DRUG QUANTITY MANAGEMENT POLICY – PER RX

POLICY: Antivirals – Valacyclovir Drug Quantity Management Policy – Per Rx
- Valtrex® (valacyclovir tablets – GlaxoSmithKline, generic)

REVIEW DATE: 04/19/2024

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Valacyclovir is a deoxynucleoside analogue DNA polymerase inhibitor indicated for:[1]

- Adults:
  - Treatment of **herpes labialis** (cold sores).
  - **Genital herpes**
    - Treatment in immunocompetent patients (initial or recurrent episode).
    - Suppression in immunocompetent or patients with human immunodeficiency virus (HIV-1) infection.
    - Reduction of transmission in immunocompetent patients.
  - **Herpes zoster**
    - Treatment in immunocompetent patients.
- Pediatric Patients:
  - Treatment of **herpes labialis** (cold sores), pediatric patients ≥ 12 years of age.
  - Treatment of **chickenpox**, immunocompetent pediatric patients 2 to < 18 years of age.

The efficacy and safety of valacyclovir has not been established in immunocompromised patients other than for the suppression of genital herpes in patients with HIV-1.[1]

Dosing

Manufacturer recommended dosing is provided in Table 1.

Table 1. FDA-Approved Indications and Dosing.[1]

Indication	Normal Dose (CrCl ≥ 50 mL/min)	Renal Dosing Adjustments†		
		CrCl ≥ 30 to ≤ 49 mL/min	CrCl ≥ 10 to ≤ 29 mL/min	CrCl < 10 mL/min
Adult				
Cold sores (Herpes labialis)	2 grams BID for 1 day	1 gram BID for 1 day	500 mg BID for 1 day	500 mg single dose
Genital herpes				
Initial episode	1 gram BID for 10 days		1 gram QD for 10 days	500 mg QD for 10 days
Recurrent episodes	500 QD for 3 days		500 mg QD for 3 days	
Suppressive therapy (immunocompetent patients)	1 gram QD OR 500 mg QD*		500 mg QD OR 500 mg Q48H*	
Suppressive therapy (HIV-infected patients)	500 mg BID		500 mg QD	
Reduction of transmission	500 mg QD	--	--	--
Herpes zoster (Shingles)	1 gram TID for 7 days	1 gram BID for 7 days	1 gram QD for 7 days	500 mg QD for 7 days

Table 1 (continued). FDA-Approved Indications and Dosing.[1]

Indication	Normal Dose (CrCl ≥ 50 mL/min)	Renal Dosing Adjustment†		
		CrCl ≥ 30 to ≤ 49 mL/min	CrCl ≥ 10 to ≤ 29 mL/min	CrCl < 10 mL/min
Pediatric				
Cold sores (Herpes labialis, age ≥ 12 years)	2 grams BID for 1 day	--	--	--
Chickenpox (age ≥ 2 to < 18 years)	20 mg/kg administered TID for 5 days; not to exceed 1 gram TID	--	--	--

CrCl – Creatinine clearance; † Patients requiring hemodialysis should receive the recommended dose of valacyclovir after hemodialysis. BID – Twice daily; QD – Once daily; * Alternative regimen in patients with a history of ≤ 9 recurrences per year; Q48H – Every 48 hours; HIV – Human immunodeficiency virus; TID – Three times daily.

Off-Label Dosing

There are data and/or guidelines to support several off-label uses of valacyclovir. Quantity limits for valacyclovir (Valtrex, generic) provide for 30 tablets per dispensing at retail or 90 tablets per dispensing at home delivery. This provides a quantity sufficient for the majority of labeled and off-label dosing. Below are situations where additional quantities of valacyclovir may be needed.

- Cytomegalovirus (CMV): For the prevention of CMV infection following solid organ transplantation (renal), the recommended dose of valacyclovir is 2 grams four times daily (QID).[2] Valacyclovir is not recommended as an option for prophylaxis in patients receiving heart, liver, pancreas, lung, intestinal, and composite tissue transplant. In hematopoietic cell transplant recipients, valacyclovir is also an option for CMV prophylaxis, with dosing ranging from 1 gram twice daily (BID) to 2 grams three times daily (TID), depending on the setting in which it is used.[3]
- Herpes simplex virus (HSV):
  - Immunocompromised patients: In adults and adolescents with HIV, valacyclovir 500 mg BID is recommended for chronic suppression of HSV.[4] Valacyclovir 500 mg BID is also recommended for the prevention of HSV in immunocompromised patients who have undergone solid organ transplant who are not already receiving CMV prophylaxis, as well as in HSV-seropositive hematopoietic cell transplant recipients.[3,5] In this same population in patients with severe mucocutaneous HSV, after initial intravenous (IV) therapy, oral therapy can be used as oral lesions begin to regress (valacyclovir 1 gram BID continued until lesions are completely healed).
  - Pregnant patients: For the suppression of HSV in a pregnant patient who has experienced a genital HSV lesion anytime during pregnancy, valacyclovir 500 mg BID starting at 36 weeks gestation and continued until delivery is a recommended alternative agent.[6]
- Herpes zoster (shingles):
  - Treatment: In adults and adolescents with HIV, guidelines recommend valacyclovir 1 gram TID for 7 to 10 days (or longer if lesions are slow to resolve) for the treatment of acute, localized, dermatomal herpes zoster (shingles).[4] Valacyclovir has been used for the treatment of localized herpes zoster (dermatomal) in solid organ transplant recipients at a dose of 1 gram TID for 7 days, or until lesions have crusted over which may be delayed in immunocompromised hosts.[7]
  - Prophylaxis: Refer to details in the VZV prophylaxis section below.
- Varicella zoster virus (VZV) [chickenpox]:
  - Treatment: In adults and adolescents with HIV, guidelines recommend valacyclovir 1 gram TID for 5 to 7 days for the treatment of uncomplicated cases of primary varicella infection (chickenpox).[4] For severe or complicated cases, patients are treated with IV therapy and are then transitioned to oral therapy with valacyclovir 1 gram TID after defervescence if no evidence of visceral involvement is notes is noted. Similar dosing is recommended in solid organ transplant recipients.[7]
  - Prophylaxis: For the short-term (3 to 6 months) prophylaxis of VZV or herpes zoster in solid organ transplant recipients who are HSV- or VZV-seropositive and not receiving cytomegalovirus (CMV) prophylaxis, valacyclovir 500 mg BID has been used.[7] It may also be considered in seronegative recipients. In hematopoietic cell transplant recipients who are VZV-seropositive, the recommended dose of valacyclovir is also 500 mg BID for 1 year following transplantation.[3] The duration may be extended in patients who require ongoing immunosuppression.

- Viral ophthalmic infections: Valacyclovir is recommended for the treatment of acute retinal necrosis, an ophthalmic reactivation of herpes zoster virus, following initial treatment with IV acyclovir.[8] Recommended doses range from 1 gram TID to 2 grams QID. In adults and adolescents with HIV and acute retinal necrosis, recommended treatment is acyclovir IV for 10 to 14 days, followed by oral valacyclovir 1 gram TID for 14 weeks or longer.[4] Valacyclovir has also been used for the management of herpes simplex keratitis at a dose of 500 mg TID for 2 weeks.[9]

Availability

Valacyclovir is available in 500 mg and 1,000 mg (1 gram) tablets.[1] Valacyclovir oral suspension (25 mg/mL or 50 mg/mL) may be prepared extemporaneously from 500 mg valacyclovir tablets for use in pediatric patients for whom a solid dosage form is not appropriate.

POLICY STATEMENT

This Drug Quantity Management program has been developed to promote dose consolidation of valacyclovir. If the Drug Quantity Management rule is not met for the requested medication at the point of service, coverage will be determined by the Criteria below. All approvals are provided for 1 year in duration.

Drug Quantity Limits

Product	Strength and Form	Retail Maximum Quantity per Rx	Home Delivery Maximum Quantity per Rx
Valtrex® (valacyclovir tablets, generic)	500 mg tablets	30 tablets	90 tablets
	1 gram tablets	30 tablets	90 tablets

Antivirals – Valacyclovir Drug Quantity Management Policy – Per Rx product(s) is(are) covered as medically necessary when the following criteria is(are) met. Any other exception is considered not medically necessary.

CRITERIA

Valacyclovir 500 mg tablets

1. If the medication is being requested for the chronic suppression or prevention of herpes simplex virus in an immunocompromised patient, approve the requested quantity, not to exceed 60 tablets per dispensing at retail or 180 tablets per dispensing at home delivery.

2. If the medication is being requested for the suppression of herpes simplex virus in pregnancy from 36 weeks of gestation until delivery, approve the requested

quantity, not to exceed 60 tablets per dispensing at retail or 180 tablets per dispensing at home delivery.

3. If the medication is being requested for the prophylaxis of herpes zoster/varicella zoster virus following solid organ transplantation or hematopoietic cell transplantation, approve the requested quantity, not to exceed 60 tablets per dispensing at retail or 180 tablets per dispensing at home delivery.

4. If the medication is being requested for a viral ophthalmic infection, approve the requested quantity, not to exceed 90 tablets per dispensing at retail or a 270 tablets per dispensing at home delivery.

Valacyclovir 1,000 mg (1 gram) tablets

1. If the medication is being requested for the prevention of cytomegalovirus infection after solid organ transplantation or hematopoietic cell transplantation, approve the requested quantity, not to exceed a 240 tablets per dispensing at retail or 720 tablets per dispensing at home delivery.

2. If the medication is being requested for the treatment of herpes simplex virus (HSV) infection in an immunocompromised patient, approve the requested quantity, not to exceed 60 tablets per dispensing at retail or 180 tablets per dispensing at home delivery.

3. If the medication is being requested for the treatment of acute local dermatomal herpes zoster in an immunocompromised patient, approve the requested quantity, not to exceed 90 tablets per dispensing at retail or 270 tablets per dispensing at home delivery.

4. If the medication is being requested for the treatment of varicella zoster virus infection in an immunocompromised patient, approve the requested quantity, not to exceed 90 tablets per dispensing at retail or 270 tablets per dispensing at home delivery.

5. If the medication is being requested for a viral ophthalmic infection, approve the requested quantity, not to exceed 240 tablets per dispensing at retail or 720 tablets per dispensing at home delivery.

REFERENCES

1. Valtrex® [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; June 2021.
2. Razonable RR and Humar A. Cytomegalovirus in solid organ transplant recipients: Guidelines of the American Society of Transplantation Infectious and Diseases Community of Practice. *Clin Transplant*. 2019;33:e13512.
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4. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Updated

September 25, 2023. Available at: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new. Accessed March 19, 2024.
5. Lee DH, Zuckerman RA, et al. Herpes simplex virus infections in solid organ transplantation: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant.* 2019;33(9):e13526.
6. American College of Obstetricians and Gynecologists. management of genital herpes in pregnancy: ACOG practice bulletin: bulletin number 220. *Obstet Gynecol*. 2020;135(5):e193-e202.
7. Pergam SA and Limaye AP on behalf of the American Society of Transplantation Infectious Diseases Community of Practice. Varicella zoster virus in solid organ transplantation: guidelines from the American Society of Transplantation Infectious Diseases Community. *Clin Transplant.* 2019;33:e13622.
8. Schoenberger SD, Kim SJ, Thorne JE, et al. Diagnosis and treatment of acute retinal necrosis: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2017;124(3):382-392.
9. Sugar A. Herpes simplex keratitis. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Last updated on May 25, 2022. Accessed on March 22, 2024.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Policy was updated to reflect the existing quantity limits when a product is obtained via home delivery. No changes to criteria.	04/06/2023
Annual Revision	**Valacyclovir 500 mg tablets:** • Override criteria for patients requesting valacyclovir for the chronic suppression or prevention of "Mucocutaneous herpes (genital, perianal, oral)" were clarified to chronic suppression or prevention of "herpes simplex virus". • Override criteria to approve for the requested quantity, not to exceed a 30-day supply per dispensing at retail or a 90-day supply per dispensing at home delivery if the medication is being requested for the suppression of herpes simplex virus (HSV) in pregnancy from 36 weeks of gestation until delivery, were updated to approve the requested quantity, not to exceed 60 tablets per dispensing at retail or 180 tablets per dispensing at home delivery. • Override criteria to approve an additional quantity if the medication is being requested for the prophylaxis of herpes zoster/varicella zoster virus following solid organ transplantation were updated to also include hematopoietic cell transplantation. • Override criteria to approve the requested quantity, not to exceed a 30-day supply per dispensing at retail or a 90-day supply per dispensing at home delivery if the medication is being requested for an ophthalmic infection were updated to approve the requested quantity, not to exceed 240 tablets per dispensing at retail or 720 tablets per dispensing at home delivery, if the medication is being requested for a viral ophthalmic infection. • Override criteria to approve a one-time override for 60 tablets at retail or home delivery for patients using acyclovir for prophylaxis of herpes gladiatorum were removed. **Valacyclovir 1,000 mg (1 gram) tablets:** • Override criteria to approve the requested quantity, not to exceed a 30-day supply at retail or a 90-day supply at home delivery if the medication is being requested for the prevention of cytomegalovirus infection after solid organ transplantation, bone marrow transplantation, or stem cell transplantation" were updated to	04/19/2024

	approve the requested quantity, not to exceed 240 tablets per dispensing at retail or 720 tablets per dispensing at home delivery if the medication is being requested for the prevention of cytomegalovirus infection after solid organ transplantation or hematopoietic cell transplantation. • Override criteria for patients requesting valacyclovir for the treatment of "mucocutaneous herpes" were clarified to treatment of "herpes simplex virus". • Override criteria were added to approve the requested quantity, not to exceed 90 tablets per dispensing at retail or 270 tablets per dispensing at home delivery if the medication is being requested for the treatment of varicella zoster virus infection in an immunocompromised patient. • Override criteria to approve the requested quantity, not to exceed a 30-day supply per dispensing at retail or a 90-day supply per dispensing at home delivery if the medication is being requested for an ophthalmic infection were updated to approve the requested quantity, not to exceed 240 tablets per dispensing at retail or 720 tablets per dispensing at home delivery, if the medication is being requested for a viral ophthalmic infection. **Exclusions:** Exclusions to not provide additional quantities of valacyclovir for the treatment of multiple sclerosis, chronic fatigue syndrome, or Epstein-Barr virus were removed.	