North Central London
Joint Formulary Committee

CICLOSPORIN EYE PREPARATIONS FACT SHEET

TREATMENT OF OCULAR INFLAMMATORY CONDITIONS

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Comments on this document should be sent to Moorfields Eye Hospital Medicines Information Department on 020 7556 2369 or to the JFC Support Pharmacist for the North Central London Medicines Optimisation Network via admin.ncl-mon@nhs.net.

This document is intended for use by Prescribers within North Central London only – the information contained within the factsheet is not suitable to be shared with patients / public or non-NHS Organisations. This factsheet has been produced to inform and review local decision making using the best available evidence at the time of publication. The information in this document may be superseded in due course.

Ciclosporin Eye Preparations
FACT SHEET - FOR THE TREATMENT OF OCULAR INFLAMMATORY CONDITIONS

Ciclosporin eye preparations should only be initiated in secondary care by a specialist in ophthalmology

Check List and Actions for GPs

- Practices must ensure that the information sheet / letter has been received from an ophthalmologist with indication for use, likely duration of treatment and evidence that the specialist has discussed with the patient that the product may be used for an off-label indication / dose (where relevant)
- Practices must ensure that the patient meets criteria for continuation of treatment (prescription initiated by a specialist in ophthalmology and patient stabilised on treatment)
- Practices must ensure that repeat prescriptions will guarantee continuation of treatment until review

Please note this is not a full summary of drug information. Always refer to the most recent BNF and/or summary of product characteristics.

NICE

NICE state that ciclosporin (Ikervis®) is recommended as a possible treatment for treating severe keratitis in adult patients with dry eye disease that has not improved despite treatment with artificial tears. https://www.nice.org.uk/guidance/ta369

Initiation

Ciclosporin eye preparation may be started in patients with the indicated diseases who have been found to be dependent on topical steroid to keep them free from sight-threatening ocular surface inflammation and/or free from severe and debilitating symptoms. No special tests or results are required before initiating treatment.

Indication

Ciclosporin eye preparations may be recommended as a treatment *option* after first-line agents (e.g. ocular lubricants / steroids) have failed or are not tolerated for:

- Atopic Keratoconjunctivitis (AKC) & Vernal Keratoconjunctivitis (VKC)
- Dry Eye Disease (DED)/ Keratoconjunctivitis Sicca (KCS)
- Blepharokeratoconjunctivitis (BKC) / Ocular Rosacea
- Thygeson's keratitis & Chronic graft versus host disease

Products

Ikervis (licensed in adults)

- Ciclosporin 1mg/ml eye drops [emulsion] – single use.
- Licensed for the treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes.
- One ml of emulsion contains 1 mg of ciclosporin and 0.05 mg cetalkonium chloride.
- Ikervis is supplied in 0.3 ml single-dose containers presented in a sealed laminate aluminium pouch (one pouch contains five single-dose containers).
- Each single-dose container is sufficient to treat both eyes. Any unused emulsion should be discarded immediately.

Verkazia (licensed in paediatrics/adolescents)

- Ciclosporin 1mg/ml eye drops [emulsion] – single use.
- Licensed for the treatment of severe vernal keratoconjunctivitis (VKC) in children from 4 years of age and adolescents.
- One ml of emulsion contains 1 mg of ciclosporin and 0.05 mg cetalkonium chloride.
- Verkazia is supplied in 0.3 ml single-dose containers presented in a sealed laminate aluminium pouch (one pouch contains five single-dose containers).
- Each single-dose container is sufficient to treat both eyes. Any unused emulsion should be discarded immediately.

Ciclosporin 0.2% eye ointment (unlicensed)

- 3.5 g tube containing ciclosporin 2.0 mg/g.
- Preservative free.

Choice of ciclosporin eye product

- The licensed ciclosporin eye product (currently Ikervis in adults and Verkazia in children/adolescents) should be used first line.
- Some patients may not tolerate ciclosporin 1mg/ml eye drops (Ikervis and Verkazia) due to sensitivity to excipients. In such patients it may be necessary to prescribe ciclosporin 0.2% eye ointment.
- Ciclosporin 0.05% eye drops (Restasis®) is unlicensed in the UK and should not be prescribed.
- Ciclosporin 2% and 0.06% eye drops (unlicensed specials) are no longer manufactured and should not be prescribed.
- Please see Figure 1 for an overview of the product choice.

Supply

- Ikervis and Verkazia: Initial supply will be made by the hospital pharmacy. Once stable, as judged by a specialist in ophthalmology, the patient may obtain further supplies from primary care, subject to providing the GP with relevant information containing indication, likely duration of treatment and evidence that a discussion with the patient has taken place regarding the unlicensed nature of the product, if applicable.
- Ciclosporin 0.2% eye ointment: Supply will be made by the hospital pharmacy throughout treatment.

Administration

- Ikervis:
  The recommended dose is one drop once daily to be applied to the affected eye(s) at bedtime.
  Occasionally more frequent administration may be required at the discretion of consultant for recalcitrant disease. Duration of therapy: Subject to the patient diagnosis, to be communicated in GP letter.
- Verkazia:
  The recommended dose is one drop up to four times a day, and can be reduced accordingly to control signs and symptoms.
- Ciclosporin 0.2% eye ointment:
  The ointment may be used up to four times daily.

Review

- Patients are to be reviewed at least every 6 months by a specialist in ophthalmology.

Therapeutic Drug Monitoring

- Therapeutic drug monitoring is not required for topically administered ophthalmic ciclosporin products.

Storage

- Ciclosporin eye products should be stored below 30°C (Ikervis and Verkazia) / below 25°C (ciclosporin 0.2% eye ointment). Do not freeze.
- Ikervis and Verkazia: After opening the aluminium pouches the single-dose containers should be kept in the pouch in order to protect from light and avoid evaporation.
- Shelf life from manufacture: 3 years (Ikervis and Verkazia) / 2 years (ciclosporin 0.2% eye ointment).
- In use expiry (Ikervis and Verkazia): opened individual single-use containers with remaining emulsion should be discarded immediately after use.

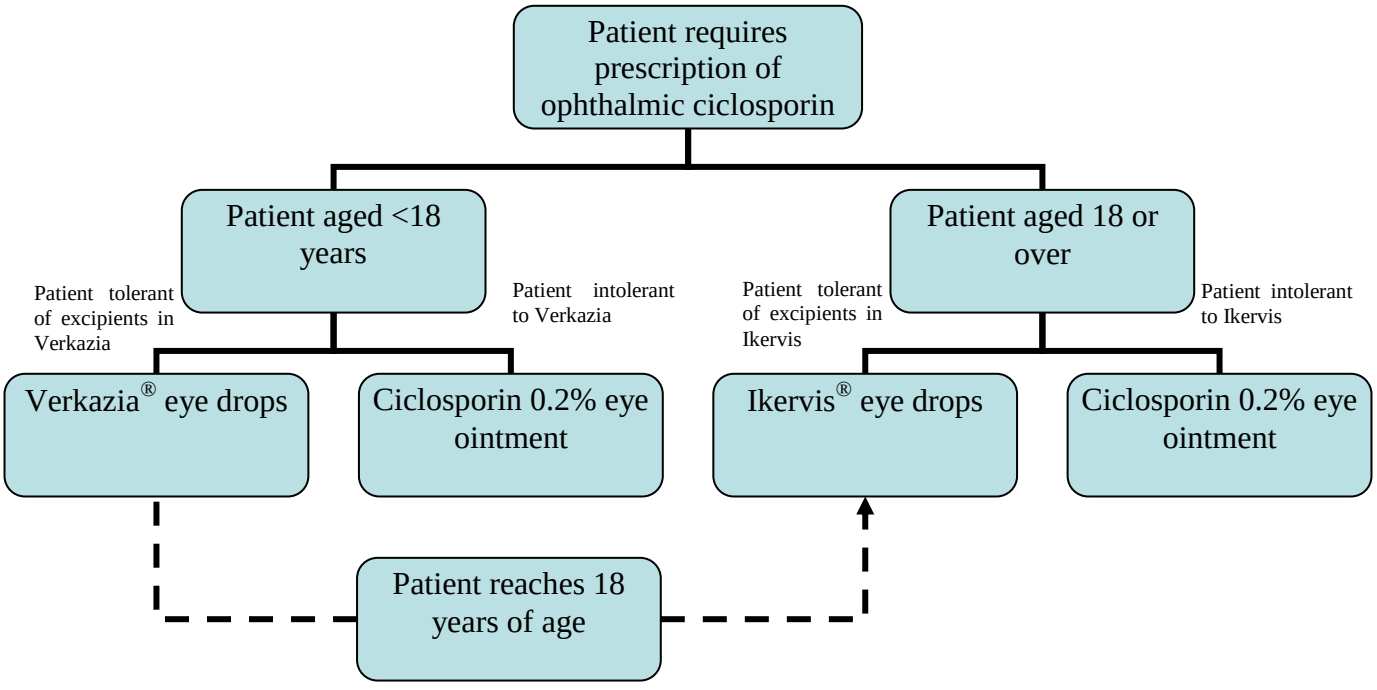
Adverse drug reactions (ADRs) reported

- Ikervis: Side effects from therapy are likely to be localised, transitory and mild to moderate in severity. The most common side effects reported were eye pain (19.2%), eye irritation (17.8%), lacrimation (6.4%), ocular hyperaemia (5.5%) and eyelid erythema (1.7%).
  Please refer to the SPC for the full list of ADRs
- Verkazia: Side effects from therapy are likely to be localised, transitory and mild to moderate in severity. The most common adverse reactions in the clinical trials were eye pain (11%) and eye pruritus (9%).
  Please refer to the SPC for the full list of ADRs
- Ikervis and Verkazia contain cetalkonium chloride which may cause eye irritation.
- Contact lens wear should be avoided unless under specialist advice.
  Please refer to the Ikervis SPC or Verkazia SPC for the full list of cautions.

Procurement

- Ikervis/Verkazia ciclosporin 1mg/ml eye drops may be obtained by community pharmacies from usual commercial wholesalers.
- Ciclosporin eye ointment may be obtained from veterinary wholesalers.

Figure 1 – Overview of the choice of ciclosporin product



Appendix 1: Quick Reference Guides

Product name & form	Ciclosporin 1mg/ml eye drops [emulsion] (Ikervis)	Ciclosporin 1mg/ml eye drops [emulsion] (Verkazia)	Ciclosporin 0.2% eye ointment
Presentation	Single-dose, single-use containers	Single-dose, single-use containers	3.5 g eye ointment
Category	Licensed medicine	Licensed medicine	POM-V (unlicensed)
Patient Groups	Adults above 18 years of age	Children and adolescents under 18 years of age	Patients intolerant to any of the excipients in the eye drop formulation
Indications of Use	1. Severe allergic eye disease: Atopic Keratoconjunctivitis (AKC) & Vernal Keratoconjunctivitis (VKC) (off-label but approved for use in primary care by NCL JFC) 2. Dry Eye Disease (DED)/ Keratoconjunctivitis Sicca (KCS) 3. Blepharo-keratoconjunctivitis (BKC) / Ocular Rosacea (off-label but approved for use in primary care by NCL JFC) 4. Thygeson's keratitis & Chronic graft versus host disease (off-label but approved for use in primary care by NCL JFC)	1. Severe Vernal Keratoconjunctivitis (VKC) in children from 4 years of age and adolescents 2. Severe Atopic Keratoconjunctivitis (AKC) (off-label) 3. Dry Eye Disease (DED)/ Keratoconjunctivitis Sicca (KCS) (off-label) 4. Blepharo-keratoconjunctivitis (BKC) / Ocular Rosacea (off-label) 5. Thygeson's keratitis & Chronic graft versus host disease (off-label)	1. Severe allergic eye disease: Atopic Keratoconjunctivitis (AKC) & Vernal Keratoconjunctivitis (VKC) 2. Dry Eye Disease (DED)/ Keratoconjunctivitis Sicca (KCS) 3. Blepharo-keratoconjunctivitis (BKC) / Ocular Rosacea 4. Thygeson's keratitis & Chronic graft versus host disease
Rationale for Use	Previous alternatives have failed to treat underlying condition	Previous alternatives have failed to treat underlying condition	Previous alternatives have failed to treat underlying condition
Dose	Normally once daily at night, however, it can be used up to four times a day	The recommended dose is one drop up to four times a day, and reduced accordingly to control signs and symptoms	Up to four times a day
Duration of Treatment	Long-term (specific duration dependant on patient diagnosis)	Long-term (specific duration dependant on patient diagnosis)	Long-term (specific duration dependant on patient diagnosis)
Cautions	• Wash hands before and after use • Do not use in pregnancy • Not recommended in women of childbearing potential not using effective	• Wash hands before and after use • Do not use in pregnancy • Not recommended in women of childbearing potential not using	• Wash hands before and after use • Do not use in pregnancy • Not recommended in women of childbearing potential not using

	contraception • Do not use when there is fungal disease in the eye unless under the direct care of a specialist and with appropriate antifungal cover Please refer to the SPC for a full list of cautions	effective contraception • Do not use when there is fungal disease in the eye unless under the direct care of a specialist and with appropriate antifungal cover Please refer to the SPC for a full list of cautions	effective contraception • Do not use when there is fungal disease in the eye unless under the direct care of a specialist and with appropriate antifungal cover
Side effects	Mild irritation in the first few days of treatment may occur. Please refer to SPC for further information.	Mild irritation in the first few days of treatment may occur. Please refer to SPC for further information.	Mild irritation in the first few days of treatment may occur
Monitoring	No specific monitoring required as systemic absorption is minimal	No specific monitoring required as systemic absorption is minimal	No specific monitoring required as systemic absorption is minimal
Storage	Store below 30°C. Do not freeze. Discard unused content of each container immediately after use	Store below 30°C. Do not freeze. Discard unused content of each container immediately after use	Store below 25°C. Do not freeze. Once opened use within one month
Review	Patients are to be reviewed at least every 6 months by a specialist in ophthalmology	Patients are to be reviewed at least every 6 months by a specialist in ophthalmology	Patients are to be reviewed at least every 6 months by a specialist in ophthalmology
Other Information	• Licensed for the treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes • Contains cetalkonium chloride, medium-chain triglycerides, glycerol, tyloxapol, poloxamer 188, sodium hydroxide (to adjust pH) and water for injections	• Licensed for the treatment of severe vernal keratoconjunctivitis (VKC) in children from 4 years of age and adolescents • Contains cetalkonium chloride, medium-chain triglycerides, glycerol, tyloxapol, poloxamer 188, sodium hydroxide (to adjust pH) and water for injections	• Licensed as an animal medicine but has been manufactured to exactly the same standards as required for licensed human medicines • Useful when patients cannot tolerate eye drops • Contains paraffin base, maize oil and lanolin alcohol
Ordering Information	Directly from commercial wholesalers	Directly from commercial wholesalers	Directly from veterinary wholesaler

Appendix 2: Background and Clinical Information

Background

Ciclosporin A is a fungal antimetabolite used as an anti-inflammatory drug due to its ability to inhibit interleukin 2 activation of lymphocytes.[1] It is used systemically to prevent graft rejection in organ and tissue transplantation as well as in the treatment of eczema and psoriasis.[2] From the 1980s reports have highlighted that topical ciclosporin can be used to treat a variety of ocular inflammatory conditions including dry eye disease, vernal & atopic keratoconjunctivitis and ocular rosacea (blepharokeratoconjunctivitis (BKC)).[3,4,5] Topical ciclosporin (CsA) also has niche applications in post adenovirus keratitis, Thygeson's keratitis and peripheral corneal melts (particularly Mooren's ulcer). Conventional long term treatment with topical steroids to reduce ocular inflammation risks severe adverse effects including cataract formation and increased intraocular pressure.[2]

Up until 2015, no licensed preparations had been available for use in the eye. However, various unlicensed preparations were available from importers, veterinary manufacturers or specials manufacturers. There are currently two licensed ciclosporin preparations available, Ikervis and Verkazia, licensed in adult and paediatric/adolescent populations, respectively.[25,26]

Many patients have encountered difficulty upon trying to obtain topical ophthalmic ciclosporin in primary care due to a reluctance of GP's to prescribe. Such decisions may be based on a lack of information regarding choice of product, indication for use, safety, treatment duration, licensing status, cost, availability and place in therapy. This protocol aims to provide information to accompany informed prescribing.

Indications & Summary of Efficacy Data

1. **Dry Eye Disease (DED) / Keratoconjunctivitis sicca (KCS)**
   DED is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolality of the tear film and inflammation of the ocular surface.[6] Use of lubricating eye drops does not directly address the ocular surface inflammation. Anti-inflammatory therapies should be considered for patients with moderate to severe disease with symptoms or evidence of corneal disease refractory to treatment.[7] The role of ciclosporin in the treatment of dry eye was reviewed in the Report of the Management and Therapy Subcommittee of the International Dry Eye Work Shop (2007). This was a consensus document by a group of highly-respected experts on ocular surface disease, including one from the UK. The report concluded that anti-inflammatory therapies should be considered for patients with moderate to severe disease with symptoms or evidence of corneal disease refractory to treatment. As part of the literature search performed by Moorfields Eye Hospital, 12 trials were identified of which ten showed a demonstrable effect on dry eye. Further details of these trials can be obtained on request from the Moorfields Eye Hospital Medicines Management Team.

2. **Atopic Keratoconjunctivitis (AKC) & Vernal Keratoconjunctivitis (VKC)**
   AKC is a bilateral inflammatory ocular disease associated with atopic dermatitis. AKC is chronic in nature with frequent corneal complications which can cause permanent loss of vision. Aetiology involves a complex immunomodulatory dysfunction including type I and IV hypersensitivity reactions with Th1

cytokine profile.[8] Corneal complications are seen in up to 70% of patients and approximately 30% require corneal transplantation.[9]

VKC is a seasonal chronic ocular allergic disease which is usually self-limiting. However in 5 -30% of cases permanent ocular changes may occur with associated visual impairment.[10] The immunopathogenetic mechanism is complex and involves an IgE-mediated immediate hypersensitivity response as well as a Th2 type immune reaction.[11]

In both VKC and AKC it is not uncommon for patients to be dependent on topical steroid treatment to control their ocular surface inflammation. These patients are at significant risk of steroid-related ocular side-effects and this risk may be mitigated by use of topical ciclosporin to reduce or eliminate steroid-dependence.

González-López et al (2012) conducted a Cochrane review on topical ciclosporin for atopic keratoconjunctivitis.[12] The authors identified three RCTs with a total of 58 participants that were eligible for inclusion. One study reported on the use of 2% CsA in maize oil and two on the use of a commercial emulsion of 0.05% CsA. Of these three studies, one showed a beneficial effect of topical CsA in controlling signs and symptoms of AKC,[13] one in controlling signs of AKC[14] and one did not show evidence of an improvement[15]. Only two studies analysed the effect of topical CsA in reducing topical steroid use; one showed a significant reduction in topical steroid use with CsA[14], but the other did not show evidence of this improvement.[15] No serious adverse events were reported in the trials.[13,14,15] The authors concluded that topical CsA may provide clinical and symptomatic relief in AKC and may help to reduce topical steroid use in patients with steroid-dependent or steroid-resistant AKC. The authors also remarked that no serious adverse events were identified in the trials.

A recent systematic review and meta-analysis of topical ciclosporin in allergic conjunctivitis reviewed results from 3 trials in AKC and 4 trials in VKC and concluded that the topical ciclosporin was more effective than placebo in alleviating the overall signs and symptoms of allergic conjunctivitis. However, the clinical and methodological heterogeneities in the studies mean that the overall efficacy should be interpreted with caution.[16]

A literature search conducted at Moorfields Eye Hospital found 14 trials where topical ciclosporin was used for atopic or vernal keratoconjunctivitis, of which 13 showed a demonstrable effect. Further details of these trials can be obtained on request from the Moorfields Eye Hospital Medicines Management Team.

3. Ocular Rosacea / (blepharokeratoconjunctivitis (BKC))

Rosacea is an oculo-cutaneous inflammatory disorder which affects the facial sebaceous glands and the meibomian glands of the eyelid. Ocular rosacea is characterised by blepharo-keratoconjunctivitis, which can range from mild punctate epithelial erosions to significant corneal neovascularization and thinning. The skin shows erythema, telangiectasia and pustules over the cheeks, nose, and forehead with thickening over the nose (rhinophyma) in the later stages of this potentially sight threatening condition. The precise pathophysiology is unknown although a proposed theory is delayed type hypersensitivity like reaction. The traditional mainstay of treatment is similar to that of posterior blepharitis with topical antibiotics and steroids.[7]

Van Zuuren et al (2011) conducted a Cochrane review on interventions for rosacea and concluded that ciclosporin 0.05% ophthalmic emulsion appears to be more effective than artificial tears for rosacea of the eyes.[17] The authors identified ciclosporin as the only drug for which there was high grade evidence of effect in the disease, based on one RCT by Schechter et al (2009).[18]

4. **Niche applications in ocular surface inflammatory diseases**

   There are case series supporting the use of topical ciclosporin in a variety of chronic ocular surface inflammatory diseases such as Thygeson's keratitis and chronic graft versus host disease.

Author	Year	Trial characteristics				Number of patients (experimental / control)	Side effects	Outcome
		Disease	Design	Intervention	Comparator			
Reinhard T et al[19]	1996	Thygeson's keratitis	Case series	2% CsA 3 times Daily for a month with reducing regimen over 6 months		31 eyes of 17 patients	Burning and stinging	Complete resolution of opacities in 21/31 at 6 months. Partial resolution in a further 8/31.
Lelli GJ et al[20]	2006	Graft versus host disease	Case series	0.05% - 2% CsA 2-4 times Daily		32 eyes of 16 patients	Irritation, burning	Corneal fluorescein staining improved in all patients. Dry eye symptoms improved in 10 patients (62.5)

Safety & monitoring

No significant systemic adverse effects have been reported in any of the trials found. Restasis has been used in the US since 2003. The most common adverse reaction reported on the Restasis prescribing information sheet is ocular burning (17%). Other reactions reported in 1% to 5% of patients included conjunctival hyperaemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).[21]

Barber et al (2005) conducted a phase III, follow on, non-randomized safety evaluation of ciclosporin 0.1% ophthalmic emulsion, administered twice daily to dry eye disease patients. 412 adult patients, previously treated with ophthalmic ciclosporin, were treated for up to 3 years (mean duration of 19.8 months). The authors concluded ciclosporin was safe, well tolerated, and not associated with systemic side effects.[22] The most common treatment-related adverse events were localised burning sensation (10.9%), stinging (3.9%) and conjunctival hyperaemia (3.4%).

The only other option open to patients with chronic inflammatory conditions are topical steroids which have a poor adverse effect profile, particularly in long term treatment. These adverse effects include cataract and raised intraocular pressure. When treated with topical steroids for 4–6 weeks 5% of the population demonstrated a rise in intraocular pressure greater than 16 mmHg and 30% demonstrated a rise of 6–15 mmHg.[23,24] Patients using topical steroids require regular monitoring at 2-6 monthly follow up visits to screen for adverse effects whereas stable patients on CSA may be reviewed once per year.

Therapeutic drug monitoring is not required for topically administered ophthalmic ciclosporin products.

References

1. Matsuda S, Koyasu S. Mechanisms of action of cyclosporine. Immunopharmacology 2000; 47: 119–25.
2. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press <http://www.medicinescomplete.com> [Accessed on [17/05/2018]]
3. Lemp MA. Management of dry eye disease. The American Journal of Managed Care 2008; 14: 88–101.
4. Ophthalmic Special Order Products, General Principles. Royal College of Ophthalmologist & UK Ophthalmic Pharmacists Group. May 2014.
5. Moorfields Eye Hospital Ophthalmic Formulary May 2018 (Version 1.22). Moorfields Eye Hospital.
6. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). The Ocular Surface 2007; 5(2): 75-92.
7. Utine CA, Stern M, Akpek EK. Clinical review: topical ophthalmic use of cyclosporin A. Ocular Immunology and Inflammation 2010; 18(5): 352-61.
8. Foster CS, Rice BA, Dutt JE. Immunopathology of atopic keratoconjunctivitis. Ophthalmology 1991; 98(8): 1190-6.
9. Power WJ; Tugal-Tutkun I; Foster CS. Long-term follow-up of patients with atopic keratoconjunctivitis. Ophthalmology 1998; 105(4): 637-42.
10. Collum LM. Vernal keratoconjunctivitis. Acta Ophthalmologica Scandinavica. Supplement 1999; (228): 14-6.
11. Baryishak YR, Zavaro A, Monselise M et al. Vernal keratoconjunctivitis in an Israeli group of patients and its treatment with sodium cromoglycate. British Journal of Ophthalmology 1982; 66(2): 118–122.
12. González-López JJ, López-Alcalde J, Morcillo Laiz R, et al. Topical cyclosporine for atopic keratoconjunctivitis. Cochrane Database Syst Rev. 2012 Sep 12.
13. Akpek EK, Dart JK, Watson S, Christen W, Dursun D, Yoo S, et al.A randomized trial of topical cyclosporin 0.05% in topical steroid-resistant atopic keratoconjunctivitis. Ophthalmology 2004; 111(3): 476–82.
14. Hingorani M, Calder VL, Buckley RJ, Lightman S. The immunomodulatory effect of topical cyclosporin A in atopic keratoconjunctivitis. Investigative Ophthalmology and Visual Science 1999; 40(2): 392–9.
15. Daniell M, Constantinou M, Vu HT, Taylor HR. Randomised controlled trial of topical ciclosporin A in steroid dependent allergic conjunctivitis. British Journal of Ophthalmology 2006; 90(4): 461–4.
16. Ho-Nam Wan K et al. Topical cyclosporine in the treatment of allergic conjunctivitis: a meta-analysis. Ophthalmology 2013; 120: 2197-2203.
17. van Zuuren EJ, Kramer S, Carter B et al. Interventions for rosacea. Cochrane Database Syst Rev 2011; 3:CD003262.
18. Schechter BA, Katz RS, Friedman LS. Efficacy of topical cyclosporine for the treatment of ocular rosacea. Advances in Therapy 2009; 26: 651–659.

19. Reinhard T et al. Local cyclosporin A therapy in Thygeson superficial punctate keratitis - a pilot study. Klinische Monatsblatter fur Augenheilkunde. 1996; 209: 224-7.
20. Lelli GJ et al. Ophthalmic cyclosporine use in ocular GVHD. Cornea 2006; 25: 635-8.
21. Restasis prescribing information sheet. Allergan.< http://www.allergan.com/assets/pdf/restasis_pi.pdf> [Accessed on [14/07/2014]]
22. Barber LD, Pflugfelder SC, Tauber J et al. Phase III safety evaluation of cyclosporine 0.1% ophthalmic emulsion administered twice daily to dry eye disease patients for up to 3 years. Ophthalmology 2005; 112(10): 1790-4.
23. Armaly MF. Statistical attributes of the steroid hypertensive response in the clinically normal eye. Investigative Ophthalmology & Visual Science 1965; 4: 187–197.
24. Becker B. Intraocular pressure response to topical corticosteroids. Investigative Ophthalmology & Visual Science 1965; 4: 198–205
25. Electronic medicines compendium. (2019) IKERVIS 1 mg/mL eye drops, emulsion (SPC) – EMC. [Online] https://www.medicines.org.uk/emc/product/6937/smpc (accessed on 26/7/19)
26. Electronic medicines compendium. (2019) Verkazia 1 mg/mL eye drops, emulsion (SPC) – EMC. [Online] https://www.medicines.org.uk/emc/product/9491/smpc (accessed on 26/7/19)