health
Department:
Health
REPUBLIC OF SOUTH AFRICA

SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 18: EYE DISORDERS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017-2019)

Medicine amendment recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of the eye chapter.

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/RETAINED
18.1.2 Conjunctivitis, allergic	Sodium cromoglycate 2% ophthalmic drops	Deleted with cross-referral to PHC STGs & EML
	Oxymetazoline 0.025%, ophthalmic drops	Deleted with cross-referral to PHC STGs & EML
	Cetirizine, oral	Deleted with cross-referral to PHC STGs & EML
18.1.3 Conjunctivitis, bacterial	Chloramphenicol 1%, ophthalmic ointment	Dosing amended
	Fluoroquinolone ophthalmic drops	Retained as a therapeutic class
	Ciprofloxacin, ophthalmic drops	Retained as an example of therapeutic class (listed in STG); dosing amended
	Ofloxacin ophthalmic drops	Retained as an example of therapeutic class
	Moxifloxacin, ophthalmic drops	Added as an example of therapeutic class
18.2 Endophthalmitis, bacterial	Ceftazidime, intravitreal	Retained
	Vancomycin, intravitreal	Retained
	Ceftiaxone, IV	Retained
18.3 Glaucoma *(open angle glaucoma)* *- a) Treatment protocol*	Beta-blocker ophthalmic drops	Retained as first line option
	Prostaglandins ophthalmic drops	Retained as second line option
	Alpha-blockers ophthalmic drops	Retained as third line option
- b) Prostaglandin analogues	Prostaglandin analogues, ophthalmic drops	Therapeutic class retained
	Bimatoprost 0.03%, ophthalmic drops	Deleted
	Bimatoprost 0.01%, ophthalmic drops	Added as an example of therapeutic class – listed in STG
	Travoprost 0.04%, ophthalmic drops	Added as an example of therapeutic class
	Lantanoprost 0.05%, ophthalmic drops	Added as an example of therapeutic class
- c) Carbonic anhydrase inhibitors	Carbonic anhydrase inhibitors	Not declared as a class
	Acetazolamide oral	Retained
- d) Combination therapy	Fixed dose combinations	Statement added that fixed-dose combinations preferred, if available
18.4 Herpes zoster ophthalmicus	Amitriptyline, oral	Deleted with a cross-referral to section 26.1.4 Management of neuropathic pain (Post-herpetic neuralgia)
18.5.1 Keratitis, herpes simplex	Aciclovir ophthalmic ointment	Retained (phase-in/out approach)
	Aciclovir, oral	Added
18.5.2 Keratitis, suppurative	Fluoroquinolone ophthalmic drops	Therapeutic class retained
	Ciprofloxacin, ophthalmic drops	Retained as an example of therapeutic class (listed in STG)
	Ofloxacin ophthalmic drops	Retained as an example of therapeutic class

	Moxifloxacin, ophthalmic drops	Added as an example of therapeutic class
	Aciclovir, oral	Added
18.7 Uveitis	Dexamethasone 0.1%, ophthalmic drops	Retained
	Prednisone/prednisolone 1% ophthalmic drops	Not added
	Cyclopegic ophthalmic drops	Not added as a therapeutic class
18.8 Surgical and diagnostic products		
- *ocular diagnostics*	Cyclopegic ophthalmic drops	Not added as a therapeutic class
- *peri-operative agents*	Acetylcholine chloride ophthalmic solution	Retained
- *local anaesthetics*	Oxybuprocaine 0.4% ophthalmic solution	Retained
	Tetracaine 1%, ophthalmic solution	Therapeutic alternative added to Adult Hospital Level therapeutic class spreadsheet

18.1.2 CONJUNCTIVITIS, ALLERGIC

Sodium cromoglycate 2% ophthalmic drops: *deleted with cross-referral to PHC STGs and EML*
Oxymetazoline 0.025%, ophthalmic drops: *deleted with cross-referral to PHC STGs and EML*
Cetirizine, oral: *deleted with cross-referral to PHC STGs and EML*

The STG was deleted with a cross reference to the PHC STGs and EML, section 18.1.1 Conjunctivitis, allergic.
However, reports of supply challenges of sodium cromoglycate eye drops were received from KwaZulu-Natal (KZN), noting that the supplier cannot meet demand - KZN consumes monthly quantities of about 14000 units per month. An evidence review for a therapeutic alternative was done.

Non-responsive to 1st line treatment (oxymetazoline)/ history of recurrent (seasonal)/chronic allergic conjunctivitis:
Anti-allergic eye drops: *recommended as a therapeutic group (consisting of mast cell inhibitor eye and mast cell inhibitor/antihistamine eye drops – see list below)*

Evidence: Further to the Owen et al meta-analysis (2004), previously reviewed for inclusion of sodium cromoglycate eye drops to the PHC EML; the Cochrane review by Castillo et al, 2015[1] was reviewed - low quality RCTs were reviewed of either RCTs comparing various agents (antihistamines and mast cell stabilisers) or vs placebo. However, RCTs were very heterogeneous and only evaluated short-term effects, ranging from one to eight weeks treatment duration. Meta-analysis was only possible for RCTs comparing olopatadine vs ketotifen, but should be interpreted with caution as studies were of low methodological quality. The authors concluded that there was some evidence suggesting that topical antihistamines and mast cell stabilisers were safe and efficacious in reducing symptoms and signs of seasonal allergic conjunctivitis compared to placebo. However, there is insufficient evidence to determine whether antihistamines or mast cells are the most effective. Furthermore, there is a paucity of good quality evidence with sufficient follow-up time for

[1] Castillo M, Scott NW, Mustafa MZ, Mustafa MS, Azuara-Blanco A. Topical antihistamines and mast cell stabilisers for treating seasonal and perennial allergic conjunctivitis. Cochrane Database Syst Rev. 2015 Jun 1;(6):CD009566. https://www.ncbi.nlm.nih.gov/pubmed/26028608

management of seasonal/perennial allergic conjunctivitis. Guidelines[2] recommends mast cell stabilisers or antihistamine/mast cell stabilisers for recurrent or persistent allergic conjunctivitis.
Recommendation: Given the continuous supply challenges of cromoglicic acid 2%, the following topical dual antihistamine/mast cell stabilizer anti-allergic eye drops are recommended to be grouped in a therapeutic group and listed on the PHC Therapeutic class spreadsheet, accordingly:

Medicine	Directions for use	Price (ZAR)*	ml	Daily dose (ml)**	Price for 30 days (ZAR)
cromoglicic acid 2%,	1 drop 6 hourly	75.59	13	0.2	34.89
lodoxamide 0.01%	1 drop 6 hourly	288.63	10	0.2	173.18
olopatadine 0.1%	1 drop 12 hourly	251.74	5	0.1	151.04
epinastine 0.05%	1 drop 12 hourly	225.61	5	0.1	135.37
ketotifen 0.025%,	1 drop 12 hourly	253.74	5	0.1	152.24
azelastine 0.05%	1 drop 12 hourly	88.70	10	0.1	39.92

* Cheapest product listed on SEP database, accessed 26 June 2019
** 1 drop = 0.05mL

Level of Evidence: II Systematic review and meta-analysis of low to moderate quality RCTs, Guidelines

Leukotriene inhibitors, oral: *not added*
Meta-analysis[3] suggests that leukotriene inhibitors are more efficacious than placebo but less efficacious than oral antihistamines in adult patients for treating allergic conjunctivitis.
Level of Evidence: I Meta-analysis

18.1.3 CONJUNCTIVITIS, BACTERIAL

Chloramphenicol 1%, ophthalmic ointment: *dosing amended*
Aligned with SAMF, 2016.
Level of Evidence: III Guidelines

Fluoroquinolone ophthalmic drops: *retained as a therapeutic class*
Ciprofloxacin, ophthalmic drops: *retained as an example of therapeutic class (listed in STG)*
Ofloxacin, ophthalmic drops: *retained as an example of therapeutic class (listed in therapeutic interchange database)*
Moxifloxacin, ophthalmic drops: *added as an example of therapeutic class (listed in therapeutic interchange database)*

Background: Comment received from Mpumalanga Provincial representative on NEMLC querying the restriction of therapeutic agents in the fluoroquinolone ophthalmic drops to only ciprofloxacin and ofloxacin. The decision was based on pragmatic implications and expert opinion with alignment to the Paediatric Hospital Level STGs and EML, 2017.

Evidence review:
- *Antimicrobials:* Cochrane review concludes that bacterial conjunctivitis is a self-limiting disease with marginal benefit from antimicrobials. Evidence suggests that topical antibiotics may "speed up the resolution of symptoms and infection"[4].

[2] Varu DM, Rhee MK, Akpek EK, Amescua G, Farid M, Garcia-Ferrer FJ, Lin A, Musch DC, Mah FS, Dunn SP; American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Conjunctivitis Preferred Practice Pattern®. Ophthalmology. 2019 Jan;126(1):P94-P169. https://www.ncbi.nlm.nih.gov/pubmed/30366797
[3] Gane J, Buckley R. Leukotriene receptor antagonists in allergic eye disease: a systematic review and meta-analysis. J Allergy Clin Immunol Pract. 2013 Jan;1(1):65-74. https://www.ncbi.nlm.nih.gov/pubmed/24229824

- *Efficacy:* Clinical evidence review[5] of 23 RCTS (low to moderate quality) conducted in children and adults, found no significant difference in rates of clinical cure between various topical antibiotics; except one RCT with methodological flaws (mismatch of the unit of randomisation (people) and the unit of analysis (eyes) and standard dose of moxicfloxacin compared to minimum dose of comparator – trimethoprim/polymixin B) showed that moxifloxacin significantly increased clinical and microbiological cure rates vs trimethoprim/polymyxin.
- *Safety:* Safety review of RCT and observational data[6] showed that moxifloxacin, ciprofloxacin and ofloxacin were associated with similar rates of overall adverse effects.
- *Fluoroquinolone therapeutic group:* Limited evidence (Sheikh, 2012; Epling, 2012) suggests that efficacy of topical antibiotics are comparable for treatment of bacterial conjunctivitis and other factors such as local microbiological resistance patterns, cost, and patient factors (e.g., allergies, compliance) should also be considered.
- *Local microbiology study:* Retrospective study in a Tertiary Hospital in Gauteng showed that in patients presenting with corneal ulcers – "gram positives isolates showed a 95.3% sensitivity to ciprofloxacin. Both second and fourth generation fluoroquinolones, ciprofloxacin and moxifloxacin respectively, showed equivalent (100%) *in vitro* activity against the gram negative isolates"[7].

Recommendation: Fluoroquinolone be recommended as a therapeutic group for treatment of bacterial conjunctivitis, including ciprofloxacin, moxifloxacin and ofloxacin. The cheapest medicine on contract to be listed as an example of class in the STG (*Tender price:* ciprofloxacin 3mg/ml 5ml: R13.47, moxifloxacin 5mg/ml 5ml: R126.49, ofloxacin 3mg/mL 5ml: R18.44[8]; *SEP:* gatifloxacin 5mg/ml 5ml: R198.16[9]).
Rationale: Despite bacterial conjunctivitis having a spontaneous resolution rate, evidence suggests that topical antibiotics may "speed up the resolution of symptoms and infection". Limited evidence shows that efficacy of topical antibiotics are comparable for treatment of bacterial conjunctivitis.
Level of Evidence: II Systematic reviews of low to moderate quality RCTs

Ciprofloxacin, ophthalmic drops: *dosing amended*
Dosing of ciprofloxacin was amended to align with dosing recommendations as recommended in RCTs and the SAMF, 2016 edition.
Level of Evidence: II RCT of low to moderate quality[10], Guidelines[11]

The narrative of the STG was updated to:

- Ciprofloxacin 0.3%, ophthalmic drops, instil 1 drop **2 hourly for 2 days.**
  - Then reduce frequency to 1 drop **4 hourly for 5 days, while awake.**

18.2 ENDOPHTHALMITIS, BACTERIAL

Ceftazidime, intravitreal: *retained*

[4] Sheikh A, Hurwitz B, van Schayck CP, McLean S, Nurmatov U. Antibiotics versus placebo for acute bacterial conjunctivitis. Cochrane Database Syst Rev. 2012 Sep 12;(9):CD001211. https://www.ncbi.nlm.nih.gov/pubmed/22972049
[5] Epling J. Bacterial conjunctivitis. BMJ Clin Evid. 2012 Feb 20;2012. pii: 0704. https://www.ncbi.nlm.nih.gov/pubmed/22348418
[6] Silver LH, Woodside AM, Montgomery DB. Clinical safety of moxifloxacin ophthalmic solution 0.5% (VIGAMOX) in pediatric and nonpediatric patients with bacterial conjunctivitis. Surv Ophthalmol. 2005 Nov;50 Suppl 1:S55-63. https://www.ncbi.nlm.nih.gov/pubmed/16257311
[7] Koetsie M. Dissertation: Microbiology results of infective corneal ulcers at a tertiary hospital in South Africa, 2011. Faculty of Health Sciences, University of the Witwatersrand, August 2011. [Accessed September 2019] http://hdl.handle.net/10539/11020
[8] Contract circular RT301-2017
[9] SEP database, accessed September 2019
[10] Leibowitz HM. Antibacterial effectiveness of ciprofloxacin 0.3% ophthalmic solution in the treatment of bacterial conjunctivitis. Am J Ophthalmol. 1991 Oct;112(4 Suppl):29S-33S. https://www.ncbi.nlm.nih.gov/pubmed/1928271
[11] SAMF, 2016

Vancomycin, intravitreal: *retained*
Ceftiaxone, IV: *retained*
The Adult Hospital Level Committee was of the opinion that intravitreal administration would only be done by opthalmologists and thus not relevant for secondary and regional level of care.
However, external comments from stakeholders were received to retain medicine management in the STG in order to ensure continued access of ceftazidime at Regional level of care (where ophthalmology care is provided in some centres).

18.3 GLAUCOMA

OPEN ANGLE GLAUCOMA

a) Treatment protocol
Beta-blocker ophthalmic drops: *retained as first line option*
Prostaglandins ophthalmic drops: *retained as second line option*
Alpha-blockers ophthalmic drops: *retained as third line option*
Fixed dose combinations: *statement added that fixed-dose combinations preferred, if available*

Collaboration took place with the South African Society of Ophthalmology, as reports were received that the current standard of care is not aligned with international guidelines.

First line:
Guidelines: The European Glaucoma Society Guidelines[12] were used to amend the treatment protocol of open angle glaucoma. Three reviewers assessed these Guidelines using the AGREE II tool, reaching agreement in most of the domains and assessing the guidelines as acceptable, with adaptation to local needs and ensuring the service delivery platform is sufficient (in terms of staffing resources, skills and training).

IOP-lowering agents: The EGS guidelines state that the goal of glaucoma treatment is to maintain patient's visual function at a sustainable cost, noting that the condition is a common cause of blindness in Africa[13]. The approach shown to be effective is lowering of intraocular pressure (IOP).[14]

Prostaglandins: A meta-analysis is described, that showed that prostaglandins (bimatoprost, travoprost and latanoprost), followed by non-selective beta-blocker (0.5% timolol) were the most effective IOP–reducing agents in primary open angle glaucoma; followed by alpha-adrenergic inhibitors (brimonidine), selective beta blocker (0.5% betaxolol) and then carbonic anhydrase (ranked in descending order of effectiveness).[15]

Beta-blockers: Beta-blockers are associated with systemic side-effects and should be used with caution in patients with cardiopulmonary conditions.

Patient adherence: Prostaglandins are administered once-daily (other agents are administered twice daily), promoting adherence.

[12] European Glaucoma Society Terminology and Guidelines for Glaucoma, 4th Edition - Chapter 3: Treatment principles and options Supported by the EGS Foundation: Part 1: Foreword; Introduction; Glossary; Chapter 3 Treatment principles and options. Br J Ophthalmol. 2017;101(6):130-195. https://pubmed.ncbi.nlm.nih.gov/28559477/
[13] Lewallen S, Courtright P. Blindness in Africa: present situation and future needs. Br J Ophthalmol. 2001;85(8):897-903. https://pubmed.ncbi.nlm.nih.gov/11466240/
[14] Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120(10):1268-1279. https://pubmed.ncbi.nlm.nih.gov/12365904/
[15] van der Valk R, Webers CA, Schouten JS, Zeegers MP, Hendrikse F, Prins MH. Intraocular pressure-lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials. Ophthalmology. 2005;112(7):1177-1185. https://pubmed.ncbi.nlm.nih.gov/15921747/

Price of medicines: Comparative prices of medicines, currently available on tender[16]:

Therapeutic class	Agent	Daily dosing	Cost/month
Prostaglandins	Bimatoprost 0.03%, 3mL*	1 drop daily	R28.64
	Travoprost 0.04%, 2.5mL	1 drop daily	R47.41
Non-selective beta-blockers	Timolol 0.25%, 5mL	1 drop 12 hourly	R11.67
	Timolol 0.5%, 5mL	1 drop 12 hourly	R10.62
	Levobunolol 0.5%, 5mL	1 drop 12 hourly	R9.17
Alpha-blocker	Brimonidine 0.15%, 5mL	1 drop 12 hourly	R37.27
	Brimonidine 0.2%, 5mL	1 drop 12 hourly	R40.86
Selective beta blockers	Betaxolol 0.25%, 5mL	1 drop 12 hourly	R23.19
	Betaxolol 0.5%, 5mL	1 drop 12 hourly	R23.92
Combination products:			
Prostaglandin + non-selective beta-blocker	Bimatoprost/Timolol 0.3/5mg/ml, 3mL	1 drop daily	R39.41
	Travoprost/Timolol 40mcg/5mg, 2.5mL	1 drop daily	R40.35
Alpha-blocker + non-selective beta-blocker	Brimonidine/Timolol 2/5mg/ml, 5mL	1 drop 12 hourly	R92.89

** The updated Adult Hospital Level STGs and EML, 2019 edition recommends lower dose bimatorprost 0.01% - limited evidence of efficacy suggests that bimatoprost 0.01% comparable to 0.03% in reducing intraocular pressure in open angle glaucoma; whilst improved tolerability with lower scores of hyperaemia experienced with lower dose bimatoprost.*

Routine use of prostaglandins is the preferred initial monotherapy agent in terms of effectiveness in reducing IOP, patient adherence and systemic safety in the patient cohort with cardiopulmonary conditions. However, prostaglandins are more expensive than non-selective beta-blockers.

Recommendation: Beta-blockers be retained as first-line option, prostaglandins as second-line and alpha-blockers as third-line.
Rationale: Meta-analysis showed that prostaglandins and timolol were the most effective in reducing IOP; mean difference from baseline (trough) reported as -7.0mmHg, -6.8mmHg, -6.5mmHg, -6.9mmHg for travoprost, latanoprost, bimatoprost and timolol, respectively. Despite daily dosing of prostaglandins improving patient adherence, these agents are more expensive than beta-blockers. The STGs recommends prostaglandins as first-line monotherapy, where beta-blockers are contra-indicated.
Level of Evidence: II Meta-analysis of disease-oriented RCTs, Expert opinion

b) Prostaglandin analogues
Prostaglandin analogues, ophthalmic drops: *therapeutic class retained*
This was reviewed and accepted by the NEMLC in the previous review cycle (2013-2015), see below:

Adult Hospital Level NEMLC Report of 10 December 2018
Prostaglandin analogues ophthalmic drops: *declared as a therapeutic class*
- *Prostaglandin analogues ophthalmic drops*[17] was verified as a therapeutic class comprising of bimatoprost 0.03% eye drops, latanoprost 0.005% and travoprost 0.004%.
  Rationale: Latanoprost, bimatoprost, and travoprost were comparable in their ability to reduce IOP in open-angle glaucoma.
  Level of Evidence: II Disease oriented RCT

Bimatoprost 0.03%, ophthalmic drops: *deleted*
Bimatoprost 0.01%, ophthalmic drops: *added as an example of therapeutic class (listed in STG)*
Travoprost 0.004%, ophthalmic drops: *added as an example of therapeutic class (listed in therapeutic interchange database)*
Latanoprost 0.005%, ophthalmic drops: *added as an example of therapeutic class (listed in therapeutic interchange database)*

[16] Contract circular HP07-2017DAI, accessed 6 June 2020
[17] Parrish RK, Palmberg P, Sheu WP; XLT Study Group. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. Am J Ophthalmol. 2003 May;135(5):688-703. PubMed PMID: 12719078.

Background: The tender for ophthalmic drops is currently in process and an ophthalmologist in the public health sector, on behalf of Allergan Pharmaceuticals has submitted a request for a deviation from the tender specification of bimatoprost 0.03% to 0.01% to the National Department of Health, Affordable Medicines Directorate. The Adult Hospital Level Committee was requested to review the evidence for this formulation.

A summary overview of the evidence follows (Bimatoprost 0.01% vs 0.03% for glaucoma, August 2019):

Bimatoprost 0.001%
vs 0.03% for Glaucor

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Bimatoprost 0.01% as opposed to 0.03% be recommended as an example of prostaglandins for reduction of intraocular pressure in open angle glaucoma in the STG. And, therapeutic class database to be updated accordingly.

Rationale: Limited evidence of efficacy suggests that bimatoprost 0.01% comparable to 0.03% in reducing intraocular pressure in open angle glaucoma; whilst improved tolerability with lower scores of hyperaemia experienced with lower dose bimatoprost.

Level of Evidence: I RCT, Observational study

c) Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors: *not declared as a class*

Acetazolamide oral: *retained*

This was reviewed and accepted by the NEMLC in the previous review cycle (2013-2015), see below:

Adult Hospital Level NEMLC Report of 10 December 2015

Carbonic anhydrase inhibitors: not declared as a class

Acetazolamide oral: retained

Carbonic anhydrase inhibitors: Small double-blinded RCT[18] showed that topical carbonic anhydrase inhibitor (dorzolamide 2%) was not as effective as systemically administered acetazolamide.

***Recommendation:** Acetazolamide oral, 250 mg 6 hourly to be recommended as the carbonic anhydrase in severe cases of glaucoma, prior to ocular surgery.*

Rationale: Topical carbonic anhydrase inhibitor (dorzolamide 2%) shown to be not as effective as systemically administered acetazolamide.

Level of Evidence: II Disease oriented RCT

d) Combination products

Combination of two agents (e.g. beta-blocker with prostaglandin) may be required to achieve the patient's individualised target IOP. However, polydrug regimens may affect patient adherence,[19] reduce efficacy through wash-out of earlier medicines with later medicines,[20] [21] and increase exposure to preservatives (causing ocular discomfort).[22] Thus, fixed dose-combinations are preferred. Fixed dose combinations generally have comparable clinical equivalence to unfixed combinations.[23]

[18] Maus TL, Larsson LI, McLaren JW, Brubaker RF. Comparison of dorzolamide and acetazolamide as suppressors of aqueous humor flow in humans. Arch Ophthalmol. 1997 Jan;115(1):45-9. PubMed PMID: 9006424.

[19] Olthoff CM, Schouten JS, van de Borne BW, Webers CA. Noncompliance with ocular hypotensive treatment in patients with glaucoma or ocular hypertension an evidence-based review. Ophthalmology. 2005;112(6):953-961. https://pubmed.ncbi.nlm.nih.gov/15885795/

[20] Chrai SS, Makoid MC, Eriksen SP, Robinson JR. Drop size and initial dosing frequency problems of topically applied ophthalmic drugs. J Pharm Sci. 1974;63(3):333-338. https://pubmed.ncbi.nlm.nih.gov/4820359/

[21] Serle JB, Toor A, Fahim MM, Polikoff LA, Ellison J. The Effect of Varying Dosing Interval on the Efficacy of Intraocular Pressure Lowering Drugs. Invest Ophthalmol Vis Science 2004;45(5):971 https://iovs.arvojournals.org/article.aspx?articleid=2406778

[22] Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. Br J Ophthalmol. 2002;86(4):418-423. https://pubmed.ncbi.nlm.nih.gov/11914211/

[23] Cox JA, Mollan SP, Bankart J, Robinson R. Efficacy of antiglaucoma fixed combination therapy versus unfixed components in reducing intraocular pressure: a systematic review. Br J Ophthalmol. 2008;92(6):729-734. https://pubmed.ncbi.nlm.nih.gov/18460539/

Recommendation: The following text is proposed for inclusion to the narrative of the STG:

Note: Fixed combination therapy, when available, is preferred to two separate instillations of agents. This improves patient adherence and decreases excess exposure to preservatives (minimising ocular discomfort).

Level of Evidence: II Meta-analysis of disease-oriented RCTs, Observational studies, Guidelines

18.4 HERPES ZOSTER OPHTHALMICUS

Post-herpetic neuralgic pain

Amitryptiline, oral: *deleted with a cross-referral to section 26.1.4 Management of neuropathic pain (Post-herpetic neuralgia).*

18.4 KERATITIS, HERPES SIMPLEX

Aciclovir, oral: *added*
Aciclovir, ophthalmic ointment: *retained (phase-in/out approach)*

Background: Aciclovir 3%, ophthalmic ointment has recently been discontinued from the South African market and thus an alternative medicine is required if ointment is unavailable.
Evidence: Cochrane review (2015)[24] showed that oral aciclovir appeared as effective as single topical antiviral agent for relative corneal epithelial healing at two weeks (RR 0.92; 95% CI 0.79 to 1.07). However, this was an old single double-blinded RCT of 60 study participants (with attrition rate of 7%) done in 1986[25]. Similarly, at 14 days healing was comparable between oral and topical acyclovir: 24/27 vs 28/29 RR 0.92 (95% CI 0.79 to 1.07); p=0.28.
Recommendation: In the event that aciclovir 3%, ophthalmic ointment is unavailable, oral aciclovir may be considered for treating herpes simplex virus epithelial keratitis.
Rationale: Limited RCT evidence suggests that oral aciclovir is as effective as topical aciclovir in healing corneal epithelia at 2 weeks.
Level of Evidence: II Systematic review of low quality RCTs.

18.5.2 KERATITIS, SUPPURATIVE

Fluoroquinolone ophthalmic drops: *retained as a therapeutic class*
Ciprofloxacin, ophthalmic drops: *retained as an example of therapeutic class (listed in STG)*
Ofloxacin ophthalmic drops: *retained as an example of therapeutic class (listed in therapeutic interchange database)*
Moxifloxacin, ophthalmic drops: *added as an example of therapeutic class (listed in therapeutic interchange database)*

Aligned to Guidelines[26], STG recommends broad spectrum antibiotic as empirical therapy for bacterial keratitis, pending microscopy and culture results.
Level of Evidence: III Guidelines

[24] Wilhelmus KR. Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis. Cochrane Database Syst Rev. 2015 Jan 9;1:CD002898. https://www.ncbi.nlm.nih.gov/pubmed/25879115
[25] Collum LM, McGettrick P, Akhtar J, Lavin J, Rees PJ. Oral acyclovir (Zovirax) in herpes simplex dendritic corneal ulceration. Br J Ophthalmol. 1986 Jun;70(6):435-8. https://www.ncbi.nlm.nih.gov/pubmed/3521717
[26] Lin A, Rhee MK, Akpek EK, Amescua G, Farid M, Garcia-Ferrer FJ, Varu DM, Musch DC, Dunn SP, Mah FS; American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Bacterial Keratitis Preferred Practice Pattern®. Ophthalmology. 2019 Jan;126(1):P1-P55. https://www.ncbi.nlm.nih.gov/pubmed/30366799

18.7 UVEITIS

Prednisone/prednisolone ophthalmic drops: *not added*

Dexamethasone ophthalmic drops: *retained*

Available RCTs could not be retrieved comparing prednisone vs dexamethasone, ophthalmic drops for uveitis – see medicine review, prednisolone 1% vs dexamethasone 0.1% ophthalmic drops for uveitis (May 2018):

PrednisoloneVsDexamethasone for Uve

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Much as corticosteroids are the main stay in the management of uveitis, there are no robust comparative studies to qualify the use of either prednisolone acetate or dexamethasone. However, prednisolone is widely used and it would be appropriate to consider as a second agent for treatment of acute non-infectious uveitis, where the cheaper option, dexamethasone is not available.

Level of Evidence: III Expert opinion, Guidelines[27]

Cyclopegic ophthalmic drops: *not added as a therapeutic class*

Various agents have varying onsets of action and duration of action (with regards to mydriasis and cyclopegia). Most agents are listed in the Adult Hospital Level STGs and EML, 2015.

Recommendation: Cyclopegic agents (cyclopentolate, phenylephrine, isopto atropine, tropicamide, isopto homatropine and homatropine) not to be grouped as a therapeutic class.

Rationale: Various procedures would require different onset and duration of action, and the cyclopegic agents had varying pharmacokinetic properties.

Level of Evidence: III Expert opinion

Cycloplegic ophthalmic drops	Onset of action	Duration of midriasis	Duration of cycloplegia	Onset of cyclopegia (minutes)
Atropine	10-15 minutes; maximum effect 30-40 minutes	2-3 weeks	6 days	45-120
Cyclopentolate	20-30 minutes; maximal effect after 60 minutes	24 hours	24 hours	30-60
Tropicamide	15-20 minutes	6-7 hours	2-6 hours	20-40 minutes
Homatropine	15 minutes; maximum effect within 30-40 minutes	6-96 hours	36-48 hours	30-60 minutes

Reference: SAMF, 2016

18.8 SURGICAL AND DIAGNOSTIC PRODUCTS

Ocular diagnostic products

Cyclopegic ophthalmic drops: *not added as a therapeutic class*

See rationale above, under section 18.7: Uveitis.

Peri-operative agents

Acetylcholine chloride (for intra-ocular irrigation): *retained*

With supply constraints of acetylcholine eye drops, a therapeutic alternative was requested. In consultation with the Ophthalmology Society of South Africa, there is only one other miotic that is registered with SAHPRA: Minims pilocarpine nitrate 2%. However, this product has also been discontinued from the South African market. Thus, S21 access would be required going forward.

[27] Espinosa G, Muñoz-Fernández S, García Ruiz de Morales JM, Herreras JM, Cordero-Coma M. Treatment recommendations for non-infectious anterior uveitis. Med Clin (Barc). 2017 Dec 20;149(12):552.e1-552.e12. https://www.ncbi.nlm.nih.gov/pubmed/28911893

Local anaesthetics

Oxybuprocaine 0.4% ophthalmic solution: *retained*

Tetracaine 1%, ophthalmic solution: *therapeutic alternative added to Adult Hospital Level therapeutic class spreadsheet*

Available evidence of very low quality (n=14) showed that there was no significant difference in anaesthesia was found between the agents at each time point over 30 minutes[28]. These agents included:

- oxybuprocaine (benoxinate) - *available on South African market*
- proxymetacaine
- amethocaine (tetracaine) – *available on South African market*

18.10.1 CHEMICAL BURN AND 18.10.2 EYE INJURY: BLUNT/PENETRATING/ FOREIGN BODY

The Adult Hospital Level Committee recommended that as the STGs are duplicates of the PHC STGs, that a cross-reference be included. Management is the same at both levels of care with referral to ophthalmological care centre for continued care.

Note: Engagement with the South African Society of Ophthalmology has been initiated for collaboration in the upcoming review.

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)
- ***Note:*** *Information was sourced from NEMLC ratified minutes and NEMLC-approved documents.*

[28] Lawrenson JG, Edgar DF, Tanna GK, Gudgeon AC. Comparison of the tolerability and efficacy of unit-dose, preservative-free topical ocular anaesthetics. Ophthalmic Physiol Opt. 1998 Sep;18(5):393-400. https://www.ncbi.nlm.nih.gov/pubmed/10023471