Policy Number	RX501.099
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Ibalizumab-uiyk

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated, and coverage is not required for non-formulary drugs.

EXCEPTION: For members residing in the state of Maine, 24-A s 2837-G and 24-A s 4234-E (for HMOs) requires all group insurance policies and all health maintenance organization group contracts that provide coverage for prescription drugs must provide coverage for off-label use in accordance with the following: A) Group policies that provide coverage for prescription drugs may not exclude coverage of any such drug used for the treatment of HIV or AIDS on the grounds that the drug has not been approved by the federal Food and Drug Administration for that indication, as long as that drug is recognized for the treatment of that indication in one of the standard reference compendia or in peer-reviewed medical literature. B) Coverage of a drug required by this subsection also includes medically necessary services associated with the administration of the drug. C) This subsection may not be construed to require coverage for a drug when the federal Food and Drug Administration has determined its use to be contraindicated for treatment of the current indication. D) A drug use that is covered pursuant to paragraph A may not be denied coverage based on a "medical necessity" requirement except for a reason that is unrelated to the legal status of the drug use. E) A contract that provides coverage of a drug as required by this subsection may contain provisions for maximum benefits and coinsurance and reasonable limitations, deductibles and exclusions to the same extent that these provisions are applicable to coverage of all prescription drugs and are not inconsistent with the requirements of this subsection. For this provision: “Off-label use" means the prescription and use of drugs for indications other than those stated in the labeling approved by the federal Food and Drug Administration. "Peer-reviewed medical literature" means scientific studies published in at least 2 articles from major peer-reviewed medical journals that present data that supports the proposed off-label use as generally safe and effective. "Standard reference compendia" means: a. The United States Pharmacopeia Drug Information or information published by its successor organization; or b. The American Hospital Formulary Service Drug Information or information published by its successor organization. This applies to Fully Insured Small Group, Mid-Market, Large Group, Student PPO, HMO, POS, EPO.

Coverage

Ibalizumab-uiyk (Trogarzo®) therapy **may be considered medically necessary** based on the U.S. Food and Drug Administration (FDA)-approved indication for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen when the following criteria are met:

- Individual has documented ribonucleic acid (RNA) viral load >1,000 copies/mL; AND
- Individual has documented resistance to at least one antiretroviral medication from three different classes of antiretroviral medications; AND
- Individual has a history of at least 6 months on antiretroviral treatment; AND
- Trogarzo is used in combination with other antiretrovirals; AND
- Trogarzo initial and maintenance dosing is in accordance with the FDA prescribing information.

Ibalizumab-uiyk (Trogarzo®) **is considered experimental, investigational and/or unproven** for all other non-FDA indications.

Policy Guidelines

None.

Description

Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV). The HIV virus attacks and weakens the immune system. A specific type of white blood cells, CD4 positive (CD4+) T cell, is infiltrated and destroyed. CD4+ T cells fight off infections. People whose CD4+ T cells are compromised, become susceptible to other diseases, infections, and complications.

The National Institutes of Allergy and Infectious Disease notes 39 million people are living with HIV around the world, but only 77% of them are on lifesaving antiretroviral therapy. In the United States, 1.2 million people are living with HIV, of whom 14 percent are unaware of their diagnosis. (2)

The HIV virus has no cure, but with ongoing research and development of treatments, people infected with HIV can live a near normal life span. Antiretroviral therapy (ART) is used in the treatment of patients with HIV infection. This treatment can require a combination of different medications.

The deputy director of the Division of Antiviral Products in the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research, noted "While most patients living with HIV can be successfully treated using a combination of two or more antiretroviral drugs, a small percentage of patients who have taken many HIV drugs in the past have multidrug resistant HIV, limiting their treatment options and putting them at a high risk of HIV-related complications and progression to death." "Trogarzo is the first drug in a new class of antiretroviral medications that can provide significant benefit to patients who have run out of HIV treatment options. New treatment options may be able to improve their outcomes." (3)

Ibalizumab-uiyk (Trogarzo®) is a recombinant humanized monoclonal antibody. The mechanism of action noted on the prescribing information for Trogarzo notes that it blocks *Human Immunodeficiency Virus* (HIV-1) from infecting CD4+ T cells by binding to domain 2 of CD4 and interfering with post-attachment steps required for the entry of the HIV-1 virus into host cells and preventing the viral transmission that occurs via cell-cell fusion. (1) Trogarzo binding to domain 2 of CD4 allows this product to block viral entry into host cells without causing immunosuppression.

Trogarzo® is administered intravenously (IV) after dilution as an infusion. The FDA recommendation notes that patients should receive a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg every 2 weeks. The common adverse reactions noted were diarrhea, nausea, dizziness, and rash. The label for Trogarzo® includes warnings and precaution information for Immune Reconstitution Inflammatory Syndrome (IRIS) which has been reported in patients treated with combination antiretroviral therapies. IRIS is an inflammatory reaction to an indolent or residual opportunistic infection that may occur when the immune system begins to recover following treatment with antiretroviral (ARV) drugs.

Regulatory Status
On March 6, 2018, Trogarzo® (ibalizumab-uiyk) was cleared for marketing by the FDA through the biologics license application process. (4) Trogarzo® also received an Orphan Drug designation. The label indication states the following: Trogarzo, in combination with other ARVs, is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen. The safety and effectiveness of Trogarzo in pediatric patients have not been established. (1)

Rationale

This medical policy is based on the U.S. Food and Drug Administration (FDA) label for Trogarzo® (ibalizumab-uiyk).

Trogarzo® (ibalizumab-uiyk) (1)
Trial TMB-301
Trial TMB-301 was a single arm, multicenter clinical trial that included 40 heavily treatment-experienced human immunodeficiency virus (HIV) infected subjects with multidrug resistant HIV-1. Subjects were required to have a viral load greater than 1,000 copies/mL and documented resistance to at least one antiretroviral medication from each of the three classes of antiretroviral medications as measured by resistance testing. Subjects must have been treated with antiretrovirals for at least 6 months and be failing or had recently failed (i.e., in the last 8 weeks) therapy.

The trial was composed of three discrete periods:

- *Control period (Day 0 to Day 6):* Subjects were either monitored on their current failing therapy or received no therapy if they had failed and discontinued treatment within the 8 weeks preceding screening. This was an observational period to establish baseline HIV viral load.
- *Function monotherapy period (Day 7 to Day 13):* All subjects received a 2,000 mg loading dose of Trogarzo on Day 7. Subjects on a failing antiretroviral therapy (ART) regimen continued to receive their failing regimen in addition to the loading dose of Trogarzo. This period was to establish the virologic activity of TROGARZO.
- *The Maintenance period (Day 14 to Week 25):* On day 14 of the treatment period, viral load was assessed for the primary endpoint, and thereafter the background regimen was

optimized to include at least one drug to which the subject's virus was susceptible. The use of an investigational drug(s) as a component of the optimized background regimen was allowed. Beginning at Day 21, an 800 mg maintenance dose of TROGARZO was administered every two weeks through Week 25. This period was to establish the safety and durability of virologic suppression of TROGARZO when used in combination with an optimized background regimen.

The majority of subjects in Trial TMB-301 were male (85%), White (55%) and between 23 and 65 years of age (mean [SD] age: 50.5 [11.0] years). At Baseline, median viral load and CD4+ T cell counts were 35,350 copies/mL and 73 cells/mm^3, respectively. The subjects were heavily treatment-experienced: 53% of participants had been treated with 10 or more antiretroviral drugs prior to trial enrollment; 98% percent had been treated with nucleoside reverse transcriptase inhibitors (NRTIs), 98% with PIs, 80% with non-nucleoside reverse transcriptase inhibitors (NNRTIs), 78% with INSTIs (INSTI HIV Self-Test), 30% with gp41 fusion inhibitors, and 20% with C-C chemokine receptor type 5 (CCR5) co-receptor antagonists.

The primary efficacy endpoint was the proportion of subjects achieving a ≥ 0.5 $\log_{10}$ decrease in viral load from the beginning to the end of the "Functional monotherapy period" as compared to the proportion of subjects achieving a ≥ 0.5 $\log_{10}$ decrease from the beginning to the end of the "Control period", as defined above. The results of the primary endpoint analysis are shown in Table 1 below.

Table 1. Proportion of Subjects Achieving a ≥ 0.5 $\log_{10}$ Decrease in Viral Load at the End of the Control and Functional Monotherapy Periods

	Proportion of Subjects Achieving a ≥ 0.5 $\log_{10}$ Decrease in Viral Load N=40	**95% CI***
End of Control Period	3%	(0.06%, 13%)
End of Functional Monotherapy Period	83%	(67%, 93%)

*exact 95% CI (confidence interval)

$p < 0.0001$ based on McNemar's test comparing the proportion of subjects achieving ≥ 0.5 $\log_{10}$ decrease in viral load at the end of the control and functional monotherapy periods.

At Week 25, viral load <50 and <200 HIV-1 RNA copies/mL was achieved in 43% and 50% of subjects, respectively. Fifty-five percent of subjects had a ≥ 1 $\log_{10}$ reduction in viral load, and 48% of subjects had a ≥2 $\log_{10}$ reduction in viral load at Week 25. An increase in the mean and median number of CD4+ T-cells (44 cells/mm^3 and 17 cells/mm^3, respectively) was observed from Baseline to Week 25. Week 25 outcomes are shown in Table 2 and Table 3.

Table 2. Trial TMB 301 Virologic Outcomes (Snapshot Algorithm) at Week 25

	TROGARZO (N=40)
HIV RNA < 50 copies/mL at Week 25	43%
HIV RNA ≥ 50 copies/mL at Week 25*	45%

HIV RNA < 200 copies/mL at Week 25 HIV RNA ≥ 200 copies/mL at Week 25**	50% 38%
No virologic data at Week 25 Discontinued due to AE or death	 13%

HIV RNA: Human Immunodeficiency Virus Ribonucleic acid
*included subjects who had ≥ 50 copies/mL in the Week 25 window, subjects who discontinued study drug due to lack of efficacy, and subjects who discontinued study drug for reasons other than an AE, death and at the time of discontinuation had a viral value ≥ 50 copies/mL.
**included subjects who had ≥ 200 copies/mL in the Week 25 window, subjects who discontinued study drug due to lack of efficacy, and subjects who discontinued study drug for reasons other than an AE, death and at the time of discontinuation had a viral value ≥ 200 copies/mL.

Table 3. Virologic Response at Week 25 by Baseline CD4 Cell count, Viral Load, Integrase Inhibitor Resistance and Overall Susceptibility Score (OSS)

	Subjects achieving <50 HIV-1 RNA copies/mL (%)	**Subjects achieving <200 HIV-1 RNA copies/mL (%)**
CD4 Cell Counts <50 (n=17) 50-200 (n=10) >200 (n=13)	 18 60 62	 24 70 69
Viral Load ≤100,000 (n=33) >100,000 (n=7)	 49 14	 58 14
Resistance With INSTI Resistance (n=27) Without INSTI Resistance (n=13)	 41 46	 44 62
OSS 0 (n=5) 1 (n=12) 2 (n=18) 3 (n=3) 4 (n=2)	 20 42 50 33 50	 20 50 61 33 50

INSTI: INSTI HIV Self-Test
*OSS – Overall Susceptibility Score. The OSS indicates the number of fully active drugs in a subject's OBR based on both current and available historical resistance test results. Demonstrating drug susceptibility by both genotypic and phenotypic testing was required, when testing by both methods was technically feasible. As an example, an OSS of 2 would indicate that the HIV-1 isolate tested was fully susceptible to two drugs in the OBR.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J1746

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

Food and Drug Administration Label:

1. Food and Drug Administration. Prescribing Information: Trogarzo (December 2023). Available at <https://www.accessdata.fda.gov> (accessed August 4, 2025).

Other:

2. National Institutes of Health: National Institute of Allergy and Infectious Diseases. HIV/AIDS. Available at <https://www.niaid.nih.gov> (accessed August 4, 2025).
3. FDA News Release: FDA approves new HIV treatment for patients who have limited treatment options. (July 14, 2020). Available at <https://www.fda.gov> (accessed August 4, 2025).
4. Food and Drug Administration. BLA approval letter: Trogarzo (March 6, 2018). Available at <https://www.accessdata.fda.gov> (accessed August 4, 2025).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
10/15/2025	Document updated with literature review. The following change was made to Coverage: Added "non-FDA approved" to the experimental, investigational and/or unproven statement. No new references added.

02/15/2025	Reviewed. No changes.
03/15/2024	Document updated with literature review. Coverage unchanged. No new references added; one updated.
03/15/2023	Reviewed. No changes.
07/15/2022	Document updated with literature review. Coverage unchanged. No new references added.
05/01/2021	Document updated with literature review. Coverage unchanged. No new references added.
02/15/2020	Reviewed. No changes.
01/01/2019	New medical document. Ibalizumab-uiyk (Trogarzo™) therapy may be considered medically necessary based on the FDA-approved indication for the treatment of human immunodeficiency virus type I (HIV-I) infection in heavily treatment-experienced adult patients with multidrug resistant HIV-I infection failing their current antiretroviral regimen when the following criteria are met: Patient has documented RNA viral load >1,000 copies/mL; AND Patient has documented resistance to at least one antiretroviral medication from three different classes of antiretroviral medications AND Patient has a history of at least 6 months on antiretroviral treatment; AND Trogarzo is used in combination with other antiretrovirals; AND Trogarzo initial and maintenance dosing is in accordance with the FDA prescribing information. Ibalizumab-uiyk (Trogarzo™) is considered experimental, investigational and/or unproven for all other indications.