INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***HIV Injectable & PrEP treatments***
-November 2022-

Background:

The Indian Health Service National Pharmacy and Therapeutics Committee (NPTC) reviewed the novel cabotegravir injection for pre-exposure prophylaxis (PrEP) of Human Immunodeficiency Virus (HIV) and cabotegravir + rilpivirine injection for treatment of HIV at the Fall meeting in November 2022. The NPTC most recently reviewed the topic of HIV in May 2021 where dolutegravir was added to the National Core Formulary (NCF) for use in HIV treatment during pregnancy. Following the November 2022 HIV treatment review, the NPTC made **no modifications** to the NCF.

Discussion:

Cabotegravir (CAB) is in the integrase strand transfer inhibitor (INSTI) class of antiviral medications. It was recently approved for once-every-two-month administration for PrEP and in combination with rilpivirine (RPV) injection for every-two-month administration in the treatment of HIV infection. The studies submitted for both product's FDA approval and guidelines for their utilization were reviewed.

Cabotegravir for PrEP: CAB 600 mg IM Q two months for PrEP was approved by the FDA in March 2022. Two phase 3 studies are outlined in the package insert supporting the approval.[2] One study demonstrated a 66% risk reduction for HIV acquisition compared to the current IHS formulary product tenofovir + emtricitabine in the U.S., Latin America, Asia and Africa.[1] The second study examined the product in women in Africa and reported an 89% risk reduction for HIV acquisition compared to tenofovir/emtricitabine. Adherence in the injection group was estimated at 93% while adherence to the oral comparator was estimated to be 40%. Adverse drug reactions were similar when comparing cabotegravir to tenofovir + emtricitabine, except for the presence of injection site reactions which accompany cabotegravir. Both studies identified INSTI class drug resistance associated with reduced adherence or mismanagement of discontinuation of cabotegravir for PrEP in cases where HIV is acquired, and resulted in a black-box warning for cabotegravir for PrEP.

Administration: Cabotegravir injection for PrEP is initiated with CAB 600 mg IM once and repeated in four weeks. It is then administered every two months. Assessment for HIV infection is required at each dose. If an HIV Ag/Ab test is used and is negative, an HIV RNA detection test should also be utilized. Subsequent CAB injection is given at two-month intervals, ± 7 days. Management of unplanned missed doses includes the following: if the second dose is missed, it can be made up if done so within two months of the missed second dose. If more than two months pass since the missed second dose, then resume with initiation. If the third or a subsequent dose is missed, CAB injection can be resumed if done so within three months of the missed dose. Every two-month dosing is then resumed. Assessment of adherence should be done in all cases of unplanned missed doses. A missed dose can be planned and managed with oral CAB 30 mg po daily until the next dose can be given. Adherence support is recommended as a routine part of care but is critical in cases of unplanned missed doses. When a patient or provider is concerned about tolerability of CAB for injection, an oral lead-in can be utilized using CAB 30 mg po daily for a month prior to the initial injection. The initiation and follow up dosing schedule, described above, are utilized if an oral lead-in period is desired. Discontinuation of CAB injection for PrEP requires special considerations. Because CAB can be detected in individuals up to 12 months after their last dose, oral PrEP must be utilized starting at two months after the last dose of CAB for injection if risk factors for HIV acquisition persist. If oral PrEP is not chosen upon discontinuation of CAB injection for PrEP, then risk factors for HIV acquisition must be clearly addressed and include regular use of condoms, abstinence, or a single partner with known HIV status.

Cabotegravir + rilpivirine for HIV treatment: CAB 600 mg + RPV 900 mg are given every two months for treatment of HIV. The product is currently approved for simplification in patients who are virologically suppressed on an HIV regimen and who have no documented or potential drug resistance to CAB or RPV or drugs in their respective classes. The "Flair" and "Atlas" trials are cited in the FDA approval documents. Both studies utilized an intention-to-treat with non-inferiority design. Standard HIV regimens were utilized as the comparator in both studies. The primary outcome was virologic failure at 48 weeks and secondary outcome was virologic suppression at week 48. The CAB + RPV combination was non-inferior in both outcomes in both studies. Injection site reactions were common with CAB + RPV. Non-injection-site-related adverse drug reactions were similar across all groups. The data from the studies were presented in a pooled analysis.[3]

Administration: CAB 600 mg + RPV 900 mg for treatment of HIV is limited to patients who are virologically suppressed and without known resistance to the components or other members of their respective drug classes. It is administered as two injections (3 ml of each component) IM in the gluteal muscles. The initial dose is given on the last day of an oral HIV regimen. The second dose is given after one month (± 7 days) and all subsequent doses are given every two months (± 7

days). Clinical monitoring for effectiveness utilizing RNA quantification (viral load testing) and adherence support is recommended for all patients. If prescribers or patients desire, a one-month run-in using oral CAB 30 mg po daily and RPV 25 mg given daily can be used but is not required. For management of unplanned missed doses, the unplanned missed second dose should be given ASAP as long as it is within two months of the initial dose. If two months have passed since the first dose, then start over. Unplanned, missed third or subsequent doses are managed with a make-up dose ASAP as long as it is within three months of the missed dose. If beyond three months from missed dose, then providers must reinitiate with the starting dose. Assessment of adherence should be done in all cases of unplanned missed doses. Planned missed doses can be managed with oral CAB 30 mg + RPV 25 mg daily (or another effective regimen) for up to two months. There is no dose adjustment for Child-Pugh 1-2 liver disease and it is not recommended in Child-Pugh 3 liver disease. No dose adjustment is required in kidney disease down to eGFR of 30 ml/minute. Increased monitoring for adverse drug reaction is recommended below 30 ml/min. Significant drug interactions exist with certain seizure drugs and anti-tuberculous drugs. There is a monthly dosing regimen of CAB 400 mg + RPV 600 mg given monthly (± 7 days) after the initial loading dose of CAB 600 mg + RPV 900 mg IM. See product information for all prescribing details.[4]

Findings:

Cabotegravir is the first HIV antiviral drug to be approved as a long-acting injection for HIV pre-exposure prophylaxis. Cabotegravir plus rilpivirine is the first complete HIV treatment regimen to be approved for administration as long acting injections. While these novel products appear effective and fill a previously unfulfilled niche in their respective arenas of HIV prevention and treatment, the committee determined that there is insufficient evidence to support their addition to the National Core Formulary at this time. They may be considered for use at the local level.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

References:

1. Indian Health Service. National Pharmacy and Therapeutics Committee. Formulary Brief: HIV Guidelines & PrEP Updates. May 2021.
2. APRETUDE (cabotegravir extended-release injectable suspension) package insert. ViiV Healthcare. Initial Approval; 2021. Reference ID: 4908014.
3. Rizardini G, Overton ET, Orkin C, et al. Long-Acting Injectable Cabotegravir + Rilpivirine for HIV Maintenance Therapy: Week 48 Pooled Analysis of Phase 3 ATLAS and FLAIR Trials. *J Acquir Immune Defic Syndr.* 2020; 85(4): 498–506.
4. CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension) package insert. ViiV Healthcare. Initial Approval: 2021. Reference ID: 4959718.