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New Drug Evaluation: Cabotegravir/Rilpivirine Inj; Cabotegravir Na Tab

Date of Review: August 2021
Generic Name: Cabotegravir/rilpivirine inj; Cabotegravir sodium tab

End Date of Literature Search: 05/31/2021
Brand Name (Manufacturer): Cabenuva, Vocabria (GlaxoSmithKline)
Dossier Received: yes

Research Questions:

1. How does the Human Immunodeficiency Virus (HIV-1) viral suppression differ between the monthly 2-drug antiretroviral drug regimen of extended-release injectable cabotegravir and rilpivirine from standard, guideline-recommended 3-drug antiretroviral regimens?
2. Do adverse effects and other harms differ between the monthly 2-drug antiretroviral drug regimen of extended-release injectable cabotegravir and rilpivirine from standard, guideline-recommended 3-drug antiretroviral regimens?
3. Are there subgroups based on demographic characteristics in which the monthly 2-drug antiretroviral drug regimen of extended-release injectable cabotegravir and rilpivirine may differ in safety or efficacy from standard, guideline-recommended 3-drug antiretroviral regimens?

Conclusions:

- Low quality evidence demonstrates that monthly injections of cabotegravir and rilpivirine are non-inferior to standard, 3-drug antiretroviral drug regimens in adults with HIV who are virologically stable and suppressed (HIV-1 RNA <50 copies/mL). The phase 3 trials were well designed, but the evidence was downgraded because of the open-label design and the caveat that uncertainty remains about the durability of these benefits beyond 48 weeks of treatment.[1-3]
- Low quality evidence also demonstrates that extended-release injectable cabotegravir and rilpivirine is associated with similar harms as other antiretroviral regimens. The proportion of patients in the extended-release injectable group who experienced adverse effects was greater than in the oral group which was partly attributable to various injection site reactions. Injection site pain was the most commonly reported injection site reaction, which occurred in up to 90% of patients; incidence decreased over the 48-week study periods.[1-3]
- Rates of virologic failure were higher for the extended-release injectable cabotegravir and rilpivirine regimen versus 3-drug oral therapy in females, patients with a higher baseline body mass index (BMI ≥30 kg/m^2) and females with a higher baseline BMI (BMI ≥30 kg/m^2); evidence for these subgroup analyses is insufficient and further evaluation is warranted.[1] The evidence for safety and efficacy of extended-release injectable cabotegravir and rilpivirine is also insufficient among patients who have a baseline K103N substitution, acquired integrase strand transfer inhibitor or non-nucleoside reverse transcriptase inhibitor resistance, or with history of treatment failure.[1]
- It is unclear whether there is an unmet clinical need for monthly antiretroviral (ARV) injectable regimens given that all oral ARV treatments options are currently on the Oregon Health Plan (OHP) Preferred Drug List (PDL). However, some patients may prefer the convenience of monthly injections versus daily oral treatment and there is potential, albeit without evidence to date, that this injectable regimen may improve adherence in specific patients.

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Recommendations:

- Maintain preferred status of cabotegravir tablets and co-packaged injectable cabotegravir and rilpivirine suspension on the OHP FFS PDL.

Background:

Chronic HIV infection has been effectively managed with diligent, life-long adherence to combination oral ARV treatment. The current ARV treatment options approved by the FDA include 29 individual ARV drugs, excluding combination products, and 2 drugs (cobicistat and ritonavir) which inhibit metabolic enzymes and increase the exposure of ARVs.[1] However, optimal management of HIV is complex and is based on individual patient needs. One opportunity to simplify ARV regimens is to extend the dosing interval with the use of long-acting ARV agents. On January 21, 2021, the U.S. Food and Drug Administration (FDA) approved the first complete extended-release (ER) injectable ARV regimen, cabotegravir and rilpivirine, in adults with HIV who are virologically stable and suppressed (HIV-1 RNA <50 copies/mL).[4] The co-packaged kit contains separate ER injectable suspensions of cabotegravir and rilpivirine (CABENUVA).[4] Cabotegravir was also developed as an oral tablet (VOCABRIA) to use in combination with oral rilpivirine.[5] In theory, monthly injections of a 2-drug ARV regimen could reduce the complexity of daily oral ARV treatment and decrease the risk of adverse effects of the third drug in a standard 3-drug ARV regimen.[1]

Cabotegravir is a second-generation integrase strand transfer inhibitor (INSTI) structurally similar to dolutegravir. Rilpivirine is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) already approved by the FDA. Both INSTIs and NNRTIs are included in most standard, guideline-recommended 3-drug ARV regimens.[6]

The cabotegravir and rilpivirine regimen consists of 2 separate once-monthly injections of cabotegravir and rilpivirine administered by a healthcare professional preceded by an oral lead-in trial of at least 28 days during which oral cabotegravir and rilpivirine tablets are taken in combination to ensure patient tolerability and verify virologic suppression (HIV-1 RNA <50 copies/mL).[4,5] Cabotegravir tablets are indicated either as an oral lead-in to assess tolerability of cabotegravir before initiating cabotegravir and rilpivirine injections, or as oral bridging therapy for missed cabotegravir and rilpivirine injections.[5]

The recommended dosage for the cabotegravir plus rilpivirine regimen consists of 3 distinct phases:

1. Oral lead-in phase: One cabotegravir 30 mg tablet and one rilpivirine 25 mg tablet taken together once daily for approximately one month;
2. Single initiation injections of cabotegravir plus rilpivirine (600 mg/900 mg, 3 mL each in separate gluteal sites) on the last day of the oral lead-in phase; and
3. Monthly maintenance injections of cabotegravir plus rilpivirine (400 mg/600 mg, 2 mL each in separate gluteal sites).

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Cabotegravir and rilpivirine was studied in two randomized, open-label, multi-centered, active-controlled, noninferiority phase 3 trials: ATLAS (Antiretroviral Therapy as Long Acting Suppression; NCT02951052) in adult patients who were already stable on oral ARV therapy, and FLAIR (First Long-Acting Injectable Regimen; NCT02938520) in ARV-naïve adult patients.[2,3] Together, the trials enrolled 1,182 patients. Patients in both trials were virologically suppressed before randomization and then either switched to cabotegravir plus rilpivirine or continued current oral 3-drug ARV therapy.[2,3] In both trials, the ER cabotegravir and

rilpivirine injectable regimen demonstrated noninferiority to the comparative oral ARV regimens based on the proportion of patients with a serum HIV-1 RNA level of 50 copies per milliliter or higher at week 48 using a noninferiority margin of 6%.[2,3]

The ATLAS trial was a 48-week, randomized, multi-center, open-label, non-inferiority, parallel-group trial that enrolled HIV-infected adult patients 18 years of age or older who were virologically suppressed on oral ARV therapy.[2] The purpose of the ATLAS trial was to establish whether switching to ER injectable cabotegravir and rilpivirine was noninferior to continuation of current oral therapy based on virologic response.[2] Key pertinent details and analysis of the trial are presented in **Table 1**. Eligible patients were randomly assigned in a 1-to-1 ratio to either continue their current oral ARV regimen or switch to cabotegravir and rilpivirine.[2] Acceptable current ARV regimens included two NRTIs plus one of the following drugs: an INSTI, an NNRTI, a boosted PI, or unboosted atazanavir.[2] Patients in the ER injectable therapy group first received 30 mg oral cabotegravir and 25 mg oral rilpivirine once daily with food for the first 4 weeks (oral lead-in phase) to assess safety and adverse effects.[2] After their eligibility for ER injectable therapy was confirmed, patients received an initial dose of 600 mg cabotegravir and 900 mg rilpivirine (3 mL injections of each drug into the gluteus muscle), followed by 400 mg cabotegravir and 600 mg rilpivirine (2 mL injections of each drug into the gluteus muscle) every 4 weeks through week 52 of the maintenance phase of the trial.[2] Oral cabotegravir and rilpivirine was available as bridge therapy for patients who were unable to attend their scheduled clinic visit within the permitted window (21 to 28 days after the previous injection for injections 2 and 3; 21 to 35 days thereafter).[2]

The primary endpoint was the percentage of patients with plasma HIV-1 RNA levels of 50 copies per milliliter or higher at week 48.[2] The key secondary efficacy endpoint was the percentage of patients with plasma HIV-1 RNA levels of less than 50 copies per milliliter at week 48.[2] Other endpoints included confirmed virologic failure (two consecutive plasma HIV-1 RNA measurements ≥200 copies/mL) and patient satisfaction with their current ARV therapy assessed at baseline and at weeks 24 and 44 with the 12-item HIV Treatment Satisfaction Questionnaire, status version (HIVTSQs).[2] The HIVTSQs assesses change in within-participant treatment satisfaction over time and is a variation of the HIV Medication Questionnaire, which was adapted from the Renal Medication Questionnaire.[7] Of note, no minimal clinically important difference has been established for the HIVTSQs in patients with HIV-1 infection.[8]

In the ATLAS trial, HIV-1 RNA levels of 50 copies per milliliter or higher at week 48 were found in 5 patients (1.6%) in the ER injectable therapy group and 3 patients (1.0%) in the oral therapy group (difference, 0.6% [95% confidence interval [CI], -1.1 to 2.4%]).[2] In analysis of the primary endpoint, non-inferiority of the ER injectable therapy was concluded if the upper limit of the CI for the difference between ER injectable therapy and oral therapy in the percentage of patients with an HIV-1 RNA level of 50 copies per millimeter or higher at week 48 was less than 6 percentage points.[2] Thus, these results met the pre-specified noninferiority criterion for the primary endpoint.[2] The ER injectable therapy was also noninferior to oral therapy with respect to the key secondary endpoint of an HIV-1 RNA level of less than 50 copies per milliliter at week 48 (92.5% and 95.5%, respectively; adjusted difference, -3.0%; 95% CI, -6.7 to 0.7%), which met the pre-specified noninferiority criterion of 10 percentage points.[2] (Note that the sum of these endpoints in these studies do not equal 100% because virologic data were not available to some patients who withdrew from study early). No evidence of heterogeneity in these between-group differences was found across randomization strata or according to baseline patient characteristics.[2] Results were also consistent in the per-protocol population (HIV-1 RNA level ≥50 copies/mL, 1.4% for long-acting therapy vs. 1.0% for oral therapy, difference 0.3% [95% CI, -1.4 to 2.1%]).[2]

Patients in the ER injectable therapy group reported greater improvement from baseline in treatment satisfaction than patients in the oral therapy group, according to the HIVTSQs. The particular HIVTSQs used in this trial was a 12-item questionnaire with a total score range from 0 (very dissatisfied) to 66 (very satisfied); both groups had a baseline HIVTSQs score of about 55 points. At 44 weeks, the adjusted mean increase in score from baseline was 5.68 points higher (95% CI, 4.37 to 6.98; $p<0.001$) in the long-acting therapy group than in the oral therapy group.[2]

Upon completion of the 52-week maintenance phase of the ATLAS trial, patients with plasma HIV-1 RNA less than 50 copies per milliliter in both the ER injectable therapy group and the oral therapy group had the option of continuing to participate in the extension phase of the trial, which was also funded by ViiV Healthcare and Janssen.[9] In this open-label, non-inferiority extension trial, 1,045 patients were randomized to cabotegravir 600 mg and rilpivirine 900 mg every 8 weeks or cabotegravir 400 mg and rilpivirine 600 mg every 4 weeks. The primary endpoint was the percentage of patients with HIV-1 RNA of 50 copies per milliliter or greater at 48 weeks, with a non-inferiority margin of 4 percentage points. The HIV-1 RNA results from the group which received cabotegravir and rilpivirine every 8 weeks was non-inferior to the group that received cabotegravir and rilpivirine every 4 weeks (HIV-1 RNA ≥50 copies/mL: 2% vs. 1%, respectively) with an adjusted treatment difference of 0.8 percentage points (95% CI, -0.6 to 2.2%). There were 8 cases (2%) of confirmed virologic failure (HIV-1 RNA ≥200 copies/mL) in 8-week group and 2 cases (<1%) of confirmed virologic failure in the 4-week group.[9]

The FLAIR trial was also a 48-week, randomized, multi-center, open-label, non-inferiority, parallel-group trial.[3] Eligible patients were adults 18 years of age or older who had not previously received ARV therapy and had a plasma HIV-1 RNA level of 1000 copies per milliliter or higher at screening.[3] Key pertinent details and analysis of the trial are presented in **Table 1**. Patients received oral induction therapy with a fixed-dose combination of 50 mg of dolutegravir, 600 mg of abacavir, and 300 mg of lamivudine once daily (or dolutegravir with a non-abacavir NRTI backbone) for 20 weeks to lower their viral load below 50 copies per milliliter.[3] Patients who achieved viral suppression with a plasma HIV-1 RNA level less than 50 copies per milliliter after 16 weeks of induction therapy were randomly assigned, in a 1-to-1 ratio, to either continue the current oral therapy during the maintenance phase or switch to ER injectable cabotegravir and rilpivirine for at least 100 weeks (but all primary and secondary endpoints were assessed at 48 weeks).[3] Patients in the ER injectable cabotegravir and rilpivirine group received oral lead-in therapy with 30 mg cabotegravir and 25 mg of rilpivirine once daily for 4 weeks to assess safety and adverse effects of the drugs before transitioning to ER injectable therapy.[3] At week 4, patients received a loading injection of 600 mg cabotegravir and 900 mg of rilpivirine administered into the gluteus muscle.[3] Maintenance injections of 400 mg of cabotegravir and 600 mg or rilpivirine were administered within a 21- to 28-day window, and bridging therapy with oral cabotegravir and rilpivirine was available for patients unable to attend a visit for their monthly injections.[3]

The primary and key secondary endpoints were the same as the ATLAS trial.[2,3] One minor difference was the use of the HIV Treatment Satisfaction Questionnaire, change version (HIVTSQc) in the FLAIR trial instead of the HIVTSQs (status version) used in the ATLAS trial.[2,3] The HIVTSQc evaluated patient satisfaction with *current* ARV therapy compared with induction therapy; total scores range from −33 (much less satisfied now) to 33 (much more satisfied now).[3] As with HIVTSQs, no minimal clinically important difference has been established for the HIVTSQc in patients with HIV-1 infection.[8]

For the primary endpoint, an HIV-1 RNA level of 50 copies per milliliter or higher at week 48 was found in 6 patients (2.1%) who received ER injectable therapy and in 7 patients (2.5%) who received oral therapy (difference of -0.4%; 95% CI, -2.8 to 2.1%), which met the pre-specified noninferiority criterion for the primary endpoint.[3] Similarly, ER injectable therapy was noninferior to oral therapy with regard to the key secondary end point of the percentage of patients with an HIV-1 RNA level of less than 50 copies per milliliter at week 48 (93.6% and 93.3%, respectively; difference of 0.4%; 95% CI, -3.7 to 4.4%), which met the pre-specified noninferiority criterion of 10 percentage points.[3] Results for the primary and key secondary endpoints were also consistent in the per-protocol population.[3] No evidence of heterogeneity in these between-group differences was found across randomization strata or according to other baseline characteristics.[3]

At week 48, the HIVTSQc total score for patient satisfaction with current treatment as compared with induction treatment was higher in the ER injectable therapy group than in the oral therapy group (adjusted mean difference, 4.1 points; 95% CI, 2.8 to 5.5 points).[3] No difference was found in the mean adjusted HIVTSQs scores at week 44 between the two groups (0.7 points; 95% CI, -0.4 to 1.9 points; p=0.22).[8] Overall, a strong and consistent finding was not found for any of the quality of life outcomes across the ATLAS and FLAIR trials.[8]

Overall, the treatment groups in both phase 3 trials had comparable virologic responses.[2,3] The primary endpoint for both trials, defined as an HIV-1 RNA level greater than 50 copies per milliliter, was found in 1.6% and 1.0% of patients in the cabotegravir and rilpivirine and oral ARV regimens, respectively, of the ATLAS trial; the ARV-naïve patient population in the FLAIR trial found 2.1% and 2.5% of patients in the cabotegravir and rilpivirine and oral ARV regimens met the primary endpoint, respectively.[2,3] Based on a 6% noninferiority margin, the results demonstrated that ER injectable cabotegravir and rilpivirine was noninferior to continuation of oral ARV therapy, with between-group treatment differences of 0.6% (95% CI, -1.1 to 2.4%) in the ATLAS trial and -0.4% (95% CI, -2.8% to 2.1%) in the FLAIR trial.[2,3] Noninferiority for the primary endpoints was also observed in the per-protocol populations.[2,3] The proportion of patients with an HIV-1 RNA viral load less than 50 copies per milliliter at week 48 was 93% and 95% in the ER injectable cabotegravir and rilpivirine group and 94% and 93% in the oral ARV group in the ATLAS and FLAIR trials, respectively.[2,3] A few further considerations may be noted:

- None of the virologic outcomes showed a statistically significant difference by relevant subgroups (sex at birth, baseline HIV-1 RNA level, and CD4+ cell count).[2,3]
- Subgroup analyses showed virologic failure rates (HIV-1 RNA ≥50 copies/mL) were higher for the cabotegravir and rilpivirine groups versus the oral groups among females, higher baseline body mass index (BMI ≥30 kg/m^2) and females with a higher baseline BMI (BMI ≥30 kg/m^2).[1] Overall, 3 female subjects with higher baseline BMI had virologic failure in the pooled cabotegravir and rilpivirine groups, compared to none in the pooled control groups. These differences cannot be interpreted as statistically significant nor clinically relevant, but the FDA advised that the durability of a 2-drug regimen beyond 48 weeks to maintain virologic suppression remains unknown; therefore, additional evaluation for differences in outcome among these subgroups is warranted.[1]
- Limited data are available on the durability of a 2-drug regimen to maintain virologic suppression beyond 48 weeks.
- The open-label nature of the trials and lack of validation of a minimum clinically important difference for the HIVTSQ endpoints prohibit any conclusions for quality of life outcomes.
- Resistance to the study drugs occurred infrequently; 6 cases of treatment-emergent resistance to cabotegravir or rilpivirine were identified between the two trials.[2,3] The efficacy of ER injectable cabotegravir and rilpivirine is unknown among patients who have a baseline K103N substitution, acquired INSTI or NNRTI resistance, or with history of treatment failure.[1]
- Adherence to both injectable and oral regimens exceeded 90 percent with low attrition bias across studies.[2,3]
- Study investigators and authors were employees of the drug sponsors and performed statistical analyses and trial data interpretation.
- The U.S. Department of Health and Human Services HIV treatment guideline recently added ER injectable cabotegravir and rilpivirine as a recommended treatment option in adults currently on oral ARV therapy with documented viral suppression.[6]

It should also be noted that a supportive phase 2b trial was conducted which found that ER injectable cabotegravir and rilpivirine was as effective as a once daily three drug oral cabotegravir-based therapy in maintaining viral suppression in adult patients with HIV-1 infection not previously treated with ARV therapy in the Long-Acting antireTroviral Treatment Enabling (LATTE)-2 trial (NCT02120352).[10]

The LATTE-2 trial was a phase 2b, randomized, multi-center, open-label, non-inferiority trial that compared the efficacy and safety of ER injectable cabotegravir and rilpivirine, administered intramuscularly every 4 weeks or every 8 weeks, with that of oral cabotegravir plus abacavir-lamivudine, through 96 weeks for patients who had achieved successful HIV-1 viral suppression with oral cabotegravir, abacavir and lamivudine during a 20-week induction period.[10] Key pertinent details and analysis of the trial are presented in **Table 1**.

Eligible patients who entered the induction period received a regimen of oral cabotegravir 30 mg, abacavir 600 mg and lamivudine 300 mg once daily for 20 weeks.[10] Rilpivirine 25 mg once daily was added 4 weeks before randomization (week 16 of the induction period) and continued until the first injection clinic visit (day 1 of maintenance phase).[10] Patients who tolerated the induction period regimen and achieved plasma HIV-1 RNA less than 50 copies per milliliter at week 16 of the induction period were eligible to enter the maintenance phase.[10] At day 1 of the 96-week maintenance phase, patients were randomly assigned to receive ER injection of cabotegravir 400 mg plus rilpivirine 600 mg (two 2 mL injections) every 4 weeks or cabotegravir 600 mg plus rilpivirine 900 mg (two 3 mL injections) every 8 weeks, or to continue receiving oral cabotegravir, abacavir and lamivudine once daily. Both 4-week and 8-week ER injectable regimens included an initial loading dose of cabotegravir 800 mg.[10]

The primary endpoints were the proportion of patients with HIV-1 RNA less than 50 copies per milliliter at week 32 of the maintenance phase and the proportion of patients with protocol-defined virologic failure (two consecutive plasma HIV-1 RNA measurements of ≥200 copies/mL).[10] Key secondary endpoints included the proportion of patients with plasma HIV-1 RNA less than 50 copies per milliliter at week 96.[10] In addition, treatment satisfaction was measured using the HIVTSQs, which was completed by patients at regular intervals throughout the study.[10] The study hypothesis for the primary endpoint that evaluated the proportion of patients with HIV-1 RNA less than 50 copies per milliliter at week 32 was that the injectable regimens were comparable to the oral regimen, defined as a proportion difference no greater than 10%.[10] A posterior probability of at least 90% was prespecified as the decision rule for claiming comparability for each comparison.[10]

At 32 weeks following randomization, both groups who received injectable dosing regimens met primary criteria for comparability in viral suppression relative to the oral comparator group.[10] Viral suppression was maintained at 32 weeks in 51 (96%) of 56 patients in the oral group, 108 (94%) of 115 patients in the 4-week group (difference 2.8% [-5.8% to 11.5%] vs. oral regimen), and 109 (95%) of 115 patients in the 8-week group (difference 3.7% [-4.8% to 12.2%] vs. oral regimen).[10] At week 96, viral suppression was maintained in 47 (84%) of 56 patients in the oral group, 100 (87%) of 115 patients in the 4-week group, and 108 (94%) of 115 patients in the 8-week group.[10] Three patients (1%) experienced protocol-defined virologic failure (two in the 8-week group; one in the oral treatment group).[10] At week 96, patients reported high levels of satisfaction on the HIVTSQs across all 3 groups, with 246 (97%) of 254 patients selecting a score of 5 or 6 on a 6-point version of this satisfaction scale.[10] A similar percentage of patients in each injectable group (99/100 in the 4-week group and 107/108 in the 8-week group) reported they would be highly satisfied to continue their current regimen, while a lower percentage would elect to continue on oral dosing (78%; 36 of 46 patients in the oral treatment group).[10] In a post-hoc analysis, patients in the 4-week, 8-week and oral treatment groups reported a median HIVTSQs total score of 63.5, 65.0 and 60.0 at week 96 (post hoc $p<0.001$).[7] Selection and performance biases were introduced with these patient satisfaction outcomes, however, because patients who discontinued the study for any reason before week 96 did not complete the questionnaire at this timepoint.[10]

Clinical Safety:

In the ATLAS trial, 95% of patients in the ER injectable cabotegravir and rilpivirine group and 71% of patients in the oral group reported at least one adverse event (see **Table 1**).[2] The differences could be attributed to injection-site reactions, which occurred in 83% of patients in the injection group.[2] Among the patients who received ER injection therapy, 99% of injection-site reactions were of mild or moderate severity; no life-threatening or fatal (grade 4 or 5) reactions were reported, and 88% of reactions resolved within 7 days (median, 3 days).[2] The most common injection-site reaction was pain (75%); nodule (12%), induration (10%), and swelling (7%) were less common.[2] Injection-site reactions occurred in 69% of patients after the initial 3-mL injections at week 4; frequencies of these reactions declined progressively after the subsequent 2-mL injections, declining to 11% at week 48.[2] At week 48, the median weight gains were 1.80 kg (interquartile range, -0.30 to 4.90 kg) in the ER injection group and 0.30 kg (interquartile range, -1.60 to 2.50 kg) in the oral group.[2] Five patients in the ER injection group and one patient in the oral group had alanine aminotransferase elevations to at least 3-times the upper limit of the normal range.[2] Among the patients who had these events, newly diagnosed hepatitis A was declared in 3 patients, hepatitis B in one patient, and hepatitis C in one patient.[2]

In the FLAIR trial, 86% of patients had at least one injection-site reaction in the ER injection group (see **Table 1**).[3] The most common injection-site reaction was pain, which was reported by 82% who received at least one injection.[3] Most of the injection-site pain events were mild (86%) or moderate (13%) severity; less than 1% were severe (grade 3), and there were no grade 4 adverse events.[3] The incidence of injection-site reactions was highest (71%) after the initial 3-mL injections at week 4 and subsequently decreased to 20% at week 48.[3] The median duration of injection-site reactions was 3 days; 88% of cases resolved within 7 days.[3]

The most common adverse events in the ER injection group, excluding injection-site reactions, were nasopharyngitis, headache and upper respiratory tract infection (see **Table 1**).[3] Overall, drug-related adverse events exclusive of injection-site reactions in the FLAIR trial were more common with ER injection group (28%) than oral group (10%).[3] Serious adverse events occurred in 18 patients (6%) who received ER injection therapy and 12 patients (4%) who received oral therapy, with no deaths.[3] Adverse events that led to early withdrawal from the trial occurred in 9 patients (3%) in the ER injection group and in 4 patients (1%) in the oral group.[3] In the ER injection group, the only events that led to withdrawal in more than 1 patient were viral hepatitis and injection-site pain (in 5 and 2 participants, respectively).[3] During the maintenance phase, 7 patients (2%) who received long-acting therapy and in 2 patients (1%) who received oral therapy were removed from the trial due to liver-related events, including 8 cases of acute viral hepatitis.[3] At week 48 of the FLAIR trial, the median weight gain from baseline was 1.3 kg (interquartile range, −1.0 to 5.0 kg) in the ER injection group and 1.5 kg (interquartile range, −1.0 to 3.9 kg) in the oral group.

In the LATTE-2 trial, total adverse events of any grade and attribution occurred in 115 (100%) patients in the 4-week group, 115 (100%) in the 8-week group, and 54 (96%) in the oral treatment group (see **Table 1**).[10] Injection-site pain, the most common injection-site reaction, was the most frequently reported adverse event in the injection groups (112 [97%] patients in the 4-week group, 110 [96%] patients in the 8-week group).[10] Most injection-site reactions were mild (grade 1; 3648 [84%] of 4360 injections) or moderate (grade 2; 673 [15%] of 4360 injections) in intensity, with median symptom duration of 3 days.[10] Serious adverse events occurred in 13 (11%) patients in each of the injection groups and nine (16%) patients in the oral group, only one of which was drug related (migraine, which occurred in the initial oral induction period of the study).[10] Serious adverse events occurred in 11 (10%) patients in each of the injection groups compared with 7 patients (13%) in the oral group.[10] However, none was considered to be related to study treatment.[10]

Resistance analyses were also performed in each trial. Three patients in the ER injection group who experienced virologic failure in the ATLAS trial were found to have rilpivirine resistance-associated reverse-transcriptase mutations upon examination of HIV-1 RNA samples; an integrase mutation N155H was also detected one of these 3 patients.[2] These mutations reduced susceptibility to rilpivirine by a factor of 6.5, and cabotegravir susceptibility was reduced by a factor of 2.7 in the patient with N155H.[2] Two patients with virologic failure in the ATLAS trial also had an identified L74I integrase polymorphism at baseline, but the investigators concluded that this mutation by itself is not known to decrease susceptibility to INSTIs.[2] No patient with virologic failure missed an injection or received injections outside the permitted window.[2] In the FLAIR trial, 3 patients had NNRTI and INSTI resistance mutations that developed during ER injection therapy; these mutations reduced susceptibility to rilpivirine in 2 patients by a factor of more than 2 and reduced susceptibility to cabotegravir in all 3 patients by a factor of more than 5.[3] These 3 patients had HIV-1 subtype A1 with the L741 integrase polymorphism at baseline.[3] However, 51 of the 54 patients in the ER injection group who had HIV-1 with the L741 integrase polymorphism at baseline did not have virologic failure.[3] In subgroup analyses of the primary endpoint, no statistically significant difference between treatments was observed in subgroups defined according to the presence or absence of the L74I integrase polymorphism.[3] In the LATTE-2 trial, 3 patients (two in the 8-week group, [week 4 and week 48], one in the oral treatment group [week 8]) met the criteria for protocol-defined virological failure through 96 weeks.[10] No treatment-emergent resistance mutations in the genes encoding viral reverse transcriptase, protease, or integrase were identified in the patient in the oral treatment group.[10] Of the two patients in the 8-week group, a mixture emerged for one at integrase codon 269 (R269R/G), which did not decrease cabotegravir susceptibility; however one of these patient had treatment-emergent reverse transcriptase mutations

K103N, E138G, and K238T, with phenotypic resistance to efavirenz, rilpivirine, and nevirapine, and an integrase mutation Q148R, with phenotypic resistance to raltegravir, elvitegravir, and cabotegravir, while remaining sensitive to dolutegravir.[10]

In summary, the proportion of patients in the ER injectable cabotegravir and rilpivirine who experienced adverse effects was greater than in the oral group. This difference was partly attributable to various injection site reactions. Injection site pain was the most commonly reported injection site reaction, which occurred in 75% and 90% of patients in the phase 3 trials, followed by injection site nodule and injection site induration.[2,3] No injection site reactions were reported as serious adverse events and early study withdrawal due to injection site reactions was low.[2,3] Exclusive of injection site reactions, the most frequent adverse events in the phase 3 trials were nasopharyngitis, headache, upper respiratory tract infection and diarrhea.[2,3] Moderate weight gain (median, 1.5 and 1.8 kg) was also noted.[2,3] Additional long-term follow-up data are anticipated to further assess cardiovascular or metabolic risks associated with weight gain.[1] The incidence of nonfatal serious adverse events was low across phase 3 trials (5% to 6%) but higher in the phase 2b trial.[2,3,10] The most serious adverse events included depressive disorders, hypersensitivity reaction and hepatotoxicity, which are associated with other INSTIs and NNRTIs, and are adequately labeled in the product prescribing information.[1,4,5] Overall, there were no deaths attributable to the study drugs.[2,3,10] Emergence of resistance to both cabotegrair and rilpivirine occurred more frequently among virologic failures in the trials and also at a higher rate than in the oral groups.[2,3,10]

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) HIV-1 RNA suppression
2) Virologic failure
3) Drug resistance
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) HIV-1 RNA levels ≥50 copies/mL at 48 weeks

Table 1. Comparative Evidence Table for Extended-release Cabotegravir and Rilpivirine.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Swindells, et al. (ATLAS)[2] Phase 3 OL, MC, PG, NI, RCT 52 weeks	1. Oral CAB 30 mg + RPV 25 mg x4 weeks; eligible patients then received long-acting CAB 600 mg + RPV 900 mg IM, followed by CAB 400 mg + RPV 600 mg IM every 4 weeks x total 52 weeks 2. Patients continued baseline NNRTI-, INSTI or PI-based oral therapy 1:1	Demographics: -Age (median): 42 y (18-62 y) -Male: 77% -White: 68% -Black: 23% -Asian: 6% -CD4+ ≥500 cells/mm^3: 74% -Baseline ARV: ▪ 2x NRTIs +NNRTI: 50% ▪ 2x NRTIs +INSTI: 33% ▪ 2x NRTIs +PI: 17%. -Current ARV median duration: 4.3 y Key Inclusion Criteria: -HIV-1 infection -Age ≥18 y -Receiving ARV regimen w/o virologic failure -No Δ in ARV regimen in past 6 months -HIV-1 RNA <50 copies/mL Key Exclusion Criteria: -HBV -h/o virologic failure -INSTI or NNRTI resistance mutations	ITT: 1. 308 2. 308 PP: 1. 294 2. 292 Attrition: 1. 26 2. 18	Primary Endpoint % w/ plasma HIV-1 RNA levels ≥50 copies/mL at week 48: 1. 1.6% 2. 1.0% Difference, 0.6% (95% CI, -1.1 to 2.4%) Key Secondary Endpoints: % w/ plasma HIV-1 RNA levels <50 copies/mL at week 48: 1. 92.5% 2. 95.5% Difference, -3.0% (95% CI, -6.7 to 0.7%) Confirmed Virologic Failure (2 consecutive plasma HIV-1 RNA measurements ≥200 copies/mL: 1. n=3 2. n=4 No statistical analysis HIVTSQ, adjusted mean difference from baseline: Week 24: 1. 6.43 (95% CI, 5.59-7.28) 2. 1.05 (95% CI, 0.81-1.91) Week 44: 1. 6.12 (95% CI, 5.21-7.03) 2. 0.44 (95% CI, -0.48-1.37) Adjusted difference at week 44: 5.68 points (95% CI, 4.37 to 6.98)	NA NA NA NA	Any AE: 1. 95% 2. 71% Any AE, excluding inj-site reactions: 1. 86% 2. 71% Grade 3 or 4 events: 1. 11% 2. 7% SAE: 1. 4% 2. 5% AE leading to study withdrawal: 1. 5% 2. 2% Inj Site Pain: 75% Inj Site Nodule: 12% Median Wt Gain: 1. 1.8 kg 2. 0.3 kg Nasopharyngitis: 1. 17% 2. 14% Headache: 1. 10% 2. 8% Upper Respiratory Tract Infection: 1. 12% 2. 6%	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) method of randomization unclear; randomization stratified by backbone agent in baseline ARV regimen (PI, INSTI, or NNRTI) and sex at birth. Performance Bias: (high) open label. Detection Bias: (high) open label; data analyzed by mITT (participants who received ≥1 dose). Results were consistent in PP population, which excluded 30 patients for protocol deviations. Attrition Bias: (low) 93% of patients completed 52-week maintenance phase; 8% in long-acting and 6% in oral therapy groups withdrew from trial early. Reporting Bias: (low) endpoints reported as described. Other Bias: (high) authors were employees of ViiV Healthcare and GSK performed statistical analyses and data interpretation. **Applicability**: Patient: participants representative sample of HIV-1 positive population; nearly all patients randomized to CAB+RPV met eligibility criteria with oral lead-in period based on tolerability before transitioning to IM. Intervention: dosing aligns with FDA approved regimen. Only 2% used oral CAB+RPV bridge (4-29 days) in the trial to cover missed or delayed inj visits. Comparator: baseline oral ARV regimen was stable and successfully managed condition during maintenance phase. Outcomes: NI concluded if upper limit of 95% CI in primary endpoint was <6%; justification was unclear but upper limit found increases confidence of NI. Note that the sum of these endpoints in these studies do not equal 100% because virologic data were not available to some patients who withdrew from study early. Setting: 115 sites in 13 countries.

2. Orkin, et al. (FLAIR)[3] Phase 3 OL, MC, PG, NI, RCT 52 weeks	1. Oral CAB 30 mg daily + RPV 25 mg daily x4 weeks; eligible patients then received long-acting CAB 600 mg + RPV 900 mg IM, followed by CAB 400 mg + RPV 600 mg IM every 21-28 days x total 52 weeks 2. DTG/ABC/3TC 50/600/300 mg PO daily 1:1	Demographics: -Age (median): 34 y -Male: 88% -White: 74% -Black: 18% -HIV-1 RNA ≥100,000 copies/mL: 20% -CD4+ ≥350 cells/mm^3: 69% (90% by start of maintenance phase) Key Inclusion Criteria: -HIV-1 positive -Age ≥18 y -ARV-naïve Key Exclusion Criteria: -Stage 3 HIV -HBV -NNRTI resistance mutations other than the K103N mutation -Moderate or severe hepatic function	ITT: 1. 283 2. 283 PP: 1. 278 2. 282 Attrition: 1. 25 2. 22	Primary Endpoint: % w/ plasma HIV-1 RNA levels ≥50 copies/mL at week 48: 1. 2.1% 2. 2.5% Difference, -0.4% (95% CI, -2.8% to 2.1%) Key Secondary Endpoints: % w/ plasma HIV-1 RNA levels <50 copies/mL at week 48: 1. 93.6% 2. 93.3% Difference, 0.4% (95% CI, -3.7% to 4.4%) Confirmed Virologic Failure (2 consecutive plasma HIV-1 RNA measurements ≥200 copies/mL: 1. n=4 2. n=3 No statistical analysis HIVTSQc, mean difference from baseline at Week 48: 1. 29.6 (SE 0.49) 2. 25.5 (SE 0.48) Adjusted mean difference: 4.1 points (95% CI, 2.8 to 5.5; p<0.001)	NA NA NA NA	Any AE: 1. 94% 2. 80% Any AE, excluding inj-site reactions: 1. 87% 2. 80% Grade 3 or 4 events: 1. 11% 2. 4% SAE: 1. 6% 2. 4% AE leading to study withdrawal: 1. 3% 2. 1% Inj Site Pain: 1. 90% Median Wt Gain: 1. 1.3 kg 2. 1.5 kg Nasopharyngitis: 1. 20% 2. 17% Headache: 1. 14% 2. 7% Upper Respiratory Tract Infection: 1. 13% 2. 10%	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) central randomization sequence generated by software that performed blocks shared across sites and stratified by baseline HIV-1 RNA level (<100,00 or ≥100,000 copies/mL) and sex at birth. Performance Bias: (high) open label. Detection Bias: (high) open label; data analyzed by mITT (participants who received ≥1 dose). Results were consistent in PP population, which excluded patients who had protocol deviations that were likely to affect efficacy assessments or lead to discontinuation of the trial drugs. Attrition Bias: (low) 98% of the 3577 expected inj visits (12 per patient by week 48) occurred in 21-35 day window from prev inj. Patient-reported adherence in oral-therapy group >90%. Reporting Bias: (low) endpoints reported as described. Other Bias: (high) Trial funded by ViiV Healthcare and Janssen which participated in design of trial and in analysis and interpretation of data. **Applicability**: Patient: participants representative sample of HIV-1 positive, ARV-naïve population; mostly younger white males. Intervention: Dosing and bridging used in trial approved and marketed in U.S. Comparator: recommended oral ARV regimen used with DTG/ABC/3TC. DTG + 2 NRTIs other than ABC permitted if adverse effects from DTG/ABC/3TC. Outcomes: NI concluded if upper limit of 95% CI for the difference in the primary endpoint was <6%; this was based on assumed 2% virologic failure rate in the oral therapy group and a treatment difference of <3% between the groups. No significant differences between treatments across randomization strata or baseline characteristics. Setting: 108 sites in 11 countries.

3. Margolis, et al. (LATTE-2)[10] Phase 2b OL, MC, PG, NI, RCT 20 week oral induction phase 96 week maintenance phase	1. long-acting CAB 400 mg + RPV 600 mg IM every 4 weeks 2. long-acting CAB 600 mg + RPV 900 mg IM every 8 weeks 3. Cabotegravir 30 mg and ABC/3TC 600/300 mg PO once daily 2:2:1	Demographics: -Age (median): 35 y -Male: 92% -White: 79% -Black: 15% -HIV-1 RNA >100,000 copies/mL: 18% -Median CD4+ 489 cells/mm^3 -Hep C: 3% Key Inclusion Criteria: -HIV-1 positive -Age ≥18 y - ≤10 days of previous ARV tx -HIV-1 RNA ≥1000 copies/mL -CD4+ ≥200 cells/mm^3 Key Exclusion Criteria: -HBV -Any major ARV resistance mutation -Moderate or severe hepatic function -Clinically relevant hepatitis -CrCl <50 mL/min -Chronic anticoagulant	ITT: 1. 115 2. 115 3. 56 PP: 1. 2. 3. Attrition: 1. 14 2. 5 3. 9	Primary Endpoints: % w/ plasma HIV-1 RNA levels <50 copies/mL at week 32: 1. 108 (94%) 2. 109 (95%) 3. 51 (91%) Difference vs. Oral: 1 vs. 3: 2.8% (95% CI, -5.8% to 11.5%) 2 vs. 3: 3.7% (95% CI, -4.8% to 12.2%) *Posterior probability for comparability met threshold at >90%.* Confirmed Virologic Failure (2 consecutive plasma HIV-1 RNA measurements ≥200 copies/mL: 1. 0 2. 2 3. 1 Key Secondary Endpoints: % w/ plasma HIV-1 RNA levels <50 copies/mL at week 96: 1. 100 (87%) 2. 108 (95%) 3. 47 (84%) Difference vs. Oral: 1 vs. 3: 3.0% (95% CI, -8.4% to 14.4%) 2 vs. 3: 10.0% (95% CI, -0.6% to 20.5%)		Any AE: 1. 100% 2. 100% 3. 96% SAE: 1. 11% 2. 11% 3. 16% Study Withdrawal from AE: 1. 7% 2. 2% 3. 2% Inj Site Pain: 1. 97% 2. 96% 3. NA Mild [Grade 1]: 84% Mod [Grade 2]: 15% Nasopharyngitis: 1. 34% 2. 30% 3. 39% Diarrhea: 1. 28% 2. 23% 3. 205 Headache: 1. 23% 2. 25% 3. 25%		**Risk of Bias (low/high/unclear)**: Selection Bias: (low) central randomization sequence generated by software that performed blocks shared across sites and stratified by baseline HIV-1 RNA level (<50 or ≥50 copies/mL). Performance Bias: (high) open label. Detection Bias: (high) open label; data analyzed by mITT (participants who received ≥1 dose). PP sensitivity analyses excluding patients with prespecified protocol deviations were not done as fewer than 5% had such deviations (threshold for conducting analysis specified in advance in the analysis plan). Posterior probability for comparability for each hypothesis confirmed if it was >90% for the primary endpoint. Q4W vs. oral =99%; Q8W vs. oral =100%; Q8W vs. Q4W =99.9%, confirming NI. Attrition Bias: (low) 21/309 (7%) failed induction phase in the mITT population. Of these, 5 were for lack of efficacy, 3 for AE, 3 met predefined liver chemistry stopping criteria (others withdrew consent, had protocol deviations, were lost to follow-up). 286 entered maintenance phase. Reporting Bias: (high) multiple primary endpoints reported without clear method of statistical analysis and hierarchy. Several endpoints reported similar to exploratory outcomes without statistical analysis. Other Bias: (high) Study funded by ViiV Healthcare and Janssen. The funders participated in the study design, data gathering, analysis, and interpretation. **Applicability**: Patient: ARV-naïve patients; mostly younger white males. Intervention: Q4W dosing regimen (group 1) approved and marketed in U.S. Comparator: Recommended oral ARV regimen used INSTI + 2 NRTIs. Outcomes: Endpoints demonstrate virologic suppression for treatment, with no significant differences between treatments during the

								trial. Primary endpoint met study threshold for comparability. Week 96 virologic suppression outcomes were: 87% (4-week grp), 94% (8-week grp), 84% (oral grp) Setting: 50 sites in the USA, Canada, Spain, France, and Germany.

Abbreviations: 3TC = lamivudine; ABC = abacavir; ARR = absolute risk reduction; ARV = antiretroviral; CAB = cabotegravir; CI = confidence interval; CrCl = creatinine clearance; DTG = dolutegravir; GSK = GlaxoSmithKline; HBV = Hepatitis B virus; HIVTSQ = 12-item HIV Treatment Satisfaction Questionnaire, status version (total score ranges from 0 (very dissatisfied) to 66 (very satisfied); HIVTSQc = HIV Treatment Satisfaction Questionnaire, change version (total score ranges from -33 (much less satisfied now) to 33 (much more satisfied now); HIV = human immunodeficiency virus; h/o = history of; IM = intramuscular; INSTI = integrase strand-transfer inhibitor; ITT = intention to treat; MC = multi-center; MCID = minimum clinically important difference; mITT = modified intention to treat; mL = milliliter; N = number of subjects; NA = not applicable; NI = non-inferiority; NNH = number needed to harm; NNRTI = nonnucleoside reverse-transcriptase inhibitor; NNT = number needed to treat; NRTI = nucleoside or nucleotide reverse-transcriptase inhibitor; OL = open label; PG = parallel group; PI = protease inhibitor (boosted); PP = per protocol; RCT = randomized controlled trial; RNA = ribonucleic acid; RPV = rilpivirine; SAE = serious adverse event; w/i = within; w/o = without; y = years.

The pharmacology and pharmacokinetic properties of ER injectable cabotegravir and rilpivirine are described in **Table 2**.

Table 2. Pharmacology and Pharmacokinetic Properties of Extended-release Injectable Cabotegravir and Rilpivirine.[4]

Parameter	Cabotegravir	Rilpivirine
Mechanism of Action	INSTI	NNRTI
Oral Bioavailability	n/a	n/a
Distribution and Protein Binding	T_{max} = 7 days Bound to plasma proteins: >99.8%	T_{max} = 3-4 days Bound to plasma proteins: 99.7%
Elimination	Total dose excreted in urine: 27% Dose excreted unchanged in urine: 0% Total dose excreted in feces: 59% Dose excreted unchanged in feces: 47%	Total dose excreted in urine: 6% Dose excreted unchanged in urine: <1% Total dose excreted in feces: 85% Dose excreted unchanged in feces: 26%
Half-Life	$T_{1/2}$ (weeks): 5.6 to 11.5	$T_{1/2}$ (weeks): 13 to 28
Metabolism	UGT1A1 UGT1A9 (minor)	CYP3A

Abbreviations: AUC = area under the plasma concentration-time curve; C_{max} = maximum plasma concentration; CYP3A = cytochrome P450 3A; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; $T_{1/2}$ = half-life; T_{max} = time to maximum plasma concentration; UGT1A1 = UDP glucuronosyltransferase 1 family, polypeptide A1; UGT1A9 = UDP glucuronosyltransferase 1 family, polypeptide A9.

References:

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VOCABRIA safely and effectively. See full prescribing information for VOCABRIA.

VOCABRIA (cabotegravir) tablets, for oral use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

VOCABRIA is a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with EDURANT (rilpivirine) for short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as:

- oral lead-in to assess the tolerability of cabotegravir prior to administration of CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions. (1)
- oral therapy for patients who will miss planned injection dosing with CABENUVA. (1)

DOSAGE AND ADMINISTRATION

- One tablet of VOCABRIA 30 mg taken orally once daily for approximately 1 month in combination with one tablet of EDURANT (rilpivirine) 25 mg taken orally once daily with a meal. (2.1)

DOSAGE FORMS AND STRENGTHS

- Tablets: 30 mg (3)

CONTRAINDICATIONS

- Previous hypersensitivity reaction to cabotegravir. (4)
- Coadministration with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, and rifapentine. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions have been reported in association with other integrase inhibitors. Discontinue VOCABRIA immediately if signs or symptoms of hypersensitivity reactions develop. (5.1)
- Hepatotoxicity has been reported in patients receiving cabotegravir. Monitoring of liver chemistries is recommended. Discontinue VOCABRIA if hepatotoxicity is suspected. (5.2)
- Depressive disorders have been reported with VOCABRIA. Prompt evaluation is recommended for depressive symptoms. (5.3)
- Risks Associated with Combination Treatment: Review the prescribing information for EDURANT for information on rilpivirine prior to initiation of VOCABRIA in combination with EDURANT. (5.5)

ADVERSE REACTIONS

The most common adverse reactions (Grades 1 to 4) observed in at least 3 subjects receiving VOCABRIA were headache, nausea, abnormal dreams, anxiety, and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Refer to the full prescribing information for important drug interactions with VOCABRIA. (4, 5.4, 7)
- Because VOCABRIA in combination with EDURANT (rilpivirine) is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended. (7.1)
- Drugs that induce uridine diphosphate glucuronosyltransferase (UGT)1A1 may decrease the plasma concentrations of cabotegravir. (4, 7.2, 7.3)

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2021

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CABENUVA safely and effectively. See full prescribing information for CABENUVA.

CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), co-packaged for intramuscular use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

CABENUVA, a 2-drug co-packaged product of cabotegravir, a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI), and rilpivirine, an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. (1)

DOSAGE AND ADMINISTRATION

- Prior to initiating treatment with CABENUVA, oral lead-in dosing should be used for approximately 1 month to assess the tolerability of cabotegravir and rilpivirine. (2.2)
- For intramuscular (IM) gluteal injection only. (2.3, 2.5)
- Recommended Dosing Schedule: Initiate injections of CABENUVA (600 mg of cabotegravir and 900 mg of rilpivirine) on the last day of oral lead-in and continue with injections of CABENUVA (400 mg of cabotegravir and 600 mg of rilpivirine) every month thereafter. (2.3)

DOSAGE FORMS AND STRENGTHS

Cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension, co-packaged as follows: (3)

CABENUVA 400-mg/600-mg Kit:

- single-dose vial of 400 mg/2 mL (200 mg/mL) cabotegravir
- single-dose vial of 600 mg/2 mL (300 mg/mL) rilpivirine

CABENUVA 600-mg/900-mg Kit:

- single-dose vial of 600 mg/3 mL (200 mg/mL) cabotegravir
- single-dose vial of 900 mg/3 mL (300 mg/mL) rilpivirine

CONTRAINDICATIONS

- Previous hypersensitivity reaction to cabotegravir or rilpivirine. (4)
- Coadministration with drugs where significant decreases in cabotegravir and/or rilpivirine plasma concentrations may occur, which may result in loss of virologic response. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions have been reported with rilpivirine-containing regimens and in association with other integrase inhibitors. Discontinue CABENUVA immediately if signs or symptoms of hypersensitivity reactions develop. (5.1)
- Serious post-injection reactions with rilpivirine were reported. Monitor and treat as clinically indicated. (5.2)
- Hepatotoxicity has been reported in patients receiving cabotegravir or rilpivirine. Monitoring of liver chemistries is recommended. Discontinue CABENUVA if hepatotoxicity is suspected. (5.3)
- Depressive disorders have been reported with CABENUVA. Immediate medical evaluation is recommended for depressive symptoms. (5.4)
- Residual concentrations of cabotegravir and rilpivirine may remain in the systemic circulation of patients up to 12 months or longer. It is essential to initiate an alternative, fully suppressive antiretroviral regimen no later than 1 month after the final injection doses of CABENUVA. If virologic failure is suspected, prescribe an alternative regimen as soon as possible. (5.6)

ADVERSE REACTIONS

The most common adverse reactions (Grades 1 to 4) observed in ≥2% of subjects receiving CABENUVA were injection site reactions, pyrexia, fatigue, headache, musculoskeletal pain, nausea, sleep disorders, dizziness, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Refer to the full prescribing information for important drug interactions with CABENUVA. (4, 5.5, 7)
- Because CABENUVA is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended. (7.1)
- Drugs that induce uridine diphosphate glucuronosyltransferase (UGT)1A1 or cytochrome P450 (CYP)3A4 may decrease the plasma concentrations of the components of CABENUVA. (4, 7.3, 7.4)
- CABENUVA should be used with caution in combination with drugs with a known risk of Torsade de Pointes. (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: After oral use of rilpivirine, exposures were generally lower during pregnancy compared with the postpartum period. (8.1)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2021