Cabotegravir

Investigational Treatment. This treatment has NOT been approved by the FDA.

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Drug Summary

Cabotegravir is an investigational integrase strand transfer inhibitor currently under study for HIV treatment and for HIV prevention (preexposure prophylaxis). Cabotegravir is a structural analogue of dolutegravir and, like dolutegravir, it is dosed once daily, has potent anti-HIV activity, and appears to have few bothersome adverse effects. Cabotegravir, however, does not have as high a barrier to resistance as dolutegravir. Cabotegravir is being studied in both an oral form (half-life 40 hours) and a long-acting, injectable nanosuspension (half-life 21-50 days). The long-acting injectable formulation likely will require an oral lead-in (induction) phase to ensure that the medication is tolerated before the long-acting intramuscular formulation is given. Cabotegravir remains present in the plasma at detectable but sub-therapeutic levels for many months after an intramuscular injection, which could potentially create risk for drug resistance to cabotegravir if a person discontinues injectable cabotegravir abruptly or misses doses. Therefore, upon discontinuation of the long-acting formulation, a person likely will need a course of standard oral antiretroviral therapy to prevent development of resistance. Further study will be required to better define the required lead-in period, the risk of resistance with missed doses, and the optimal antiretroviral therapy tail upon discontinuation of cabotegravir.

Key Clinical Trials

For antiretroviral treatment-naïve persons with chronic HIV infection, cabotegravir has been studied as a component of 3-drug antiretroviral therapy and as a 2-drug regimen in combination with rilpivirine, with the 2-drug regimen serving as maintenance therapy after a lead-in phase with 3-drug therapy. The phase 2b LATTE trial randomized treatment-naïve adults to one of three doses of daily oral cabotegravir (10 mg, 30 mg, or 60 mg) or daily oral efavirenz, each with two oral NRTIs, for a 24-week induction period; individuals in the cabotegravir groups with an HIV RNA less than 50 copies/mL continued their assigned cabotegravir oral dose but replaced their two NRTIs with rilpivirine whereas the efavirenz plus two NRTI's group continued without change [LATTE]. Twenty-four weeks after the switch to dual maintenance therapy, 82% (149/156) in the cabotegravir plus rilpivirine group had HIV RNA below 50 copies/mL as compared to 71% (44/62) in the efavirenz group. After 72 weeks of maintenance therapy, the proportion with HIV RNA below 50 copies/mL was 76% in the combined cabotegravir arms versus 63% in the efavirenz arm. Efficacy rates in the various

cabotegravir dose arms were similar, and the 30 mg dose was chosen to proceed in further study. Fifteen percent of individuals in the efavirenz arm discontinued treatment due to adverse events as compared to 3% in the cabotegravir arms. In a similar study (LATTE-2) investigators evaluated injectable long-acting cabotegravir and injectable long-acting rilpivirine in antiretroviral-naïve adults [LATTE-2]. Participants received a 20-week lead-in of oral cabotegravir plus oral abacavir-lamivudine, then, if HIV RNA was below 50 copies/mL, were randomized 2:2:1 to intramuscular (IM) cabotegravir plus IM rilpivirine every 4 weeks, IM cabotegravir plus IM rilpivirine every 8 weeks, or continued oral cabotegravir plus abacavir-lamivudine. Thirty-two weeks after randomization, 94% of participants in the every 4-week IM arm and 95% in the every 8-week arm maintained HIV RNA below 50 copies/mL as compared to 91% in the oral arm. Injection site reactions were common (92% of participants) but were mild-to-moderate in severity and overall the injectable therapy was well tolerated. Ongoing and future studies involving long-acting cabotegravir include use in combination with long-acting rilpivirine as a regimen to switch to in adults who are virologically suppressed [FLAIR and ATLAS] and as long-acting injectable cabotegravir alone for preexposure prophlyaxis [ECLAIR and HPTN 083].