BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

JULUCA™ (dolutegravir sodium-rilpivirine hydrochloride) oral Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Juluca (dolutegravir and rilpivirine) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Infectious Disease Specialist or HIV/AIDS Specialist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of HIV-1 infection, to replace the current antiretroviral regimen

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual with **ALL** of the following:
    a. Viral suppression as determined by HIV-1 RNA < 50 copies per mL (within the last 6 months)
    b. Has been on a stable antiretroviral regimen for at least 6 months
    c. No history of treatment failure
    d. No known amino acid substitutions associated with resistance to the individual components

6. Individual has received and completed the **baseline liver function tests** before initiation of treatment and with continued monitoring as clinically appropriate

7. There are **NO** FDA- label contraindications such as:
    a. Previous hypersensitivity reaction to dolutegravir or rilpivirine
    b. Use with Tikosyn (dofetilide) and dofetilide generics
    c. Use with drugs that significantly decrease rilpivirine plasma concentrations, which may result in loss of virologic response (e.g., carbamazepine, dexamethasone [multiple doses], oxcarbazepine, phenobarbital, phenytoin, proton pump inhibitors, rifampin, rifapentine, St. John's wort)

8. Individual does not have severe hepatic impairment (Child-Pugh Class C)

9. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Juluca (dolutegravir and rilpivirine) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Infectious Disease Specialist or HIV/AIDS Specialist

2. Individual's condition has not worsened while on therapy with worsening defined as the following:
    a. HIV-1 RNA > 50 copies per mL
    b. Decreasing CD4 cell counts
    c. Evidence for drug resistance

3. Individual has been adherent with the medication

4. **If available** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use as follows:

a. Contraindications as listed in the criteria for initial therapy section
b. Significant adverse effect such as:
    i. Severe skin and hypersensitivity reactions (e.g., drug reaction with Eosinophilia and Systemic Symptoms (DRESS))
    ii. Hepatotoxicity
    iii. Severe depression, suicide ideation or attempt, dysphoria, or negative thoughts

6. Individual does not have severe hepatic impairment (Child-Pugh Class C)

7. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Juluca (dolutegravir and rilpivirine) is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (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 for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Juluca.

Juluca contains dolutegravir, a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) and rilpivirine, a HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI). Dolutegravir binds to the integrase active site and inhibits the strand transfer step of HIV-1 DNA integration necessary for HIV replication. Rilpivirine binds to reverse transcriptase and consequently blocks RNA-dependent and DNA-dependent DNA polymerase activities, including HIV-1 replication.

Dolutegravir is also found in Tivicay (dolutegravir sodium). Rilpivirine is found in Edurant (rilpivirine hydrochloride), Odefsey (rilpivirine hydrochloride, emtricitabine, tenofovir alafenamide), and Complera (rilpivirine hydrochloride, emtricitabine, tenofovir fumarate).

Background:
The life cycle of HIV can be broken down into 6 steps: (1) entry (binding and fusion); (2) reverse transcription; (3) integration; (4) replication (transcription and translation); (5) assembly; and (6) budding and maturation.

For all patients with early HIV infection, drug resistance testing should be done after the initial diagnosis regardless of whether treatment is being considered. Fifteen to twenty percent of patients may be infected with an

isolate having at least 1 drug resistance mutation. The presence of mutations in transmitted strains is strongly influenced by antiretroviral drug use patterns in the source.

As in chronic infection, antiretroviral therapy (ART) is effective in suppressing serum viral RNA levels and increasing CD4 cell counts in the vast majority of patients with acute and early HIV infection. Initiation of ART earlier after initial HIV infection is associated with a greater chance of immune reconstitution to normal or near normal CD4 cell levels.

HIV enters CD4 cells via the CD4 receptor in conjunction with one of its co-receptors: the chemokine coreceptor 5 (CCR5) or the CXC chemokine coreceptor 4 (CXCR4). Agents that block CCR5 exert their antiviral activity against HIV by blocking entry of CCR5-tropic viruses into the CD4 T cell, maraviroc is a CCR5 antagonist. Fusion inhibitors bind to the envelope glycoprotein 41 (gp41) of HIV to prevent viral fusion to the CD4 T cell. Enfuvirtide is an injectable fusion inhibitor. Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are backbone of ART regimens and are usually given in pairs. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) are typically given with an NRTI. Regimens with integrase strand transfer inhibitors (INSTIs), are the preferred third agent for treatment-naïve individuals used in combination with two nucleoside analogues. Protease inhibitors (PIs) are used with an NRTI combination; however, they can also be used as part of a nucleoside-sparing/limiting regimen. PIs should be administered with a boosting agent like ritonavir or cobicistat. They can also be used for patients who are treatment-naïve and are often the preferred agent for patients failing their initial ART regimen.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Classification of antiretroviral drugs (agents listed alphabetically):

Drug (abbreviations)	US Brand Name
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)	
Abacavir (ABC)	Ziagen
Emtricitabine (FTC)	Emtriva
Lamivudine (3TC)	Epivir
Stavudine (d4T)	Zerit
Tenofovir alafenamide (TAF)	Vemlidy
Tenofovir disoproxil fumarate (TDF)	Viread
Zidovudine (ZDV, AZT)	Retrovir
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
Delavirdine (DLV)	Rescriptor
Doravirine (DOR)	Pifeltro

Efavirenz (EFV)	Sustiva
Etravirine (ETR)	Intelence
Nevirapine (NVP)	Viramune, Viramune XR
Rilpivirine (RPV)	Edurant
Protease inhibitors (PIs)	
Atazanavir (ATV)	Reyataz
Atazanavir-cobicistat (ATV/COBI)	Evotaz
Darunavir (DRV)	Prezista
Darunavir-cobicistat (DRV/COBI)	Prezcobix
Fosamprenavir (FPV)	Lexiva
Indinavir (IDV)	Crixivan
Lopinavir/ritonavir boosting (LPV/r)	Kaletra
Nelfinavir (NFV)	Viracept
Ritonavir (RTV) (used as a pharmacokinetic boosting agent)	Norvir
Saquinavir (SQV)	Invirase
Tipranavir (TPV)	Aptivus
Fusion inhibitor	
Enfuvirtide (T-20)	Fuzeon
Integrase strand transfer inhibitors (INSTIs)	
Cabotegravir (CAB; oral formulation)	Vocabria
Dolutegravir (DTG)	Tivicay
Elvitegravir (EVG)	Vitekta
Raltegravir (RAL)	Isentress, Isentress HD
CCR5 antagonist	
Maraviroc (MVC)	Selzentry
Attachment inhibitor	
Fostemsavir	Rukobia
Post-attachment inhibitor	

Ibalizumab-uijk	Trogarzo
Fixed-dose combinations	
Abacavir-lamivudine (ABC/3TC)	Epzicom
Abacavir-lamivudine-zidovudine (ABC/3TC/ZDV)	Trizivir
Bictegravir-emtricitabine-tenofovir alafenamide (BIC/FTC/TAF)	Biktarvy
Darunavir-cobicistat-emtricitabine-tenofovir alafenamide (DRV/COBI/FTC/TAF)	Symtuza
Dolutegravir-abacavir-lamivudine (DTG/ABC/3TC)	Triumeq
Dolutegravir-lamivudine (DTG/3TC)	Dovato
Dolutegravir-rilpivirine (DTG/RPV)	Juluca
Doravirine-lamivudine-tenofovir disoproxil fumarate (DOR/3TC/TDF)	Delstrigo
Efavirenz-emtricitabine-tenofovir disoproxil fumarate (EFV/FTC/TDF)	Atripla
Efavirenz- lamivudine -tenofovir disoproxil fumarate (EFV/FTC/TDF)	Symfi, Symfi Lo
Elvitegravir-cobicistat-emtricitabine-tenofovir alafenamide (ECF/TAF or EVG/COBI/FTC/TAF)	Genvoya
Elvitegravir-cobicistat-emtricitabine-tenofovir disoproxil fumarate (ECF/TDF or EVG/COBI/FTC/TDF)	Stribild
Rilpivirine-emtricitabine-tenofovir alafenamide (RPV/FTC/TAF)	Odefsey
Rilpivirine-emtricitabine-tenofovir disoproxil fumarate (RPV/FTC/TDF)	Complera
Tenofovir alafenamide-emtricitabine (TAF/FTC)	Descovy
Tenofovir disoproxil fumarate-emtricitabine (TDF/FTC)	Truvada
Zidovudine-lamivudine (ZDV/3TC)	Combivir
Injectable combination	
Cabotegravir plus rilpivirine (CAB/RPV; extended-release injectable formulation)	Cabenuva

Amino acid substitutions for resistance:

Dolutegravir-resistant viruses

E92Q, G118R, S153F or Y, G193E, or R263K

Rilpivirine-resistant viruses

L100I; K101E; V106I and A; V108I; E138K and G, Q, R; V179F and I; Y181C and I; V189I; G190E; H221Y; F227C; and M230I and L

Cross resistance:

Integrase strand transfer inhibitor-resistant substitutions

T66K, I151L, S153Y, T66K/L74M; E92Q/N155H; G140C/Q148R; G140S/Q148H, R or K; Q148R/N155H; T97A/G140S/Q148, E138/G140/Q148

Non-nucleoside reverse transcriptase inhibitor-resistant mutations

K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M184I, M230I, or M230L, K103N and L1001

Resources:

Juluca (dolutegravir/rilpivirine) tab product information, revised by ViiV Healthcare Company 04-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 25, 2024.

Fletcher CV. Overview of antiretroviral agents used to treat HIV. In: UpToDate, Sax PE, Mitty J (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through November 2024. Topic last updated February 02, 2023. Accessed December 31, 2024.

Sax PE. Acute and early HIV infection: Treatment. In: UpToDate, Gandhi RT, Mitty J (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through November 2024. Topic last updated May 21, 2024. Accessed December 31, 2024.

Wood BR. Switching antiretroviral therapy for adults with HIV-1 and suppressed viral load. In: UpToDate, Hirsch MS, Sax PE, Mitty J (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through November 2024. Topic last updated August 03, 2023. December 31, 2024.