Cabotegravir

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Cabotegravir (CAB, Vocabria)
Cabotegravir for Intramuscular Injection (CAB, Apretude)
Cabotegravir and Rilpivirine for Intramuscular Injections (IM CAB and RPV, Cabenuva)

Formulations

Tablets

- [Vocabria] Cabotegravir: 30 mg

Single-Dose Vial for Intramuscular Injection

- [Apretude] Cabotegravir 600-mg/3-mL (200-mg/mL) suspension for intramuscular injection for use as HIV pre-exposure prophylaxis only

Co-Packaged Formulation

- [Cabenuva Kit] Cabotegravir 400-mg/2-mL (200-mg/mL) and rilpivirine 600-mg/2-mL (300-mg/mL) suspension for intramuscular injection (each drug packaged in a separate syringe)
- [Cabenuva Kit] Cabotegravir 600-mg/3-mL (200-mg/mL) and rilpivirine 900-mg/3-mL (300-mg/mL) suspension for intramuscular injection (each drug packaged in a separate syringe)

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

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

[Apretude] Cabotegravir for Intramuscular Injection

- Cabotegravir (CAB) 600 mg/3 mL for intramuscular (IM) injection is approved by the U.S. Food and Drug Administration (FDA) for use as HIV pre-exposure prophylaxis (PrEP) in adults and adolescents weighing ≥35 kg; an oral dosing lead-in period of approximately 1 month is optional. See package insert for additional information about dosing and administration of CAB as PrEP; this indication is not addressed in the Pediatric Antiretroviral Guidelines.

[Cabenuva] Cabotegravir and Rilpivirine for intramuscular injection (IM CAB and RPV)

Pediatric Dose

- CAB tablets and co-packaged IM CAB and RPV are not FDA approved for the treatment of HIV in children aged <12 years.

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 IM injection
- Weight gain

Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and *Adult Dose*

- CAB and RPV is a two-drug co-packaged product for IM injection that is FDA approved as a complete regimen for the treatment of HIV-1 in patients 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 lead-in dosing with CAB and RPV for at least 28 days can be used to assess tolerability prior to initiating IM CAB and RPV injections, or patients can proceed directly to IM CAB and RPV on the last day of their current ARV regimen.
- Refer to the package insert for instructions about changing the frequency of IM injections, i.e., from monthly to every-2-month dosing or from every-2-month to monthly dosing.

Oral Lead-In Dosing

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

Dosing for Monthly Administration of IM CAB and RPV

- On the last day of oral lead-in therapy or the current oral ARV regimen, a loading dose of CAB 600 mg (3 mL) and RPV 900 mg (3 mL) should be given as two separate IM injections in separate ventrogluteal sites.
- Continuation therapy of CAB 400 mg (2 mL) and RPV 600 mg (2 mL) IM is given 1 month after the loading dose and once a month thereafter, with allowance for a ±7-day administration window.

Dosing for Every-2-Month Administration of IM CAB and RPV

- To initiate every-2-month dosing, CAB 600 mg (3 mL) and RPV 900 mg (3 mL) should be given as two separate IM injections in separate ventrogluteal sites on the last day of oral lead-in or the current oral ARV regimen and 1 month after the initial injections.
- After these two initiation injections 1 month apart for 2 months, continuation therapy with IM CAB 600 mg (3 mL) and RPV 900 mg (3 mL) is administered every 2 months, with allowance for a ±7-day administration window.

Patients should be monitored for approximately 10 minutes for post-injection reactions. A 23-gauge, 1.5-inch IM 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 a body mass index >30 kg/m^2. The Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV recommends that providers review instructions available with the package insert prior to beginning IM administration of CAB and RPV. In-person training also may be helpful and can be requested from the manufacturer (ViiV).

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.
- IM CAB and RPV is a complete regimen. Coadministration with other ARV drugs is not recommended.
- When IM 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 prolonging the QTc interval or causing Torsades de Pointes (for more information, see CredibleMeds).

Metabolism/Elimination

- CAB is metabolized by uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1).
- 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

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* Cabotegravir (CAB) is metabolized primarily by uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1). 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 oral 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 oral RPV
  - Rifampin or rifapentine and CAB
  - Rifabutin and intramuscular (IM) CAB and RPV

Major Toxicities

- *More common:* Injection site reactions, insomnia, headache, rash, elevated creatine phosphokinase serum concentrations
- *More common:* 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 stimulation test (peak cortisol level <18.1 micrograms/dL). In a study of adolescents, 6 of 30 patients (20%) developed this abnormality.[1] The clinical significance of these results is unknown.
- *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
- *Rare:* RPV drug-induced liver injury has been reported.[2]

Resistance

The International Antiviral Society–USA maintains a list of updated HIV Drug Resistance Mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

CAB oral tablets (Vocabria) and co-packaged CAB and RPV for injection (Cabenuva) are approved by the U.S. Food and Drug Administration (FDA) for the treatment of HIV in children or adolescents aged ≥12 years and weighing ≥ 35 kg (2022) and adults (2021). They are not approved for use in children aged <12 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 IM CAB and RPV or as an oral interim treatment when patients miss planned injections.[1,3] CAB and RPV co-packaged extended-release injectable suspensions for IM use are approved for use in patients (monthly or every 2 months) 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.[1]

In December 2021, the FDA approved CAB IM (Apretude) for HIV pre-exposure prophylaxis (PrEP) in adults and adolescents weighing at least 35 kg; an oral lead-in period of approximately 1 month may be used to assess safety and tolerability but is optional. Refer to the package insert for additional information about dosing and administration,[4] and see the Centers for Disease Control and Prevention Guidelines for Pre-exposure Prophylaxis for the Prevention of HIV in the United States (PDF) for further information about the use of CAB for PrEP.

Efficacy and Pharmacokinetics in Clinical Trials

Clinical Trials in Pediatric Patients 12 years to <18 years

The safety and efficacy of CAB, an HIV-1 integrase inhibitor, given in combination with RPV, a non-nucleoside reverse transcriptase inhibitor (NNRTI), has been characterized in a series of clinical trials conducted in adults, which form the basis for approval.

International Maternal Pediatric Adolescent AIDS Clinical Trials (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 (MOCHA Trial) and has reported initial results leading to FDA approval in this age group. MOCHA evaluated 23 virologically suppressed adolescents on stable therapy who received either a 4-week lead-in of oral CAB followed by IM CAB 600 mg at Week 4 and 400 mg at Weeks 8 and 12 (n = 8) or a lead-in of oral RPV followed by IM RPV 900 mg at Week 4 and 600 mg at Weeks 8 and 12 (n = 13). Injection site reactions were observed but none led to treatment discontinuations. Two adolescents experienced Grade 3 adverse events, one due to insomnia (CAB arm) and one due to hypersensitivity reaction to oral RPV which led to discontinuation.[5] In a concurrent assessment of adolescent and parental experiences with IM treatment in MOCHA, overall perceptions of the injectable treatment were favorable. Of the 21 adolescents who received all three study injections, >90% “definitely” or “probably” wanted to continue IM treatment.[6] It should be noted, however, that none of the MOCHA participants received both monthly IM CAB and monthly IM RPV as a dual complete regimen, and

clinical experience with this product remains very limited. The Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV notes that significant questions remain regarding the use of IM CAB and RPV in pediatric patients, including whether an oral lead-in is beneficial in the adolescent population, whether there are additional adverse effects specific to the pediatric population, whether the use of a two-drug nucleoside-sparing regimen for children with significant ARV treatment history is appropriate, and what potential implementation challenges might exist.

Clinical Trials in Adults

The Phase 3 Antiretroviral Therapy as Long-Acting Suppression (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 IM injections. The initial assessment at 48 weeks demonstrated that switching to monthly IM CAB and RPV was noninferior to continuing a three-drug oral therapy. After 48 weeks, participants were allowed to transition to injections every 2 months in a follow-up study (ATLAS-2M, see below); 52 patients remaining on the original ATLAS study were included in the 96-week analysis. 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.[7] The ATLAS-2M trial randomized participants to monthly IM CAB 400 mg and RPV 600 mg (n = 523) or every-2-month injections of CAB 600 mg and RPV 900 mg (n = 522); it enrolled both new patients and those continuing from the ATLAS trial. After 96 weeks, the every-2-month injections were noninferior to monthly injections, with 11 (2%) confirmed virologic failures in the every-2-month injection group and 6 (1%) in the monthly injection group. No new safety signals were identified, and the rate of injection site reactions—the most common adverse event—were similar across treatment arms. Of those failing the every-2-month injection regimen, a majority had NNRTI resistance–associated mutations.[8]

The First Long-Acting Injectable Regimen (FLAIR) study enrolled 631 treatment-naive adults and initiated treatment with a standard oral ARV regimen consisting of dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) for 20 weeks. Those patients with documented HIV-1 RNA <50 copies/mL after 16 weeks were randomized to either continue oral DTG/ABC/3TC (n = 283) or switch to oral CAB and RPV for 4 weeks, followed by monthly injections of CAB and RPV (n = 283). After 96 weeks of randomized therapy, nine participants (3.2%) in each arm had HIV RNA >50 copies/mL. Adverse events were common in both treatment groups, but adverse events leading to withdrawal from the study were observed in only 14 (5%) participants in the IM CAB and RPV group and 4 (1%) in the oral standard care group. Injection site reactions were the most common adverse events, reported by 245 (88%) participants in the IM CAB and RPV group, and lasted a median of 3 days.[9] The FLAIR study was extended to include an assessment of switching those participants remaining in the oral ARV arm after 120 weeks to IM CAB and RPV either with or without the initial oral lead-in phase. There were no differences between the lead-in group and the direct-to-injection group in terms of safety, tolerability, or efficacy through an additional 24 weeks on the study.[10]

These studies demonstrated noninferiority of switching to monthly IM CAB and RPV compared to continuing oral ART. In all studies, adult patients expressed a high degree of treatment satisfaction and preference for the IM CAB and RPV regimen. Although documented virologic failure with the IM CAB and RPV regimen has been rare to date, investigators have attempted to assess the baseline factors associated with treatment failure. In a multivariate analysis of the adult IM CAB and RPV Phase 3 trials, presence of at least two baseline factors of RPV resistance–associated mutations, HIV-

1 subtype A6/A1, and body mass index >30 kg/m^2 was associated with increased risk of virologic failure at 48 weeks.[11]

Pharmacokinetics

IM 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 longer. Due to 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.[1] The PK profiles observed in adolescents enrolled in MOCHA were comparable to those observed in adults receiving monthly IM CAB and RPV in the ATLAS and FLAIR studies described above.[5]

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