BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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SYMTUZA™ (darunavir, cobicistat, emtricitabine, tenofovir alafenamide) 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.**

SYMTUZA™ (darunavir, cobicistat, emtricitabine, tenofovir alafenamide) oral tablet (cont.)

Criteria:

- **Criteria for initial therapy:** Symtuza (darunavir-cobicistat-emtricitabine-tenofovir alafenamide) 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
  3. A confirmed diagnosis of HIV-1 infection
  4. Individual with **ONE** of the following:
     - No prior use of antiretroviral treatment
     - Viral suppression determined by HIV-1 RNA < 50 copies/mL on a stable antiretroviral regimen for at least 6 months
  5. No known amino acid substitutions associated with resistance to darunavir or tenofovir
  6. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     - Hepatitis B virus co-infection
     - Comprehensive metabolic panel
     - Urinalysis for glucose and protein
  7. There are **NO** contraindications.
     - Contraindications include:
       - Co-administered with certain drugs for which altered plasma concentrations are associated with serious and/or life-threatening events or which may lead to loss of therapeutic effect of Symtuza and development of resistance (See Definitions section)
  8. Will not be used with other antiretroviral medications for the treatment of HIV-1 infection
  9. Will not be used in an individual with an estimated creatinine clearance of < 30 mL/min
  10. Will not be used in an individual with severe hepatic impairment (Child-Pugh Class C)
  11. Will not be used during pregnancy in a woman of child bearing age

  Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Symtuza (darunavir-cobicistat-emtricitabine-tenofovir alafenamide) 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

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2. Individual's condition responded while on therapy
    - Response is defined as:
        - Achieved and maintains HIV-1 RNA < 50 copies/mL
        - Achieved and maintains a CD4 cell count ≥ 200 cells/mm^3
        - No 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:
        - Exacerbation of hepatitis B
        - Severe skin reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson syndrome, toxic epidermal necrolysis
        - Hepatotoxicity
        - Drug induced hepatitis
        - Acute renal failure
        - Fanconi syndrome
        - Lactic acidosis
        - Diabetic ketoacidosis

5. There are no significant interacting drugs

Renewal duration: 12 months

Description:

Symtuza (darunavir (DRV)-cobicistat (COBI)-emtricitabine (FTC)-tenofovir alafenamide (TAF)) is a four drug combination indicated as a complete regimen for the treatment of HIV-1 infection in adults who have no prior antiretroviral treatment history or who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir.

Darunavir is a protease inhibitor (PI) of HIV-1, cobicistat is an inhibitor of cytochrome P450 metabolism, emtricitabine, a synthetic nucleoside analog of cytidine, is a HIV nucleoside reverse transcriptase inhibitor (NRTI), and tenofovir alafenamide is also an NRTI.

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
  - 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:

Interactions – not an all-inclusive list

Symtuza is contraindicated with the following co-administered drugs due to the potential for serious and/or life-threatening events or loss of therapeutic effect:

- Alpha 1-adrenoreceptor antagonist: alfuzosin

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- Antianginal: ranolazine
- Antiarrhythmic: dronedarone
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin
- Anti-gout: colchicine, in patients with renal/and or hepatic impairment
- Antimycobacterial: rifampin
- Antipsychotics: lurasidone, pimozide
- Ergot derivatives, e.g., dihydroergotamine, ergotamine, methylergonovine
- GI motility agent: cisapride
- Herbal product: St. John's wort (*Hypericum perforatum*)
- Hepatitis C direct acting antiviral: elbasvir/grazoprevir
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- PDE-5 inhibitor: sildenafil when used for treatment of pulmonary arterial hypertension
- Sedatives/hypnotics: orally administered midazolam, triazolam

Use is not recommended with:

- Antibacterial: clarithromycin, erythromycin, telithromycin – used alternative ABX
- Direct acting oral anticoagulants: rivaroxiban
- Anticonvulsants: eslicarbazepine, oxcarbazepine use alternative AED or antiretroviral
- Antifungals: voriconazole, unless risk/benefit justifies use
- Antimycobacterial: rifabutin, rifapentine
- Antipsychotics: quetiapine, avoid or use alternative antiretroviral
- Hepatitis C direct acting antiviral: simeprevir
- Inhaled beta agonists: salmeterol
- PDE-5 inhibitor: avanafil
- Platelet inhibitor: ticagrelor

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
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

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Fixed-dose combinations	
Abacavir-lamivudine (ABC/3TC)	Epzicom
Abacavir-lamivudine-zidovudine (ABC/3TC/ZDV)	Trizivir
Darunavir--cobicistat-emtricitabine-tenofovir alafenamide (DRV/COBI/FTC/TAF)	Symtuza
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

Resources:

Symtuza. Package Insert. Revised by manufacturer 7/20/18. Accessed 8/23/18.

UpToDate: Overview of antiretroviral agents used to treat HIV. Current through Aug 2018. 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 Aug 2018. 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 Aug 2018. 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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UpToDate: Patient monitoring during HIV antiretroviral therapy: Treatment. Current through Aug 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/patient-monitoring-during-hiv-antiretroviral-therapy?sectionName=FREQUENCY%20OF%20IMMUNOLOGIC%20AND%20VIROLOGIC%20MONITORING&topicRef=3717&anchor=H9&source=see_link#H9

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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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Pharmacy Prior Authorization Request Form

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.