Cabotegravir (CAB, Vocabria)

Cabotegravir and Rilpivirine for Intramuscular Injections (IM CAB and RPV, Cabenuva) (Last updated April 7, 2021; last reviewed April 7, 2021)

Formulations

Tablets:

Cabotegravir: 30 mg

Co-Packaged Formulation

- [Cabenuva] Cabotegravir 200 mg/mL and rilpivirine 300 mg/mL suspension for intramuscular injection

When using the co-packaged formulation, refer to the Rilpivirine section for additional information.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Pediatric Dose

- Cabotegravir (CAB) tablets and co-packaged cabotegravir and rilpivirine intramuscular injections (IM CAB and RPV) are not approved by the Food and Drug Administration (FDA) for use in children or adolescents aged <18 years.

[Cabenuva] Cabotegravir and Rilpivirine (IM CAB and RPV)

Adult Dose

- CAB and RPV is a two-drug co-packaged product for intramuscular injection that is FDA approved as a complete regimen for the treatment of HIV-1 in adults with HIV RNA levels <50 copies/mL, on a stable antiretroviral (ARV) regimen, with no history of treatment failure, and no known or suspected resistance to CAB or RPV.
- Oral (PO) lead-in dosing with CAB and RPV for at least 28 days is used to assess tolerability.

Oral Lead-In Dosing

- CAB 30 mg PO and RPV 25 mg PO once daily with a meal for at least 28 days.

Loading Dose to Be Given on Last Day of Oral therapy

- CAB 600 mg (3 mL) and RPV 900 mg (3 mL), given as two separate injections in separate ventrogluteal sites.

Continuation Therapy to Begin 1 Month After the Loading Dose

- CAB 400 mg (2 mL) and RPV 600 mg (2 mL), given as two separate injections in separate ventrogluteal sites once a month with allowance for a ±7-day

Selected Adverse Events

- Depression
- Insomnia
- Headache
- Rash (can be severe and include drug reaction with eosinophilia and systemic symptoms) or hypersensitivity
- Hepatotoxicity
- Altered adrenocorticotropic hormone stimulation test of uncertain clinical significance
- Injection site reactions
- Creatine phosphokinase elevation following intramuscular injection
- Weight gain

Special Instructions

- Coadministering oral RPV with drugs that increase gastric pH may decrease plasma concentrations of RPV. Refer to the RPV package insert for specific instructions regarding use of these products during the oral lead-in dosing.
- If monthly injections are missed or delayed by more than 7 days and oral therapy has not been taken, clinically reassess the patient to determine if resumption of injection dosing remains appropriate. Refer to the package insert for information about managing planned and unplanned missed doses.

administration window.

Patients should be monitored for approximately 10 minutes for post-injection reactions. A 23-gauge, 1½ inch intramuscular needle is recommended for the injection and is provided in the packaging. Longer, 2-inch needles (not included with packaging) should be used in patients with BMIs over 30 kg/m².

- IM CAB and RPV is a complete regimen. Coadministration with other ARV drugs is not recommended.
- When CAB and RPV injections are stopped, residual concentrations may remain measurable for up to 12 months or longer. It is essential to initiate an alternative, fully suppressive ARV regimen no later than 1 month after the final injections of IM CAB and RPV.
- Use CAB and RPV with caution when coadministering it with a drug that has a known risk of Torsades de Pointes (for more information, see CredibleMeds).

Metabolism/Elimination

- CAB is metabolized by uridine diphosphate-glucuronosyl transferase (UGT)1A1.
- RPV is a cytochrome P450 3A substrate.

Dosing in Patients with Hepatic Impairment

- No dose adjustment of CAB or IM CAB and RPV is necessary in patients with mild or moderate hepatic impairment.

Dosing in Patients with Renal Impairment

- RPV decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but it does not affect glomerular filtration.
- No dose adjustment of CAB or IM CAB and RPV is necessary in patients with mild or moderate renal impairment. However, IM CAB and RPV should be used with caution in patients with severe renal impairment or end-stage renal disease. These patients should be monitored more frequently for adverse events.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- *Metabolism:* Cabotegravir (CAB) is metabolized primarily by uridine diphosphate-glucuronosyl t ransferase (UGT)1A1. Drugs that are strong inducers of UGT1A1 may decrease CAB concentrations and decrease effectiveness.
- Rilpivirine (RPV) is a cytochrome P450 (CYP) 3A substrate and RPV concentrations may be affected when administered with CYP3A-modulating medications.
- A patient's medication profile should be carefully reviewed for potential drug interactions before CAB plus RPV is administered.

- CAB and RPV are both highly protein bound and unlikely to be removed by hemodialysis.
- Coadministering oral RPV with drugs that increase gastric pH may decrease plasma concentrations of RPV.
  - Antacids should not be taken less than 2 hours before or less than 4 hours after oral RPV.
  - H2 receptor antagonists should not be administered less than 12 hours before or less than 4 hours after oral RPV.
  - Do not use oral RPV with proton pump inhibitors.
- Rifamycin drugs significantly reduce CAB and RPV plasma concentrations. For patients who are concomitantly receiving rifabutin and RPV, the dose of RPV should be doubled to 50 mg once daily and taken with a meal. Coadministration of the following drugs is contraindicated:
  - Rifampin and RPV
  - Rifampin or rifapentine and CAB
  - Rifabutin and IM CAB and RPV

Major Toxicities

- *More common:* Injection site reactions, insomnia, headache, rash, elevated creatine phosphokinase serum concentrations.
- *Less common (more severe):* Depression or mood changes, suicidal ideation.
- *Rare:* Hepatotoxicity, post-injection reactions including dyspnea, agitation, abdominal cramping, flushing, sweating, oral numbness, and changes in blood pressure
- In studies of adults, 7.3% of patients who were treated with RPV showed a change in adrenal function characterized by an abnormal 250-microgram adrenocorticotropic hormone (ACTH) stimulation test (peak cortisol level <18.1 micrograms/dL). In a study of adolescents, 6 out of 30 patients (20%) developed this abnormality.[1] The clinical significance of these results is unknown.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance database offers a discussion of each mutation.

Pediatric Use

Approval

CAB oral tablets and co-packaged CAB and RPV for injection are not approved by the Food and Drug Administration (FDA) for use in children or adolescents aged <18 years. CAB tablets were approved by the FDA in 2021 for use in adults as part of the oral lead-in prior to beginning injectable intramuscular CAB and RPV or as an oral interim treatment when patients will miss planned injections.[2] CAB and RPV co-packaged extended-release injectable suspensions for intramuscular use were approved for use in adult patients who are virologically suppressed on a stable antiretroviral (ARV) regimen with no history of virologic failure or known resistance affecting either of the component drugs.[3]

Efficacy in Clinical Trials

The safety and efficacy of long-acting injectable (LAI) CAB, an HIV-1 integrase inhibitor, given in combination with LAI RPV, an NNRTI, have been evaluated in a series of clinical trials conducted in adults. To date, all studies have included a 4-week oral lead-in period to assess for toxicity prior to initiating the injectable CAB and RPV regimen.

The Phase 3 ATLAS study randomized stable, virologically suppressed adults to receive either CAB and RPV (N = 308) or continue their oral antiretroviral therapy (ART) (N = 308). Patients assigned to CAB and

RPV initiated therapy with an oral regimen for 4 weeks prior to beginning monthly intramuscular injections. After 48 weeks, 92.5% of patients receiving IM CAB and RPV maintained HIV-1 RNA <50 copies/mL compared to 95.5% of those continuing their initial oral ART. Virologic failure was identified in three study participants receiving injectable ART compared to four receiving oral ART. Adverse events were more common among patients receiving injectable ART; injection site reactions were common, but only 1% withdrew from the study because of these events.[4]

The FLAIR study enrolled 631 treatment-naive adults and initiated treatment with a standard oral ARV regimen consisting of dolutegravir/abacavir/lamivudine for 20 weeks. Those patients with documented HIV-1 RNA <50 copies/mL after 16 weeks were randomized to either continue oral dolutegravir/abacavir/lamivudine (N = 283) or switch to oral CAB and RPV for 4 weeks followed by monthly injections of CAB and RPV (N = 283). After 48 weeks of randomized therapy, 93.6% of patients receiving injectable ART had HIV-1 RNA <50 copies/mL compared with 93.3% of those receiving oral ART. Adverse events were common in both treatment groups, but the injectable ART group experienced more Grade 3 events than the oral ART group (11% vs. 4%) and more drug-related events (28%, excluding injection site reactions, vs. 10%).[5]

These studies demonstrated noninferiority of switching to monthly injectable CAB and RPV compared to continuing oral ART. In both studies, adult patients expressed a high degree of treatment satisfaction and preference for the LAI ART. IMPAACT Study 2017, More Options for Children and Adolescents (MOCHA), is currently in progress to evaluate the safety, tolerability, acceptability, and pharmacokinetics of this injectable regimen in adolescents (NCT03497676).

While not FDA approved for this indication, studies evaluating injectable CAB for use in pre-exposure prophylaxis (PrEP) have reported promising results. HPTN 083 was a randomized, blinded study that evaluated LAI CAB given every 2 months compared to daily oral emtricitabine/tenofovir disoproxil fumerate for HIV PrEP in men and transgender women who have sex with men. Among the 4,566 participants, 2,282 received injectable CAB for up to 3 years (median follow-up 1.4 years). At the time of analysis, 13 HIV infections had been reported in the CAB arm and 39 infections in the oral PrEP arm—a 66% reduction in infections—demonstrating superiority of injectable CAB as PrEP. About 2% of participants receiving injectable CAB discontinued their injections because of an injection-related adverse event.[6] A substudy of HPTN 083 is evaluating injectable CAB as PrEP in adolescent males (NCT04692077). A similarly designed study of LAI CAB (HPTN 084) in women has recently reported superiority to oral PrEP, with an 89% reduction in HIV infections compared to the oral regimen.[7]

Pharmacokinetics

LAI CAB reaches its maximum plasma concentration in adults in about 7 days and has a mean half-life of 5.6 to 11.5 weeks. Measurable levels of CAB can be detected in plasma for up to a year or more. Because of this prolonged drug exposure, it is essential to initiate an alternative, fully suppressive ARV regimen no later than 1 month after the final injections of CAB and RPV to minimize the potential risk of developing viral resistance.[3]

References

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