BlueCross BlueShield Arizona

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PHARMACY COVERAGE GUIDELINES	
SECTION: DRUGS	
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JULUCA™ (dolutegravir sodium-rilpivirine hydrochloride) oral tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Juluca (dolutegravir and rilpivirine) is considered ***medically necessary*** and will be approved when **ALL** of 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. A confirmed diagnosis of HIV-1 infection, to replace the current antiretroviral regimen

  4. 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

  5. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     a. Negative pregnancy test in a woman of childbearing potential
     b. Liver function tests

  6. There are **NO** FDA- label contraindications.
     a. Contraindications include:
        i. Previous hypersensitivity reaction to dolutegravir or rilpivirine
        ii. Use with Tikosyn (dofetilide) and dofetilide generics
        iii. Use with drugs where significant decreases in rilpivirine plasma concentrations may occur, 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)

  7. The individual does not have severe hepatic impairment (Child-Pugh Class C)

  8. There are no significant interacting drugs

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Juluca (dolutegravir and rilpivirine) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  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

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a. Worsening is defined as:
   i. HIV-1 RNA > 50 copies per mL
   ii. Decreasing CD4 cell counts
   iii. Evidence for drug resistance

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
   a. Contraindications as listed in the criteria for initial therapy section
   b. Significant adverse effect:
      i. Severe skin and hypersensitivity reactions
      ii. Hepatotoxicity
      iii. Severe depression, suicide ideation or attempt, dysphoria, or negative thoughts

5. The individual does not have severe hepatic impairment (Child-Pugh Class C)

6. There are no significant interacting drugs [see above 6 a iii]

Renewal duration: 12 month

- 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.

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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:

Classification of antiretroviral drugs (agents listed alphabetically):

Drug (abbreviations)	US Brand Name
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)	
Abacavir (ABC)	Ziagen
Didanosine (ddI)	Videx, Videx EC
Emtricitabine (FTC)	Emtriva
Lamivudine (3TC)	Epivir
Stavudine (d4T)	Zerit

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Tenofovir alafenamide (TAF)	Vemlidy
Tenofovir disoproxil fumarate (TDF)	Viread
Zalcitabine (ddC) (no longer marketed in most countries)	Hivid
Zidovudine (ZDV, AZT)	Retrovir
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
Delavirdine (DLV)	Rescriptor
Efavirenz (EFV)	Sustiva
Etravirine (ETR)	Intelence
Nevirapine (NVP)	Viramune, Viramune XR
Rilpivirine (RPV)	Edurant
Protease inhibitors (PIs)	
Amprenavir (APV) (no longer marketed in most countries)	Agenerase
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)	
Dolutegravir (DTG)	Tivicay
Elvitegravir (EVG)	Vitekta

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Raltegravir (RAL)	Isentress
CCR5 antagonist	
Maraviroc (MVC)	Selzentry
Fixed-dose combinations	
Abacavir-lamivudine (ABC/3TC)	Epzicom
Abacavir-lamivudine-zidovudine (ABC/3TC/ZDV)	Trizivir
Dolutegravir-abacavir-lamivudine (DTG/ABC/3TC)	Triumeq
Dolutegravir-rilpivirine (DTG/RPV)	Juluca
Efavirenz-emtricitabine-tenofovir disoproxil fumarate (EFV/FTC/TDF)	Atripla
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

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

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Resources:

Juluca (dolutegravir / rilpivirine) product information, revised by ViiV Healthcare Company 07-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 15, 2021.

Fletcher CV. Overview of antiretroviral agents used to treat HIV. In: UpToDate, Sax PE, Mitty J (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Topic last updated March 03, 2021. Accessed December 15, 2021.

Sax PE. Acute and early HIV infection: Treatment. In: UpToDate, Gandhi RT, Mitty J (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Topic last updated January 21, 2020. Accessed December 15, 2021.

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. Topic last updated February 19, 2021. Accessed December 15, 2021.