Treatment of COVID-19 with molnupiravir

Note:

This information has been compiled by CPhA's Pharmacist Editors to provide information about molnupiraviruntil a Health Canada—approved monograph is available.

Key Points:

- On December 23, 2021, the U.S. Food and Drug Administration approved the use of molnupiravir, an oral antiviral, for the treatment of mild-to-moderate COVID-19 in nonhospitalized patients.[1] Molnupiravir was approved for use in the United Kingdom on November 4, 2021.[2]
- In the MOVe-OUT trial, treatment with molnupiravir was associated with a 30% relative decrease in hospitalizations among unvaccinated high-risk patients.[3]
- Molnupiravir is currently under review by Health Canada.[4]

Dose: 800 mg orally per day for 5 days initiated within 5 days of symptom onset

Overview of Available Evidence:

Molnupiravir is an orally bioavailable prodrug of N4-hydroxycytidine (NHC), a nucleoside analog, which has invitro activity against SARS-CoV-2 and other RNA viruses. NHC is phosphorylated intracellularly to NHC triphosphate (NHC-TP), which in turn is incorporated into viral RNA, leading to the accumulation of deleteriouserrors in the viral genome, finally leading to the inhibition of replication.[5,6]

EVIDENCE OF EFFICACY:

Initial Phase II, double-blind, placebo-controlled studies showed that molnupiravir 800 mg daily for 5 days may decrease time to viral RNA clearance and decrease risk of hospitalization and death when compared with placebo.[7,8]

Interim analysis of the MOVe-Out Phase III randomized, placebo-controlled trial showed a significant relative reduction (50%) in hospitalization.[9] However, subsequent analysis has shown that treatment with molnupiravir was associated with only a 30% relative decrease in hospitalizations among unvaccinated high-risk patients:[3]

- 1433 nonhospitalized patients with mild-to-moderate disease (laboratory confirmed) and at least1 risk factor for progression to severe illness (e.g., age >60 years, obesity, diabetes) were enrolled.
- Patients at high-risk of hospitalization within 48 hours were excluded from the study.
- Treatment with molnupiravir (800 mg daily for 5 days) or placebo was initiated within 5 days of symptom onset. Of note: around 50% of patients initiated therapy within 72 hours of symptomonset.
- Hospitalization or death was observed in 6.8% of patients in the molnupiravir group, compared with 9.7% in the placebo group (absolute difference of 2.9%).

EVIDENCE OF SAFETY:

No significant difference in adverse effects was observed between patients who received molnupiravir and patients who received placebo. However, long-term safety has not been evaluated and the following risks areor particular concern:

1. Risk of embryotoxicity and teratogenicity: pregnant patients and those of childbearing age unwilling to receive a form of contraception during and 4 days after treatment with molnupiravir were excluded from the study. Preclinical animal reproductive toxicity data are conflicting, with highmaternal doses administered in the rat model demonstrating possible teratogenic effects, although no evidence of similar effects was observed in the rabbit model.[10]
2. Risk of mutagenicity and genotoxicity: molnupiravir has been shown to cause mutations in Chinese hamster ovary cells.[11] However, evidence from in vivo models of mutagenicity suggest that such risk is low.[12]

Additionally, concerns have been raised regarding the theoretical risk of molnupiravir, inducing viable mutations and more aggressive variants of SARS-CoV-2. No evidence of such a risk is currently available.

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