Cabotegravir plus Rilpivirine (Cabenuva)
Extended Release Injectable Suspension

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**Indication**

- Replace antiretroviral regimen in persons with HIV RNA <50 copies/mL
- On stable antiretroviral regimen
- No history of treatment failure
- No known or suspected resistance to cabotegravir or rilpivirine
Cabotegravir and Rilpivirine
Oral and Injectable Preparations

**Oral: Lead-In for 1 Month**

Cabotegravir + Rilpivirine
- Cabotegravir: 30 mg
- Rilpivirine: 25 mg

**Injection: Loading Dose & Monthly**

Cabotegravir + Rilpivirine
- Cabotegravir: 200 mg/mL
- Rilpivirine: 300 mg/mL

Source: Cabenuva Prescribing Information
**Cabotegravir and Rilpivirine (Cabenuva) Dosing Schedule**

**Oral Lead-In x 1 month (≥28 days)**
Cabotegravir 30 mg daily + Rilpivirine 25 mg daily

**Initiation Injections (x 1)**
Cabotegravir (600 mg): 3 mL IM + Rilpivirine (900 mg): 3 mL IM

**Continuation Injections (Monthly)**
Cabotegravir (400 mg): 2 mL IM + Rilpivirine (600 mg): 2 mL IM

*Administer injections at opposite gluteal sites (or at least 2 cm apart) and give both during the same visit.*

Source: Cabenuva Prescribing Information
Oral Lead in

Cabotegravir

Initiation Injection

Continuation Injections*

Rilpivirine

*Patients may receive cabotegravir and rilpivirine up to 7 days before or after the date of the scheduled monthly injection dosing visit.

Source: Cabenuva Prescribing Information
Summary of Key Phase 3 Studies
Cabotegravir and Rilpivirine Long-Acting Injectable

- Phase 3 Trials in Treatment Experienced
  - ATLAS: Switch to monthly IM CAB-RPV or stay on 3-drug ART
  - ATLAS-2M: switch to IM CAB-RPV every 4 or 8 weeks

- Phase 3 Trials in Treatment Naïve
  - FLAIR: IM CAB-RPV every month versus oral DTG-ABC-3TC
Long-Acting Cabotegravir and Rilpivirine for HIV Maintenance

ATLAS Study
Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance
ATLAS Study: Design

**Study Design:**

- **Background**: Phase 3, randomized, open-label trial assessing IM cabotegravir plus IM rilpivirine after oral induction for adults taking a 3-drug oral antiretroviral therapy regimen

- **Inclusion Criteria**
  - Age ≥18 years
  - Taking 2NRTI + INSTI, NNRTI, or PI
  - Stable ARV regimen ≥6 months
  - HIV RNA <50 copies/mL ≥6 months
  - No history of virologic failure
  - No INSTI or NNRTI resistance (K103N allowed)
  - No chronic hepatitis B

**Lead-In**

- IM CAB + RPV every 4 weeks (n = 308)

**Maintenance**

- Week 4
- Week 48
- Oral CAB + RPV
- IM CAB + RPV every 4 weeks (n = 308)
- Continue 3-drug Oral Antiretroviral Therapy (n = 308)

Abbreviations: CAB = cabotegravir; RPV = rilpivirine

Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance
ATLAS Study: Results

Weeks 48: Virologic Response by FDA Snapshot Analysis

HIV RNA < 50 copies/mL (%)

IM Cabotegravir + Rilpivirine

3-Drug Oral ART

HIV RNA ≥50 copies/mL at 48 weeks: 1.6% CAB + RPV, 1.0% 3-drug oral ART

Cabotegravir and Rilpivirine Every 2 Months for HIV Maintenance

ATLAS-2M
Cabotegravir and Rilpivirine Every 2 Months for HIV Maintenance

ATLAS-2M Study: Design

**Study Design:**

- **Background:** Phase 3, randomized, open-label trial assessing IM CAB-RPV maintenance ART administered every 8 weeks versus every 4 weeks

- **Inclusion Criteria**
  - Age ≥18 years
  - Taking an uninterrupted first or second oral standard of care ART regimen for ≥6 months
  - HIV RNA <50 copies/mL ≥6 months at screening and >2x in prior year
  - No history of virologic failure
  - No INSTI or NNRTI resistance (K103N allowed)

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<thead>
<tr>
<th>Lead-In</th>
<th>Maintenance</th>
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<tr>
<td>Week 4</td>
<td>Week 48</td>
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**Oral CAB + RPV**

- IM CAB 600 mg + RPV 900 mg (two separate 3 mL injections) Every 8 weeks (n = 522)

- IM CAB 400 mg + RPV 600 mg (two separate 2 mL injections) Every 4 weeks (n = 523)

*Some individuals enrolled after participating in the ATLAS trial; individuals already receiving IM CAB + RPV through ATLAS did not require oral lead-in for ATLAS-2M

Cabotegravir and Rilpivirine Every 2 Months for HIV Maintenance
ATLAS-2M Study: Results

Weeks 48: Virologic Response by FDA Snapshot Analysis

HIV RNA <50 copies/mL (%)

- IM CAB + IM RPV every 8 weeks: 491/516 (94%)
- IM CAB + IM RPV every 4 weeks: 484/514 (93%)

HIV RNA ≥50 copies/mL at 48 weeks: 9/522 (2%) in q8-week arm, 5/523 (1%) in q4-week arm

Long-Acting Cabotegravir and Rilpivirine after Oral Induction

FLAIR Study
Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction FLAIR Study: Design

**Study Design:**

- **Background:** Phase 3, randomized, open-label, trial assessing IM CAB + RPV after oral induction for treatment-naïve adults

- **Inclusion Criteria**
  - Age ≥18 years
  - Antiretroviral-naïve
  - HIV RNA ≥1,000 copies/mL
  - Any CD4 cell count
  - No chronic hepatitis B
  - No NNRTI resistance

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<tr>
<th>Induction Phase</th>
<th>Maintenance Phase</th>
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<tr>
<td>Week 0</td>
<td>Week 16</td>
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*Randomized 1:1

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<tr>
<th>Oral CAB + RPV</th>
<th>IM CAB + RPV every 4 weeks (n = 283)</th>
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<tr>
<td>DTG-ABC-3TC oral daily (n = 603)</td>
<td>Continue Oral DTG-ABC-3TC (n = 283)</td>
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*Randomized if HIV RNA <50 copies/mL at week 16

Oral lead in dosing: cabotegravir 30 mg daily and rilpivirine 25 mg daily x 4 weeks
Loading injections: cabotegravir 600 mg IM and 900 mg rilpivirine IM x 1
Maintenance injections: cabotegravir 400 mg IM and 600 mg rilpivirine IM monthly

Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction FLAIR Study: Results

Weeks 48: Virologic Response by FDA Snapshot Analysis

- **IM CAB + RPV**: 93.6%
  - 265/283

- **Oral DTG-ABC-3TC**: 93.3%
  - 264/283

*HIV RNA ≥50 copies/mL at 48 weeks: 2.1% CAB-RPV, 2.5% DTG-ABC-3TC

Adverse Effects
Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction
FLAIR Study: Injection Site Reactions

Resistance
Emergence of Drug Resistance on Cabotegravir + Rilpivirine
Pooled analysis from FLAIR, ATLAS, ATLAS-2M

- 7/591 (1.2%) with virologic failure (HIV RNA ≥200 copies/mL)
- 5 of 7 had baseline HIV-1 subtype A1 and L74I polymorphic accessory mutation
- 2 of 7 had baseline HIV-1 subtype AG and without L74I mutation
- 6 of 7 from Russia (prevalence of HIV-1 subtypes A, A1, AG high in Russia)*
- HIV-1 subtypes A, A1, AG are uncommon in U.S. (B subtype dominant)
- 2 of 7 developed Q148R mutation
- 1 of 7 developed N155H

*HIV-1 subtypes A, A1, AG are uncommon in United States (HIV-1 B subtype dominant)
Special Dosing Considerations
Timing Flexibility of Cabotegravir and Rilpivirine Injections

What if they arrive 3 days early for their injection?
What if they are 5 days late for their injection?
Timing Flexibility of Cabotegravir and Rilpivirine Injections

What if they arrive 3 days early for their injection?
What if they are 5 days late for their injection?

Patients may receive cabotegravir and rilpivirine up to 7 days before or after the date of the scheduled monthly injection dosing visit.
Planned Missed Cabotegravir and Rilpivirine Injections
(Time from last injections is greater than 1 month + 7 days)

What if they are traveling out of country and are planning to miss at least 1 injection?

*Oral therapy = cabotegravir 50 mg plus rilpivirine 25 mg, both taken once daily with food
Planned Missed Cabotegravir and Rilpivirine Injections (Time from last injections is greater than 1 month + 7 days)

What if they are traveling out of country and are planning to miss at least 1 injection?

• Take daily oral therapy to replace up to 2 consecutive monthly injection visits.
• Start oral therapy* approximately 1 month after the last injection doses.
• Continue oral therapy* until the day injection dosing is restarted.

*Oral therapy = cabotegravir 50 mg plus rilpivirine 25 mg, both taken once daily with food
Cabotegravir and Rilpivirine

Dosing Schedule with Oral Bridge (up to 2 months)

*Patients may receive cabotegravir and rilpivirine up to 7 days before or after the date of the scheduled monthly injection dosing visit.

Source: Cabenuva Prescribing Information
Oral Lead in

Cabotegravir

Initiation Injection

Rilpivirine

Continuation Injections*

Gap

Oral Bridge

Months on Treatment

0 1 2 3 4 5 6

*Patients may receive cabotegravir and rilpivirine up to 7 days before or after the date of the scheduled monthly injection dosing visit.

Source: Cabenuva Prescribing Information
Timing Flexibility of Cabotegravir and Rilpivirine Injections

What if they temporarily drop out of care and miss >1 injections?
Recommendation for Resumption of Injections After Missed Injections (>1 month + 7 days)

- If oral therapy has not been taken…
  - Reassess to ensure resumption of injections is appropriate

- Time Since last injection ≤2 months
  - Resume with 2 mL standard monthly dosing

- Time Since last injection >2 months
  - Resume with 3 mL x 1 initiation dose, followed by 2 mL monthly dose
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