

Emtricitabine/Rilpivirine/Tenofovir (Complera™)**Criteria for Use
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives and Office of Public Health

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES. The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or <http://vawww.pbm.va.gov> for further information.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive rilpivirine containing product.*

- Patient infected with HIV-2
- Patients with creatinine clearance less than 50mL/min or requiring dialysis
- Known resistance to rilpivirine (refer to issues for consideration)
- Co-administration with non-nucleoside reverse transcriptase inhibitor (NNRTI) (except when supplemental rilpivirine is required with the co-administered of rifabutin)
- Co-administration of rilpivirine and proton pump inhibitor
- Co-administration of rilpivirine and drugs with significant CYP3A enzyme induction including anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin), antimycobacterials (rifampin, rifapentine), systemic dexamethasone (more than a single dose), and St. John's wort

Inclusion Criteria *The answers to all of the following must be fulfilled in order to meet criteria.*

- Use is approved by an experienced VA HIV practitioner
- Patient with pre-treatment HIV RNA \leq 100,000 copies/mL
- Patient with CD4 count $>$ 200 cells/mm³

Dosage and Administration

The coformulated fixed dose product of emtricitabine 200mg/rilpivirine 25mg/tenofovir 300mg is administered as one tablet once daily. Rilpivirine must be administered with a meal (preferably high fat).

Recommended Monitoring

In addition to standard monitoring in a patient receiving antiretroviral therapy,

- New onset or worsening renal impairment including acute renal failure or Fanconi syndrome with tenofovir component: Assess creatinine clearance before initiating treatment with coformulated rilpivirine product. Monitor creatinine clearance serum phosphorus, urine glucose and urine protein in patients at risk. Avoid administering with concurrent or recent use of nephrotoxic drugs (e.g., high-dose or multiple NSAID drugs).
- Decrease in bone mineral density with tenofovir: Monitor in patients with history of pathologic fracture or other risk factors of osteoporosis or bone loss. Consider supplementation with calcium and vitamin D.
- Depressive disorders: Severe depressive disorders have been reported with rilpivirine. Patients with severe depressive symptoms should seek immediate medical evaluation; providers should assess possibility that symptoms are related to coformulated rilpivirine product and if so, determine whether risks of continued therapy outweigh the benefits.
- Hepatotoxicity: Hepatic adverse events have been reported in patients with underlying liver disease, including hepatitis B or C co-infection, or in patients with elevated baseline transaminases. A few cases of hepatotoxicity have occurred in patients with no pre-existing hepatic disease. Monitor liver function tests before and during treatment with rilpivirine-containing regimen in patients with underlying hepatic disease, such as hepatitis B or C co-infection, or marked elevations in transaminase. Also consider monitoring liver functions tests in patients without pre-existing hepatic dysfunction or other risk factors.

Issues for Consideration

- FDA indication: complete regimen for the treatment of HIV-1 infection in (1) adult patients with no antiretroviral treatment history and with HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy, and (2) in certain virologically-suppressed (HIV-1 RNA $<$ 50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen. The following should be considered when initiating therapy in treatment naïve patients with this coformulated product: 1) More rilpivirine treated subjects with HIV-1 RNA $>$ 100,000 copies/mL at the start of therapy experienced virologic failure compared to subjects with HIV-1 RNA $<$ 100,000 copies/mL at the start of therapy; 2)

Regardless of HIV-1 RNA at the start of therapy, more rilpivirine treated subjects with CD4+ cell count less than 200 cells/mm³ at the start of therapy experienced virologic failure compared to subjects with CD4+ cell count greater than or equal to 200 cells/mm³; 3) Observed virologic failure rate in rilpivirine treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz; and more subjects treated with rilpivirine developed lamivudine/emtricitabine associated resistance compared to efavirenz.

- DHHS Guidelines for Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents: rilpivirine/tenofovir/emtricitabine is listed as one of the recommended initial antiretroviral regimen options in patients with pre-treatment HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm³.
- Rilpivirine-containing regimens (i.e., the fixed drug combination Complera™) may also be used for salvage therapy in patients who are failing to respond or who are intolerant of other anti-retroviral regimens.
- If patient experiences efavirenz-intolerance due to depression suicide attempt, or suicidal ideation, provider should consider changing to a non-rilpivirine containing regimen (and consulting with mental health, as applicable). In clinical trials, depressive disorders (regardless of causality, severity) occurred at a slightly higher rate in the rilpivirine group compared to efavirenz, 8% versus 6%, respectively; most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders was 1% for both rilpivirine and efavirenz. The frequency of depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) and discontinuations because of depressive disorders were similar between rilpivirine and efavirenz. In addition, providers should consider consultation or follow-up with mental health for patients with underlying depressive disorders. In comparison, dizziness, abnormal dreams, rash, and hyperlipidemia were more frequent with efavirenz compared with rilpivirine in the clinical trials.
- Drug-drug interactions:
 - Rilpivirine is primarily metabolized by cytochrome P4503A and drugs that induce or inhibit CYP3A can affect the clearance of rilpivirine. Coadministration of rilpivirine and certain CYP3A inducers may result in significant decrease in rilpivirine plasma concentrations, which can lead to loss of virologic response and possible resistance and cross-resistance to the class of NNRTI.
 - Drugs that increase gastric pH may decrease plasma concentrations of rilpivirine. Proton pump inhibitors should not be co-administered with rilpivirine while histamine-2 blockers and antacids require separation. Histamine-2 blockers may be taken at least 12 hours before or at least 4 hours after rilpivirine. Antacids may be taken at least 2 hours before or at least 4 hours after rilpivirine.
 - Torsade de Pointes: Use caution when coadministered with drug that has known risk of Torsade de Pointes.
- Resistance: Resistance testing must be performed prior to initiating rilpivirine in patients who have previously or currently experienced virological failure to efavirenz-, nevirapine- or delavirdine- containing regimen. The single NNRTI substitutions K101P, Y181I and Y181V conferred 52-fold, 15-fold and 12-fold decreased susceptibility to rilpivirine, respectively, while the combination of E138K and M184I showed 6.7-fold reduced susceptibility to rilpivirine. The K103N substitution by itself did not confer reduced susceptibility to rilpivirine. Combinations of 2 or 3 NNRTI resistance-associated substitutions gave decreased susceptibility to rilpivirine.
- Pregnancy Category B: According to Prescribing Information, there are no adequate and well-controlled studies in pregnant women; therefore, coformulated product should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Co-infection with Hepatitis B: Prior to initiating antiretroviral therapy, HIV infected patients should be tested for presence of chronic hepatitis B. Severe acute exacerbations of hepatitis B have been reported in patients with HIV-1 and HBV who have discontinued emtricitabine or tenofovir, which are components of the coformulated rilpivirine product. Hepatic function should be monitored closely in these patients and if appropriate, initiation of anti-hepatitis B therapy may be warranted.

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