Paxlovid™ (nirmatrelvir/ritonavir) – FDA's Antimicrobial Drugs Advisory Committee recommends Paxlovid

- On March 16, 2023, the FDA's Antimicrobial Drugs Advisory Committee (AMDAC) recommended (16 yes and 1 no) that Paxlovid (nirmatrelvir/ritonavir) has a favorable benefit-risk assessment when used for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

    - Paxlovid has been submitted for full FDA approval in adults with an expected Prescription Drug User Fee Act (PDUFA) date in May 2023. The FDA will consider the AMDAC's vote when making its decision for approval.
    - Paxlovid was authorized through emergency use authorization (EUA) in December 2021 for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.
    - The EUA for Paxlovid was amended in February 2023, removing the requirement of SARS-CoV-2 viral testing.
    - The Paxlovid EUA will remain in effect for adolescents 12 to < 18 years of age until data becomes available to support an application for full approval.

- Paxlovid's pivotal study in 2,113 unvaccinated adults, EPIC-HR, was reviewed. The primary endpoint, COVID-19 related hospitalization or death from any cause through day 28, was experienced in 0.9% of Paxlovid treated patients (n=977) vs. 6.5% of placebo patients (n=989). This was a relative risk reduction of 86% (95% CI: 72, 93) and an absolute risk reduction of 5.6% (95% CI: 4.0, 7.3).

- Two additional supportive studies, EPIC-SR and EPIC-PEP were reviewed. These studies did not meet their primary endpoints but were used in the assessment of key review issues (safety review and effectiveness in vaccinated population vs. nonvaccinated population).

- Real world effectiveness was presented. Five studies have been published in peer reviewed journals.

    - Across all studies, effectiveness based on time of diagnosis or test ranged from 44% to 60%.
    - One study reported effectiveness of 80% (95% CI: 34, 94), when Paxlovid was given within 5 days of symptom onset.

- The AMDAC discussed several questions.

    1. Comment on the strength of evidence for use of Paxlovid for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death, in the following populations:

        - Individuals who are vaccinated against COVID-19 or had prior SARS-CoV-2 infection:
            - more data is needed to determine who is benefiting from Paxlovid;
            - physicians should make decision on an individualized manner based on patient's risk factors and potential side effects of Paxlovid;
            - currently we don't know how effective vaccination is at what point in time.
        - Individuals infected with Omicron subvariants:

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        - *in vitro* data very helpful for showing effectiveness across a wide variety of variants;
        - although in small numbers, clinical data also has shown no resistance;
        - new emerging variants need to be monitored.
    - Individuals who are immunocompromised:
        - EPIC-IC trial is currently being conducted to further address this population;
        - ongoing data is needed for length of treatment;
        - individual populations need to be addressed (eg, HIV, transplant, cancer).

2. Comment on the strength of evidence for an association between use of Paxlovid in the treatment of mild-to-moderate COVID-19 and 'COVID-19 rebound':

    - additional information is needed with definition of rebound;
    - individuals who can clear infection and then have additional symptoms one or two weeks later may be what we mean;
    - further information from a historical perspective needs to be in the literature to show how often it occurs and what is the clinical ramification.