South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Eye conditions

MEDICINE REVIEW:

1. Executive Summary

Date: May 2018
Medicine (INN): Prednisolone 1%, ophthalmic drops
Medicine (ATC): S01BA04
Indication (ICD10 code): Uveitis (H20.0)
Patient population: Adult patients on topical steroidal treatment of non-infectious uveitis.
Prevalence of condition:75 to 204 per 100,000 annually world wide
Level of Care: Hospital level
Prescriber Level: Medical officer
Current standard of Care: Dexamethasone 0.1%, ophthalmic drops
Efficacy estimates: n/a
Motivator/reviewer name(s): JM Nabyoma
PTC affiliation: N/A

2. **Name of author(s)/motivator(s):** JM Nabyoma

3. **Authors affiliation and conflict of interest details:**
North West Department of Health: Lehurutshe Hospital; Adult Hospital Level Committee (2017-2020). No conflict of interest to declare

4. **Introduction**
Uveitis is a heterogeneous group of intraocular inflammatory diseases of the anterior, intermediate, and posterior uveal tract. It is the fifth most common cause of vision loss, accounting for 5% to 20% of legal blindness, with the highest incidence of disease in the working age population. The pharmacological treatment of uveitis is controversial, with limited high level evidence to inform most of the key treatment decisions that face the patient and clinician on a daily basis due to paucity of trial evidence to inform these important clinical decisions
Corticosteroids are the mainstay of acute treatment for all anatomical subtypes of non-infectious uveitis and can be administered orally, topically with drops or ointments, periocular or intravitreal injection or by surgical implantation

5. **Purpose /Objective of Review:** To compare the efficacy and safety of prednisolone acetate eye drops and dexamethasone 0.1% ophthalmic drops for treatment of non-infectious uveitis

Population	Adult patients with non-infectious uveitis
Intervention	Dexamethasone 0.1%, ophthalmic drops
Comparison	Prednisolone, ophthalmic drops
Outcomes	Relief of pain and photophobia, Elimination of inflammation, Prevention of structural complications such as synechiae, secondary cataract and glaucoma Preservation or restoration of good visual function

6. **Methods**
   a. **Data sources:** The following databases were searched; PubMed, Science direct, and Cochrane
   b. **Search strategy:** various searches conducted for RCT's and systematic review, also looked at the reference lists ofstudy reports, citation databases, and abstracts and clinical study presentations from professional meetings.

      ((((((("prednisolone"[MeSH Terms] OR "prednisolone"[All Fields]) OR ("prednisolone acetate"[Supplementary Concept] OR "prednisolone acetate"[All Fields])) AND ("dexamethasone"[MeSH Terms] OR "dexamethasone"[All Fields])) OR (("dexamethasone"[MeSH Terms] OR "dexamethasone"[All Fields]) AND phospate[All Fields])) OR (("dexamethasone"[MeSH Terms] OR "dexamethasone"[All Fields]) AND ("sodium"[MeSH Terms] OR ("sodium"[All Fields] AND "sodium"[All Fields] OR MeSH Terms]) AND phospate[All Fields])) AND ("uveitis"[MeSH Terms] OR "uveitis"[All Fields])) OR (non[All Fields] AND infectious[All Fields] AND ("uveitis"[MeSH Terms] OR "uveitis"[All Fields]))"uveitis"[All Fields]))

   c. **Selection of studies:** No study with head to head comparison of the prednisolone acetate and dexamethasone ophthalmic preparation. Included were RCTs comparing either agent to other corticosteroid preparation in management of uveitis, reviews, expert opinions and practice guidelines were also included.

7. **Evidence synthesis:** (**Note:** No RCTs could be retrieved comparing prednisone/prednisolone to dexamethasone eye drops).

Author	Population	N	Corticosteroid ophthalmic (topical)	Follow-up	Key results
(Biswas *et al.*, 2004)	Patients with acute, chronic and recurrent anterior uveitis	78	Rimexolone vs prednisolone acetate ophthalmic suspensions	3-7 days	• Rimexolone is as effective as prednisolone acetate ophthalmic suspension in the treatment of anterior uveitis. • The largest difference found was 0.1 in the flare reaction (statistically insignificant; p = 0.3) and 0.2 score units (statistically significant; p = 0.01) in the cells. • Overall, comparison of the drugs shows no clinical significance in the treatment of anterior uveitis by either drug. • Difference in intraocular pressure (IOP) was also statistically insignificant (p > 0.05). However, three patients in the prednisolone acetate group and 1 patient from the rimexolone group showed a rise in IOP.
(Foster *et al.*, 1996)	Patients with acute uveitis, recurrent iridocyclitis, or chronic uveitis treatable by topical corticosteroid	276	Rimexolone 1% ophthalmic suspension vs 1% prednisolone acetate	36 to 72 hours	• When anterior chamber cell and flare were measured, rimexolone 1% was found to be as effective as 1% prednisolone. • The largest difference observed between treatments was 0.5 score unit, not clinically significant. • There were no statistically significant differences in cell scores in either study (P > .05). • No statistically significant differences in flare scores were found except at Day 28 in Study One (P = .04). • Also, prednisolone was found to be more likely than rimexolone to cause a clinically significant increase (10 mm Hg or more) in intraocular pressure (1.7 times more likely in Study One, eight
Sheppard et al., 2014 This phase III, double-masked, noninferiority study randomized patients with mild to moderate endogenous AU	Patients with mild to moderate endogenous AU	110	Difluprednate 0.05% vs prednisolone acetate 1%	14 days	• At day 14, the mean change in anterior chamber cell grade with difluprednate was no inferior to that with prednisolone acetate (-2.2 vs. -2.0, P = 0.16). • The proportions of difluprednate-treated patients versus prednisolone acetate-treated patients demonstrating complete clearing of anterior chamber cells at day 3 were 13.0% vs. 2.1% (P = 0.046) and at day 21 were 73.9% vs. 63.8% (P = 0.013). • A significant difference between the groups in the mean intra ocular pressure (IOP) increase was seen at day 3 (2.5 mm Hg for difluprednate-treated patients and 0.1 mm Hg for prednisolone acetate-treated patients, P = 0.0013) but not at other time points. The mean IOP values in both groups remained less than 21 mm Hg throughout the study. • Difluprednate 0.05% four times daily is well tolerated and is no inferior to Prednisolone acetate 1% eight times daily for the treatment of endogenous AU.

Guidelines

Treatment recommendations for non-infectious anterior uveitis (AU) (Espinosa *et al.*, 2017)

- *Aim:* Develop recommendations on the use of immunodepressors in patients with non-infectious, non-neoplastic anterior uveitis (AU) based on best evidence and experience.
- *Conclusions:* In patients with non-infectious, non-neoplastic AU, corticosteroids are recommended. It is also recommended that the choice of the route of administration is based on the severity of the disease with topical steroids recommended for mild uveitis.

See Appendix A for AGREE II scoring sheet.

Penetration

(Awan *et al.*, 2009) A systematic review of literature indexed by Ovid MEDLINE & EMBASE was performed up to December 2008. There are few studies on their aqueous penetration in human subjects. The penetration of different ocular corticosteroids into human aqueous humour along with the therapeutic implications on management of ocular surface diseases, immune-related corneal diseases, anterior uveitis and postoperative anti-inflammatory use were discussed. In the context of the paucity of well-constructed, prospective clinical trials comparing the efficacy of different corticosteroids, it provides guiding principles for the use of topical corticosteroids. Dexamethasone alcohol 0.1% and prednisolone acetate 1% are potent corticosteroids, but the latter achieves the highest aqueous concentration within 2 h and maintains higher levels for 24 h. Subconjunctival corticosteroids provide very high concentrations in the aqueous which maintain higher concentrations for longer periods.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	**SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS**
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident: [ ] Not confident: [x] Uncertain: [ ]	See evidence synthesis table, above.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: [x] Harms outweigh benefits: [ ] Benefits = harms or Uncertain: [ ]	See evidence synthesis table, above.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes: [x] No: [ ] Dexamethasone 0.1% ophthalmic drops Prednisolone 1% ophthalmic drops List specific exclusion from the group: n/a	Rationale for therapeutic alternatives included: Aligned with guideline recommendations. References: Epinosa et al, 2017 Rationale for exclusion from the group: n/a References: n/a

VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor ☐ Major ☐ Uncertain ☒ x **Is the option acceptable to key stakeholders?** Yes ☐ No ☐ Uncertain ☒ x	
RESOURCE USE	**How large are the resource requirements?** More intensive ☐ Less intensive ☐ Uncertain ☒ x	Cost of medicines/ month: **Medicine** | **Cost (ZAR)*** Prednisolone 1% 5ml. eye drops | 49.79 Dexamethasone 0.1% 5ml eye drops | 11.60 *Contract circular HP07-2017DAI **Additional resources:** n/a
EQUITY	**Would there be an impact on health inequity?** Yes ☐ No ☐ Uncertain ☒ x	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes ☐ No ☐ Uncertain ☒ x	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☒ X	☐	☐

Recommendation: Dexamethasone 0.1% ophthalmic drops be retained in the Adult Hospital Level EML for uveitis.

Rationale: 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

Other Factors and Considerations:

- Cost implication
- Efficacy in non-acute uveitis

,Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
x		X

VEN status:

Vital	Essential	Necessary
	X	

NEMLC MEETING OF 26 SEPTEMBER 2019

NEMLC accepted the medicine review and the proposed recommendations proposed by the Adult Hospital Level Committee.

Monitoring and evaluation considerations

Research priorities: Controlled head to head studies for topical steroids need to be prioritised especially prednisolone and dexamethasone

References

- Biswas J, Ganeshbabu TM, Raghavendran SR, Raizada S, Mondkar SV, Madhavan HN. Efficacy and safety of 1% rimexolone versus 1% prednisolone acetate in the treatment of anterior uveitis--a randomized triple masked study. Int Ophthalmol. 2004 May;25(3):147-53.
- Foster CS, Alter G, DeBarge LR, Raizman MB, Crabb JL, Santos CI, Feiler LS, Friedlaender MH. Efficacy and safety of rimexolone 1% ophthalmic suspension vs 1% prednisolone acetate in the treatment of uveitis. Am J Ophthalmol. 1996 Aug;122(2):171-82.
- Sheppard JD, Toyos MM, Kempen JH, Kaur P, Foster CS. Difluprednate 0.05% versus prednisolone acetate 1% for endogenous anterior uveitis: a phase III, multicenter, randomized study. Invest Ophthalmol Vis Sci. 2014 May 6;55(5):2993-3002.
- 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.

APPENDIX A

AGREE II scoring sheet:

Domains	Criteria	Score	Comments
Domain 1: Scope and Purpose	The overall objective(s) of guideline is (are) specifically described	6	To develop recommendations on the use of immunodepressors in patients with non-infectious, non-neoplastic anterior uveitis (AU) based on best evidence and experience.
	The health questions(s) covered by guideline is (are) specifically described	3	Not very clear when to start and stop population differentiation.
	Population (patients, public etc.) to whom guideline is meant to apply to is specifically described	4	Yes – patients with non-infectious, non-neoplastic anterior uveitis (AU) based on best evidence and experience.
Domain 2: Stakeholder Involvement	The guideline development group includes individuals from all relevant professional groups	6	Multidisciplinary panel
	The views and preferences of the target population (patients, public, etc.) have been sought	1	Patient groups included in the studies used not stated if are from limited resource settings.
	Target users of the guideline are clearly defined	6	Strongly agree
Domain 3: Rigour of Development	Systematic methods were used to search for evidence	4	It is stated in the methodology though not clearly stated how it was done
	The criteria for selecting evidence are clearly described	5	Not clearly defined
	The strengths and limitations of the body of evidence are clearly described	5	Agree
	The methods for formulating the recommendations are clearly described	6	Clearly described in the methods
	The health benefits, side effects, and risks have been considered in formulating the recommendations	1	Not clearly defined
	There is an explicit link between the recommendations and the supporting evidence	6	Strongly agree
	The guideline has been externally reviewed by experts prior to its publication	6	Strongly agree
	A procedure for updating the guideline is provided	1	None
Domain 4: Clarity of Presentation	The recommendations are specific and unambiguous	6	Strongly agree
	The different options for management of the condition or health issue are clearly presented	6	Strongly agree. Different categories of uveitis are presented
	Key recommendations are easily identifiable	6	Strongly agree
Domain 5: Applicability	The guideline describes facilitators and barriers to its application	3	Not clear
	The guideline provides advice and/or tools on how recommendations can be put into practice	6	Strongly agree
	The potential resource implications of applying the recommendations have been considered	3	Not clear
	The guideline presents monitoring and/or auditing criteria	3	Not clear
Domain 6:Editorial independence	The views of the funding body have not influenced the content of the guideline	3	Not clear
	The competing interests of guideline development group members have been recorded and addressed.	6	Not clear, recorded but not clearly addressed