BlueCross BlueShield of 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.**

JULUCA™ (dolutegravir sodium-rilpivirine hydrochloride) oral tablet (cont.)

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 (rilpivrine 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
  - (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
  - 15-20% 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

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- 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
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

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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
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

Juluca (dolutegravir sodium-rilpivirine hydrochloride)

Medication class:

Antiretroviral, Integrase Inhibitor; Antiretroviral, Reverse Transcriptase Inhibitor, Non-nucleoside

FDA-approved indication(s):

- Juluca is indicated as a maintenance treatment regimen of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies per mL) on a

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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

Recommended Dose:
- One tablet once daily
- When used with rifabutin, take an additional 25-mg tablet of rilpivirine with Juluca once daily for the duration of the rifabutin use

Maximum dosage
- Not stated

Available Dosage Forms:
- Each tablet contains:
  - 50 mg of dolutegravir (equivalent to 52.6 mg dolutegravir sodium)
  - 25 mg of rilpivirine (equivalent to 27.5 mg rilpivirine hydrochloride)

Warnings and Precautions:
- Addition of other antiretroviral medications for the treatment of HIV-1 is not recommended
- Discontinue Juluca immediately if signs or symptoms of severe skin or hypersensitivity reactions develop
- The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of rilpivirine or dolutegravir is unknown
- Hepatotoxicity has been reported with the use of rilpivirine- or dolutegravir-containing regimens, monitoring for drug-induce liver injury or acute liver failure is recommended
- Depressive disorders (depressed mood, dysphoria, major depression, suicide ideation and attempts) have been reported with the use of rilpivirine- or dolutegravir-containing regimens
- High doses of rilpivirine (≥ 75 mg) can prolong QTc interval, consider alternatives to Juluca when used with a drug known risk of Torsade de pointes
- Use with polyvalent cation-containing products may lead to decreased absorption of dolutegravir, doses of Juluca should be given 4-hours before or 6-hours after
- Take Juluca 4-hours before or 12-hours after a histamine-2 receptor blocker
- Woman of child bearing age should not breast feed an infant or child, due to concern for HIV-1 transmission to an HIV-negative infant or child, concern for development of resistance in an HIV-positive infant or child, and concern for adverse effects in the infant or child
- Cross-resistance to efavirenz, etravirine, and/or nevirapine is likely after virologic failure and development of rilpivirine resistance

Criteria:

- **Criteria for initial therapy:** Juluca is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is an Infectious Disease Specialist or HIV/AIDS specialist

2. Individual is 18 years of age or older

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3. A confirmed diagnosis of HIV-1 infection

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

5. There are **NO** contraindications.
   - Contraindications include:
     - Previous hypersensitivity reaction to dolutegravir or rilpivirine
     - Use with dofetilide
     - Use with drugs where significant decreases in rilpivirine plasma concentrations may occur, which may result in loss of virologic response
       - Drugs that are contraindicated include:
         a. Carbamazepine, oxcarbazepine, phenobarbital, phenytoin
         b. Rifampin, rifapentine
         c. Dexamethasone
         d. St. John's wort
         e. Proton pump inhibitors

Initial approval duration: 12 months

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

1. Individual continues to be seen by an Infectious Disease Specialist or HIV/AIDS specialist

2. Individual's condition has not worsened while on therapy
   - Worsening is defined as:
     - HIV-1 RNA > 50 copies per mL
     - Decreasing CD4 cell counts
     - Evidence for drug resistance

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
   - Contraindications as listed in the criteria for initial therapy section
   - Significant adverse effect:
     - Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
       - Signs and symptoms may include: fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection, eosinophilia is often present

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- Hypersensitivity
  - Signs and symptoms may include: hives over neck and face, itching, nasal congestion, difficulty breathing, swelling of lips, mouth, tongue or throat
- Hepatotoxicity
  - Signs and symptoms may include: right sided abdominal pain, bruising, yellow skin or eyes, dark brown urine, severe nausea or vomiting, fatigue, light colored pale stools, itching, confusion

5. There are no significant interacting drugs

Renewal duration: 12 months

Resources:

Juluca. Package Insert. Revised by manufacturer 11/2017. Accessed 01/08/2018.

UpToDate: Overview of antiretroviral agents used to treat HIV. Current through Dec 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/overview-of-antiretroviral-agents-used-to-treat-hiv?search=hiv%20treatment&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3

UpToDate: Acute and early HIV infection: Clinical manifestations and diagnosis. Current through Dec 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/acute-and-early-hiv-infection-clinical-manifestations-and-diagnosis?search=hiv&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H18410843

UpToDate: Acute and early HIV infection: Treatment. Current through Dec 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/acute-and-early-hiv-infection-treatment?search=hiv&source=search_result&selectedTitle=4~150&usage_type=default&display_rank=4

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.