnupiravir ……200 mg
Approved colours used in capsule shell.

3. DOSAGE FORM AND STRENGTH
Molnupiravir Capsules 200 mg

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications
Molnupiravir is indicated for treatment of adults patients with COVID-19, with SpO2 > 93%and who have high risk of progression of the disease including hospitalization or death.

4.2 Posology and Method of Administration

Adult Patients
800 mg (4 capsules of 200 mg administered orally every 12 hours for 5 days (10 doses total) plus standard of care.

The safety and efficacy of Molnupiravir when administered for periods longer than 5 days have not been established.

Molnupiravir should be administered as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset.

Missed dose
If the patient misses a dose of Molnupiravir within 10 hours of the time it is usually taken, the patient should take as soon as possible and resume the normal dosing schedule. If a patient misses a dose by more than 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

Special populations
Elderly
No dose adjustment of Molnupiravir is required based on age.

Renal impairment
No dose adjustment is required for patients with renal impairment.

Hepatic impairment
No dose adjustment is required for patients with hepatic impairment.

Paediatric population
The safety and efficacy of Molnupiravir in patients below 18 years of age have not been established. No data are available.

Method of administration
For oral use.
Molnupiravir capsules can be taken with or without food.
The capsules should be swallowed whole with a sufficient amount of fluid (e.g., a glass of water). The capsules should not be opened, crushed or chewed

4.3 Contraindications
- Molnupiravir is contraindicated in patients with known hypersensitivity to any ingredient of Molnupiravir Capsules.

4.4 Special Warnings and Precautions for Use

Molnupiravir is not authorized –

i. For use in patients less than 18 years of age
ii. For initiation of treatment in patients requiring immediate hospitalization due to COVID-19 at that stage, (however, if it was initiated before hospitalization due to COVID 19, it may be continued).
iii. For use for longer than 5 consecutive days.
iv. For pre-exposure or post-exposure prophylaxis for prevention of COVID-19
v. For pregnant women
vi. Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir.
vii. Males of reproductive potential who are sexually active with females of child bearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose.

Endocrine disorders:

Patients with a history of acute or chronic pancreatitis are not recommended for the treatment with Molnupiravir unless the benefit outweighs the risk.

Renal disorders

Patients with a history of acute or chronic pancreatitis are not recommended for the treatment with Molnupiravir unless the benefit outweighs the risk.

History of Infections:

Patients who have a history of Hepatitis B or C infection are not recommended for the treatment with Molnupiravir unless the benefit outweighs the risk.

Hepatobiliary disorders:

Patients who have a history of cirrhosis, en-stage liver disease and aspartate aminotransferase (AST) and/ or alanine aminotransferase (ALT) > 3 times are not to be recommended for treatment with Molnupiravir.

Women with child bearing potential:

Women who need to be treated with Molnupiravir need to have a pregnancy test at day 1 of the treatment.

Patient Monitoring Recommendations:
Given the limited experience with Molnupiravir at the recommended dose and duration, patients should have appropriate clinical and laboratory monitoring to aid in early detection of any potential adverse events while receiving Molnupiravir.

4.5 Drug Interactions
No drug interactions have been identified based on the limited available data. No clinical interaction studies have been performed with Molnupiravir. Molnupiravir is hydrolysed to n-hydroxycytidine (NHC) prior to reaching systemic circulation. Uptake of NHC and metabolism to NHC-TP are mediated by the same pathways involved in endogenous pyrimidine metabolism. NHC is not a substrate of major drug metabolising enzymes or transporters. Based on *in vitro* studies, neither Molnupiravir nor NHC are inhibitors or inducers of major drug metabolising enzymes or inhibitors of major drug transporters. Therefore, the potential for Molnupiravir or NHC to interact with concomitant medications is considered unlikely.

4.6 Use in Special Populations
Pregnancy
There are no data from the use of Molnupiravir in pregnant women. Studies in animals have shown reproductive toxicity.
Molnupiravir is not recommended during pregnancy. Women of childbearing potential should use effective contraception for the duration of treatment and for 4 days after the last dose of Molnupiravir.

Breast-feeding
It is unknown whether Molnupiravir or any of the components of Molnupiravir are present in human milk, affect human milk production, or have effect on the breastfed infant. Animal lactation studies with Molnupiravir have not been conducted.
Based on the potential for adverse reactions on the infant from Molnupiravir, breast-feeding is not recommended during treatment and for 4 days after the last dose of Molnupiravir.

Fertility
There were no effects on female or male fertility in rats at NHC exposures approximately 2 and 6 times respectively, the exposure in humans at the recommended human dose (RHD)
Pediatric Patients

Safety and effectiveness of Molnupiravir for the treatment of COVID-19 have not been assessed in Pediatric patients.

Geriatric Patients

Safety and effectiveness of Molnupiravir for the treatment of COVID-19 have not been assessed in patients above 60 years of age.

Patients with Renal Impairment

Safety and effectiveness of Molnupiravir for the treatment of COVID-19 have not been assessed in patients with renal impairment.

Patients with Hepatic Impairment

Safety and effectiveness of Molnupiravir for the treatment of COVID-19 have not been assessed in patients with hepatic impairment.

4.7 Effects on Ability to Drive and Use Machines
No data is available on the effect of Molnupiravir on ability to drive and use machines.

4.8 Undesirable Effects

Tabulated list of adverse reactions
A total of 47 adverse events by 46 patients were reported in the entire study, in that 25 AE's were reported in MOLN group and 22 AE's in SOC group.
Out of 25 AE's in MOLN group, 08 AE's were in Gastrointestinal disorders, 09 AE was in General disorders, 07 AE's were in Nervous system disorders and 01 AE were in pulmonary disorders.
Out of 22 AE's in SOC group, 06 AE's are in Gastrointestinal disorders out of one AE was elevated liver enzymes (of SGOT and SGPT) on day 5 which were not more than 4 times of upper normal limit, 08 AE's are in General disorders, 02 AE's were in Nervous system disorders and 06 AE were in pulmonary disorders. All the reported AE's were mild and moderate in severity and all AE's were recovered.
In MOLN group reported AE's, 04 AE's were possibly related to the study drug, 05 AE's were unlikely related to the study drug and 16 AE's were unrelated to the study drug.
In SOC group, 01 AE's were possibly related to the study drug, 19 AE's were unrelated to the study drug and 02 AE's were unassessable/ unclassifiable.
No SAE's and deaths were reported in the study.
Analysis of adverse events

System Organ Class (Preferred Term)
Gastrointestinal disorders
Diarrhea
Vomiting
Constipation
Gastritis, hiccups
Elevated liver enzymes (SGOT and SGPT)
General disorders and administration site conditions
Giddiness
Itching
rashes
Dizziness
Sneezing
Drowsiness
Dry Cough
Weakness
Fever
Loss of sleep
Felt sleepy
Loss of smell
Nervous system disorders
Headache
Pulmonary disorders
Reduction in SpO2

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on **1800 180 3024** or you can report to MSN Labs on **+91- 40 38265227**. By reporting side effects, you can help provide more information on the safety of this product.

4.9 Overdose
There is no human experience of acute over dosage with Molnupiravir. Treatment of overdose with Molnupiravir should consist of general supportive measures, including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with Molnupiravir.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties
Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, ATC code: not yet assigned.

Mechanism of action
Molnupiravir is a prodrug that is metabolised to the ribonucleoside analogue N-hydroxycytidine (NHC) which distributes into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHCTP acts by a mechanism known as viral error catastrophe. NHC-TP incorporation into viral RNA by the viral RNA polymerase, results in an accumulation of errors in the viral genome leading to inhibition of replication.

Antiviral Activity
NHC was active in cell culture assays against SARS-CoV-2 with 50% effective concentrations (EC50) ranging between 0.67 to 2.66 µM in A-549 cells and 0.32 to 2.03 µM in Vero E6 cells. NHC had similar activity against SARS-CoV-2 variants B.1.1.7 (Alpha), B.1351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) with EC50 values of 1.59, 1.77 and 1.32 and 1.68 µM, respectively. No impact was observed on the *in vitro* antiviral activity of NHC against SARS-CoV-2 when NHC was tested in combination with abacavir, emtricitabine, hydroxychloroquine, lamivudine, nelfinavir, remdesivir, ribavirin, sofosbuvir, or tenofovir.

Efficacy conclusion as per the Clinical Study Report
Test product Molnupiravir Capsule 200 mg (4×200 mg) + Standard of Care Treatment (SOC) when compared with Reference product Standard of Care Treatment (SOC) showed significant improvement in all the primary and secondary end points. Hence it can be concluded that the Molnupiravir Capsule 200 mg (4×200 mg) is effective in the treatment of patients with Mild Coronavirus Disease (COVID-19).

Pharmacodynamic effects
The relationship between NHC and intracellular NHC-TP with antiviral efficacy has not been evaluated clinically.

Resistance
No amino acid substitutions in SARS-CoV-2 associated with resistance to NHC have been identified in Phase 2 clinical trials evaluating molnupiravir for the treatment of COVID-19. Studies to evaluate selection of resistance to NHC with SARS-CoV-2 in cell culture have not been completed.

5.2 Pharmacokinetic Properties

Pharmacokinetic Properties
Molnupiravir is a 5´-isobutyrate prodrug that is hydrolysed to NHC prior to reaching systemic circulation. The pharmacokinetics of NHC are similar in healthy subjects and patients with COVID-19.
The pharmacokinetics of NHC at steady-state following administration of 800 mg molnupiravir every 12 hours are provided below in Table 3.

Table 3: Pharmacokinetics of NHC after administration of 800mg Molnupiravir every 12 hours

NHC Geometric Mean (%CV)		
AUC0-12hr (ng×hr/mL)*	Cmax (ng/mL) †	C12hr (ng/mL)*
8260 (41.0)	2970 (16.8)	31.1 (124)
%CV: Geometric coefficient of variation. * Values were obtained from population PK analysis. †Values were obtained from a Phase 1 study of healthy subjects.		

Absorption
Following twice daily oral administration of 800 mg Molnupiravir, the median time to peak plasma NHC concentrations (T_{max}) was 1.5 hours.

Effect of Food on Oral Absorption
In healthy subjects, the administration of a single 200 mg dose of Molnupiravir with a high-fat meal resulted in a 35% reduction in NHC peak concentrations (C_{max}), AUC was not significantly affected.

Distribution
NHC does not bind to plasma proteins.

Elimination
The effective half-life of NHC is approximately 3.3 hours. The fraction of dose excreted as NHC in the urine was ≤3% in healthy participants.

Other special populations

Gender, Race, Age

Population pharmacokinetic analysis showed that age, gender, race and ethnicity do not meaningfully influence the pharmacokinetics of NHC.

Paediatric Patients

Molnupiravir has not been studied in paediatric patients.

Renal Impairment

Renal clearance is not a meaningful route of elimination for NHC. No dose adjustment in patients with any degree of renal impairment is needed. In a population PK analysis, mild or moderate renal impairment did not have a meaningful impact on the pharmacokinetics of NHC. The pharmacokinetics of Molnupiravir and NHC has not been evaluated in patients with eGFR less than 30 mL/min or on dialysis (see section 4.2).

Hepatic Impairment

The pharmacokinetics of Molnupiravir and NHC has not been evaluated in patients with hepatic impairment. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination therefore hepatic impairment is unlikely to affect NHC exposure. No dose adjustment in patients with hepatic impairment is needed.

Special Populations

Sex, Race and Age

Pharmacokinetic differences based on sex, race, and age have not been evaluated.

Pediatric Patients

Pharmacokinetic differences were not evaluated in paediatric patients.

Patients with Renal Impairment

Pharmacokinetic differences were not evaluated in patients with renal impairment.

Patients with Hepatic Impairment

Pharmacokinetic differences were not evaluated in patients with Hepatic impairment.

6. Preclinical safety data

General Toxicity

Reversible, dose-related bone marrow toxicity affecting all haematopoietic cell lines was observed in dogs at ≥17 mg/kg/day (0.4 times the human NHC exposure at the recommended human dose (RHD)). Mild decreases in peripheral blood cell and platelet counts were seen after 7 days of Molnupiravir treatment progressing to more severe haematological changes after 14 days of treatment. Neither bone marrow nor haematological toxicity was observed in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD) and a 3-month toxicity study in rats up to 1,000 mg/kg/day (9.3 and 15 times the human NHC exposure at the RHD in females and males, respectively).

Bone and cartilage toxicity, consisting of an increase in the thickness of physeal and epiphyseal growth cartilage with decreases in trabecular bone was observed in the femur and tibia of rapidly growing rats in a 3-month toxicity study at ≥ 500 mg/kg/day (5.4 times the human NHC exposure at the RHD). There was no bone or cartilage toxicity in a 1-month

toxicity study in rapidly growing rats up to 500 mg/kg/day (4.2 and 7.8 times the human NHC exposure at the RHD in females and males, respectively), in dogs dosed for 14 days up to 50 mg/kg/day (1.6 times the human NHC exposure at the RHD), or in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD). Growth cartilage is not present in mature skeletons; therefore the bone and cartilage findings are not relevant for adult humans. The clinical significance of these findings for paediatric patients is unknown.

Carcinogenesis

Carcinogenicity studies with Molnupiravir have not been conducted.

Mutagenesis

Molnupiravir and NHC were positive in the *in vitro* bacterial reverse mutation assay (Ames assay) with and without metabolic activation. In 2 distinct *in vivo* rodent mutagenicity models (Pig-a mutagenicity assay and cII Locus transgenic rodent assay) Molnupiravir did not induce increased mutation rates relative to untreated historical control animals, and therefore is not mutagenic *in vivo*. Molnupiravir was negative for induction of chromosomal damage in *in vitro* micronucleus (with and without metabolic activation) and *in vivo* rat micronucleus assays. Based on the totality of the genotoxicity data, Molnupiravir is of low risk for genotoxicity or mutagenicity in clinical use.

Impairment of Fertility

There were no effects on fertility, mating performance or early embryonic development when Molnupiravir was administered to female or male rats at NHC exposures approximately 2 and 6 times, respectively, the human NHC exposure at the recommended human dose (RHD).

Development

In an embryo foetal development (EFD) study in rats, Molnupiravir was administered orally to pregnant rats at 0, 100, 250, or 500 mg/kg/day from gestation days (GDs) 6 to 17. Molnupiravir was also administered orally to pregnant rats at up to 1,000 mg/kg/day from GDs 6 to 17 in a preliminary EFD study. Developmental toxicities included post-implantation

losses, malformations of the eye, kidney, and axial skeleton, and rib variations at 1,000 mg/kg/day (8 times the human NHC exposure at the RHD) and decreased foetal body weights and delayed ossification at ≥500 mg/kg/day (2.9 times the human NHC exposure at the RHD). There were no developmental toxicities at ≤250 mg/kg/day (0.8 times the human

NHC exposure at the RHD). Maternal toxicities included decreased food consumption and body weight losses, resulting in the early sacrifice of individual animals at 1,000 mg/kg/day, and decreased body weight gain at 500 mg/kg/day.

In an EFD study in rabbits, Molnupiravir was administered orally to pregnant rabbits at 0, 125, 400, or 750 mg/kg/day from GDs 7 to 19. Developmental toxicity was limited to reduced foetal body weights at 750 mg/kg/day (18 times the human NHC exposures at the RHD). There was no developmental toxicity at ≤400 mg/kg/day (7 times the human NHC

exposures at the RHD). Maternal toxicities included reduced food consumption and body weight gains, and abnormal faecal output at 750 mg/kg/day.

7. PHARMACEUTICAL PARTICULARS

7.1 Incompatibilities

The compatibility of Molnupiravir Capsules and medications other than saline is not known.

7.2 Packaging Information

10's ALU-ALU Blister Pack.

7.3 Storage and Handling Instructions

Store below 30^{0}C.

8. PATIENT COUNSELLING INFORMATION

You are being given a medicine called Molnupiravir for the treatment of coronavirus disease 2019 (COVID-19). This PI contains information to help you understand the risks and benefits of taking Molnupiravir, which you have received or may receive.

Receiving Molnupiravir may benefit certain people in the hospital with COVID-19. Read this PI for information about Molnupiravir. Talk to your healthcare provider if you have questions.

9. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited
(Formulations Division), Plot No. 42,
Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325,
Telangana, India.

10. DETAILS OF MANUFACTURING LICENCE NUMBER

38/MD/AP/2007/F/CC

11. DATE OF REVISION

Jan 2022.

B33010-00

FACT SHEET
MOLNUPIRAVIR

Molnupiravir Capsules 200mg

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

Molnupiravir is not authorized –

i. For use in patients less than 18 years of age
ii. For initiation of treatment in patients requiring immediate hospitalization due to COVID-19 at that stage, (however, if it was initiated before hospitalization due to COVID 19, it may be continued).
iii. For use for longer than 5 consecutive days.
iv. For pre-exposure or post-exposure prophylaxis for prevention of COVID-19
v. For pregnant women
vi. Females of childbearing potential should use a reliable method of contraception correctly and consistent ly, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir.
vii. Males of reproductive potential who are sexually active with females of child bearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose.

What is in this leaflet

1. What Molnupiravir is and what it is used for
2. What you need to know before you take Molnupiravir
3. How to take Molnupiravir
4. Possible side effects
5. How to store Molnupiravir
6. Contents of the pack and other information

1. What Molnupiravir is and what it is used for

Molnupiravir is indicated for treatment of adults patients with COVID-19, with SpO2 > 93%and who have high risk of progression of the disease including hospitalization or death.

2. What you need to know before you take Molnupiravir

Do not take Molnupiravir

- if you are allergic to Molnupiravir or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking Molnupiravir.

Children and adolescents

Do not give this medicine to children and adolescents aged less than 18 years. The use of Molnupiravir in persons aged less than 18 years has not yet been studied.

Other medicines and Molnupiravir

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

Animal studies with Molnupiravir have shown harmful effects to the unborn animal. **Molnupiravir is not recommended in pregnancy**. Molnupiravir has not been studied in pregnancy and it is not known if Molnupiravir will harm your baby while you are pregnant.

If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor for advice. If you can become pregnant, you should use effective birth control while you are taking Molnupiravir and for 4 days after the last dose of Molnupiravir.

If you are breast-feeding or are planning to breastfeed, tell your doctor before taking this medicine. Breast-feeding is not recommended during treatment and for 4 days after the last dose of Molnupiravir. **This is because it is not known if Molnupiravir gets into breast milk and will be passed to the baby.**

Driving and using machines

No studies on the effects on the ability to drive and use machines have been performed.

Molnupiravir contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose of 4 capsules, that is to say essentially 'sodium-free'.

3. How to take Molnupiravir

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

You should start Molnupiravir within 5 days of the onset of COVID-19 symptoms.

How much to take

The recommended dose of Molnupiravir is four 200 mg capsules, every 12 hours for 5 days.

How to take

- Swallow the capsule whole with plenty of fluid (for instance a glass of water)
- Do not open, break, or crush the capsules.
- This medicine can be taken with or without food.

If you take more Molnupiravir than you should

If you take more Molnupiravir than you should, contact your doctor straight away

If you forget to take Molnupiravir

- It is important that you do not miss or skip doses of this medicine.
- If you forget to take a dose within 10 hours of the time it is usually taken, you should take it as soon as possible and take the next one at the usual time.
- If you forget to take a dose by more than 10 hours, you should not take the missed dose and instead take the next one at the usual time.
- Do not take a double dose to make up for a missed dose.
- If you are not sure what to do, call your doctor or pharmacist.

Do not stop taking Molnupiravir

Do not stop taking Molnupiravir without talking to your doctor first. This will give the medicine the best chance to keep you from becoming severely ill from COVID-19.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects as below, although not everybody gets them.
Headache
Diarrhoea
Giddiness
Gastritis,
Hiccups,
Constipation
Vomiting
Sneezing
Feeling sleepy
Rash
Lack of sleep
Oxygen saturation levels decreased
Fever
Loss of smell

Reporting of side effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at **pharmacovigilance@msnlabs.com** or through company website **www.msnlabs.com**->Contact us->Medical Enquiry/ to report a side effect. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on **1800 180 3024** or you can report to MSN Labs on **+91- 40 38265227**. By reporting side effects, you can help provide more information on the safety of this product.

5. How to store Molnupiravir

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and blister. The expiry date refers to the last day of that month.

This medicinal product does not require any special temperature storage conditions. Store in the original package.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Molnupiravir contains

The active substance is molnupiravir. Each hard gelatin capsule contains 200 mg of Molnupiravir.

Marketing Authorisation Holder:

MSN House: Plot No: C-24, Industrial Estate, Sanathnagar, Hyderabad -500 018, Telangana, India.

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