molnupiravir – FDA's Antimicrobial Drugs Advisory Committee Review

- On November 30, 2021, the FDA's Antimicrobial Drugs Advisory Committee (AMDAC) met to discuss the emergency use authorization (EUA) application for molnupiravir oral capsules for treatment of mild to moderate COVID-19 in adults who are at risk for progressing to severe COVID-19 including hospitalization or death.

- Molnupiravir is an oral pro-drug that is activated in the cell and inhibits viral replication by causing fatal errors in the viral genome leading to inhibition of replication. It is given as a short course: 800 mg twice daily for 5 days total.

- Efficacy data was reviewed. In a phase 3 study, the full population of 1,433 participants were randomized to molnupiravir or placebo. A total of 1,408 participants completed treatment. The primary endpoint was all cause hospitalization or death at day 29.

    - All cause hospitalization or death was seen in 6.8% of the molnupiravir-treated patients vs. 9.7% of placebo patients (3.0% reduction; 95% CI: 0.1, 5.9; p=0.0218).
    - A total of nine patients died in the placebo group vs. 1 patient in the molnupiravir group.

- Molnupiravir was generally well tolerated from a safety perspective with a side effect profile similar to placebo. Notably, there was a lower incidence of serious adverse events and deaths among molnupiravir recipients than placebo.

    - A key safety concern is the potential for toxicity during pregnancy. Animal studies indicated the potential for embryofetal toxicity and Merck is not recommending use in pregnant patients. Caution will be recommended in women of child-bearing age.

    - If authorized, Merck will establish a Pregnancy Surveillance program to monitor for adverse events.

- Mutagenicity was extensively discussed because the mechanism of action for molnupiravir is to create errors in viral RNA and a theoretical concern exists about viral evolution leading to new variants of concern that may not respond to current therapies.

    - The FDA considered the overall risk of mutagenicity in humans to be low based on nonclinical data and the limited course of therapy (5 days).

- Molnupiravir is not currently being studied for pediatric patients. Additional safety studies need to be completed before Merck will undertake studies in children.

- The Advisory Committee was asked to discuss two questions and then vote on recommending EUA.

- **Question 1:** Discuss the potential use of molnupiravir during pregnancy – both in terms of risk and benefit. The Committee raised the following key issues:

    - Pregnancy itself is a risk for progression to severe COVID-19.
    - Unvaccinated women are most at risk for progression to severe COVID-19.
    - Monoclonal antibodies are being used in pregnant women; however, some areas do not have access and there could be possible questions about effectiveness based on the circulating variants.
    - Molnupiravir is potentially harmful in pregnant women based on animal studies and its mechanism of action.

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- Ultimately, the use of molnupiravir in pregnant women needs to be assessed for each individual woman's situation.

- **Question 2:** Discuss the concern regarding the observed increased rate of viral mutations involving the spike protein among participants receiving molnupiravir.

  - Immunocompromised patients and household contacts may be at risk of prolonged viral replication/shedding and this may lead to potential mutations.
  - Viral mutations arise as part of the normal course of infection.
  - Poor adherence to molnupiravir may contribute to resistance and mutations.

Voting Question for the Committee:

- Do the known and potential benefits of molnupiravir outweigh the known and potential risks of molnupiravir when used for the treatment of mild-moderate COVID-19 in adult patients who are within 5 days of symptom onset and are at high risk of severe COVID-19, including hospitalization or death?

  - The Committee voted 13-10 in favor of the question.
  - Those voting "Yes" cited the unmet need among high-risk individuals, particularly the unvaccinated.
  - Those voting "No" cited the many questions and not enough answers, particularly about inconsistencies in the efficacy data.
  - There was universal recognition of the potential risk in pregnancy and the need for caution.

What's Next:

- The FDA will review the recommendations of the AMDAC and decide about the EUA for molnupiravir.

- If authorized by the FDA, the EUA will likely limit use to high-risk individuals and provide guidance on how it defines "high risk" similar to the EUAs for the monoclonal antibodies. It will also probably define how providers should assess and handle use in women of child-bearing age.

- If the EUA is approved for molnupiravir, the U.S. government has agreed to purchase 3.1 million courses of treatment.