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Herpes Simplex Keratitis (HSK) Prescribing Protocol and Treatment Guideline

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1. Introduction and purpose

These Guidelines were developed in conjunction with Corneal Research Group at the University of Sydney Save Sight Institute. The aim of the document is to provide guidance to ophthalmologists around the prescribing protocol for the treatment of Herpes Simplex Keratitis.

2. Clinical Criteria

Herpes Simplex Keratitis is a clinical condition and diagnosis is based on the following clinical criteria:

- Epithelial keratitis (dendritic ulcer)
- Stromal keratitis: vascularisation, scarring, lipid keratopathy, ulceration
- Endothelial keratitis: Stromal oedema and keratic precipitates
- Keratouveitis: Corneal epithelial and/or stromal edema, stromal keratitis, keratic precipitates, and anterior chamber cells

Investigations required include Herpes simplex virus (HSV) PCR.

3. Contraindications and Precautions

Identified allergy to aciclovir and valaciclovir is a contra-indication. Precautions to note when prescribing include:

- Renal
- Increased risk of neurological adverse effects in renal impairment
- Dose adjustment is required

Pregnancy

- Valaciclovir is metabolised rapidly to aciclovir; limited data do not suggest an increased risk of congenital malformations, however, aciclovir is preferred as there is more clinical experience valaciclovir may be used from 36 weeks of pregnancy

Breastfeeding

- Safe to use

4. Proposed place in Therapy

Medical practitioners are required to state whether the drug is to be used as first, second or third line. Aciclovir or valaciclovir are used as first line therapy for herpes simplex keratitis.

5. Dosage and Duration of therapy

It is recommended that the Ophthalmologist adjust dosage for specific patient groups.

	Local Treatment Dosage	Systemic Treatment Dosage
Epithelial HSK	Topical aciclovir 5 times a day for 1-2 weeks	Immunocompromised patients Non-compliance, inability to use or tolerate, or ocular toxicity from topical aciclovir Oral Valaciclovir 500 mg BD for 7 days
	Without epithelial ulcer	With epithelial ulcer:
Stromal HSK	ORAL Valaciclovir 500 mg ONCE a day during topical steroid use PLUS Prednisolone 1% eye drops 4-6 times a day tapered over > 10 weeks	Oral Valaciclovir 1 g TDS for 7-10 days* PLUS Prednisolone 1% eye drops BD tapered slowly as disease comes under control
Endothelial HSK	ORAL Valaciclovir 500 mg to 1 g ONCE a day to TDS for 7-10 days* † PLUS Prednisolone 1% eye drops 4-6 times a day tapered over > 10 weeks	
Keratouveitis	ORAL Valaciclovir 1 g TDS for 7-10 days* PLUS Prednisolone 1% eye drops 4-6 times a day tapered over > 10 weeks Refer patient to cornea/uveitis clinic, respectively depending on degree of cornea or uveal involvement	
Prophylaxis	Indications: <ul style="list-style-type: none"> • Multiple recurrences of any type of HSK, especially stromal HSK • Patients with a history of ocular HSV: <ul style="list-style-type: none"> ➢ following any ocular surgery, including penetrating keratoplasty ➢ during immunosuppressive treatment Oral Aciclovir 400 mg BD OR Oral Valaciclovir 500 mg ONCE a day	
* Reduce Valaciclovir to prophylactic dose after 7-10 days and maintain for as long as frequent topical steroids are in use † There is a lack of clinical evidence to guide dosage in this situation		

Adult Renal Dosing for oral antivirals

CrCl(mL/min)	Dose	Frequency
Normal dosage Valaciclovir 500 mg ONCE a day		
<30	500 mg	Every 48 hours
Normal dosage Valaciclovir 500 mg BD		
<30	500 mg	Every 24 hours
Normal dosage Valaciclovir 1 g TDS		
30-49	1 g	Every 12 hours
10-29	1 g	Every 24 hours
<10	500 mg	Every 24 hours
Normal dosage Aciclovir 400mg BD		
0-10	200 mg	Every 12 hours

Use in Pregnancy

Aciclovir	Preferred due to more clinical experience. Category B3
Valaciclovir	Limited data do not suggest increased risk of congenital malformations. May be used from 36 weeks of pregnancy. Category B3.



Paediatric Dosing

Aciclovir	Drug of choice
Valaciclovir	Must only be used in children >12 years old

	Local treatment
3 months to 18 years	Epithelial HSK: Topical aciclovir 5 times a day for 14 days or for at least 3 days after healing, whichever is shorter

Systemic treatment dosage

Indications:

- Stromal HSK
- Skin involvement
- Coexistent systemic disease
- Non-compliance, inability to use or tolerate, or ocular toxicity from topical aciclovir
- Immunocompromised patients – seek advice from a Paediatric Infection Diseases Physician

Birth (at term) to 3 months	Seek advice from Paediatric Infection Diseases Physician
3 months to 12 years	Oral aciclovir 10 mg/kg (max 400 mg) 5 times a day for 5-7 days¹ or until there are no new lesions PLUS Prednisolone 1% eye drops BD-QID a day. (For severe inflammation, consider hourly dosing for 1-2 days ¹)
12 years to 18 years	Oral aciclovir 10 mg/kg (max 400 mg) 5 times a day for 5-7 days¹ or until there are no new lesions OR Oral Valaciclovir 500 mg BD for 5 days² if first episode (longer if new lesions appear during treatment or healing is incomplete) Oral Valaciclovir 500 mg BD for 3-5 days² if recurrent episode PLUS Prednisolone 1% eye drops BD-QID a day. (For severe inflammation, consider hourly dosing for 1-2 days ¹)
¹ Dosages taken from Australian Medical Handbook Children's Dosing Companion	
² Dosages taken from British National Formulary for children	

Important Drug Interactions

• **Mycophenolate**

Mycophenolate may increase aciclovir/valaciclovir concentration; renal excretion of both drugs may be reduced in renal impairment, may increase risk of adverse effects, e.g. neutropenia; dosage adjustment not usually necessary.

• **Theophylline**

Aciclovir/valaciclovir may increase theophylline concentration and risk of adverse effects; monitor theophylline concentration and for adverse effects; decrease theophylline dose as needed.

Administration Instructions:

- With systemic treatment, ensure adequate hydration (especially if receiving high doses) to minimise renal adverse effects
- Patient to be advised to take tablets with a full glass of water
- Need to ensure patients have the correct technique for administration for eye drops / ointment

6. Monitoring requirements

- Patient needs to be reviewed by ophthalmologist once the therapy has started according to the guidelines. Monitoring requirements to ascertain safety of use include:
 - **Blood and lymphatic system disorders:** Very rare: anaemia, leukopenia, thrombocytopenia.
 - **Immune system disorders:** Rare: anaphylaxis.
 - **Psychiatric and nervous system disorders:** Common: headache, dizziness, confusion, hallucinations, somnolence, convulsions. Very rare: agitation, tremor, ataxia, dysarthria, psychotic symptoms, encephalopathy, coma. The above events are reversible and usually reported in patients with renal impairment in whom the dosage was in excess of that recommended, or with other predisposing factors.
 - **Respiratory, thoracic and mediastinal disorders:** Rare: dyspnoea.
 - **Gastrointestinal disorders:** Common: nausea, vomiting, diarrhoea, abdominal pains.
 - **Hepatobiliary disorders:** Rare: reversible rises in bilirubin and liver related enzymes. Very rare: hepatitis, jaundice.
 - **Skin and subcutaneous tissue disorders:** Common: pruritus, rashes (including photosensitivity). Uncommon: urticaria, accelerated diffuse hair loss. Rare: angioedema.
 - **Renal and urinary disorders:** Rare: increases in blood urea and creatinine. Very rare: acute renal failure, renal pain. Renal pain may be associated with renal failure.
 - **General disorders:** Common: fatigue, fever.

7. Evaluating effectiveness

Drug treatment effectiveness is indicated by improvement of vision acuity and of clinical signs including:

- Resolution of epithelial defect or punctate corneal staining
- Reduction in inflammation of cornea stromal or anterior chamber
- Resolution stromal infiltrates

8. Management of complications

If complications such as changes in renal function during systemic treatment occur, best practice involves the following approaches:



- Rehydration
- Dosage reduction
- Stopping the drug

9. References

1. Herpes Simplex Virus keratitis: a treatment guideline. Michelle Lee White and James Chodosh. Department of Ophthalmology, Harvard Medical School. June 2014
2. Guess S, Stone D, Chodosh J. Evidence-based treatment of Herpes Simplex Virus Keratitis: A Systematic Review. *The Ocular Surface*. 2007 5(3): 240-50
3. Barron BA, Gee L, Hauck WW, Kurinij N, Dawson CR, Jones DB, et al. Herpetic Eye Disease Study. A controlled trial of oral acyclovir for herpes simplex stromal keratitis. *Ophthalmology*. 1994;101(12):1871-82.
4. A controlled trial of oral acyclovir for the prevention of stromal keratitis or iritis in patients with herpes simplex virus epithelial keratitis. The Epithelial Keratitis Trial. The Herpetic Eye Disease Study Group. *Archives of Ophthalmology*. 1997;115(6):703-12.
5. Acyclovir for the prevention of recurrent herpes simplex virus eye disease. Herpetic Eye Disease Study Group. *N Engl J Med*. 1998;339(5):300-6.
6. Australian Medical Handbook Children’s Dosing Companion
7. British National Formulary for children

10. Record of amendments to this document

Page	Details of Amendment	Date amended
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