New Medicine Recommendation

Verkazia eye drops, emulsion (Ciclosporin A 0.1% (1 mg/ml))

Indication: Treatment of severe vernal keratoconjunctivitis in children from 4 years of age and adolescents.

Recommendation: Amber 0

- Suitable for prescribing in primary care following recommendation or initiation by a specialist.
- Little or no specific monitoring required.
- Patient may need a regular review, but this would not exceed that required for other medicines routinely prescribed in primary care.
- Brief prescribing document or information sheet may be required.

Primary care prescribers must be familiar with the drug to take on prescribing responsibility or must get the required information.

When recommending or handing over care, specialists should ask primary care prescribers to take over prescribing responsibility, and should give enough information about the indication, dose, monitoring requirements, use outside product licence and any necessary dose adjustments to allow them to confidently prescribe.

Summary of supporting evidence:

- The pivotal study was a multicentre, randomised, double-blind, double masked, vehicle controlled phase III trial (VEKTIS) investigating the efficacy and safety of Ciclosporin A 0.1% eye drops (Verkazia) given either two times (BD) or four times daily (QDS) to children and adolescents with severe vernal keratoconjunctivitis (VKC) (grade 3 or 4 of Bonini scale) including corneal involvement (grade 4 or 5 on the modified Oxford scale).
- The double blind evaluation phase was 4 months followed by an 8 month extension period in which patients were allowed to receive active treatment, resulting in a total observation period of 12 months.
- The improvement in corneal surface defects and in symptoms observed with Verkazia in patients with severe VKC are clinically relevant
- Treatment up to 12 months was well tolerated with mainly transient ocular adverse reactions
- In general, Verkazia was well tolerated with mostly ocular adverse events such as eye pain and eye pruritis which usually occurred during instillation and resolved shortly after.

Produced: September 2019 NHS Midlands and Lancashire

Details of Review

Name of medicine (generic & brand name)**:** Ciclosporin A 0.1% (1 mg/ml) / Verkazia
Strength(s) and form(s): 1 mg/ml eye drops, emulsion
Dose and administration: The recommended dose is one drop of Verkazia 4 times a day (morning, noon, afternoon and evening) to be applied to each affected eye during the VKC season. If signs and symptoms of VKC persist after the end of the season, the treatment can be maintained at the recommended dose or decreased to one drop twice daily once adequate control of signs and symptoms is achieved. Treatment should be discontinued after signs and symptoms are resolved and reinitiated upon their recurrence.
BNF therapeutic class / mode of action: Inflammatory eye conditions / immunosuppressants
Licensed indication(s) Treatment of severe vernal keratoconjunctivitis (VKC) in children from 4 years of age and adolescents.
Proposed use (if different from, or in addition to, licensed indication above): As per licenced indication
Course and cost: Most patients are likely to need it for 8 months in a year. NHS List price is £288 for 120 single dose containers. Each single-dose container is sufficient to treat both eyes[1] with any unused emulsion being discarded immediately.
Current standard of care/comparator therapies: Ciclosporin A 0.1% (1 mg/ml) – Ikervis, £72 for 30 single dose containers. Off label indication Ciclosporin 0.05% eye drops – Restasis £501 for 60 single dose containers. Unlicensed, imported special Ciclosporin 0.2% eye ointment – Optimmune £77.28 per 3.5g. Unlicensed for human use (veterinary medicine)
Relevant NICE guidance: Ciclosporin for treating dry eye disease that has not improved despite treatment with artificial tears NICE TA369 – for Ikervis. No NICE review scheduled for Verkazia Ciclosporin has been designated as an orphan medicine by the European Medicines Agency for this indication. SMC 2111 – Ciclosporin 1mg/ml (Verkazia) is accepted for use within NHS Scotland for the treatment of severe vernal keratoconjunctivitis (VKC) in children from 4 years of age and adolescents AWMSG 2908 - Ciclosporin 1mg/ml (Verkazia) is recommended as an option for use within NHS Wales for the treatment of severe vernal keratoconjunctivitis in children from 4 years of age and adolescents (until the age of 18).

Background and context

Vernal keratoconjunctivitis is a rare allergic eye condition normally affecting both eyes.[2] It is differentiated from other allergic eye conditions as it involves various complex immune reactions and is characterised by inflammation of the conjunctiva and cornea.[2,3] Symptoms include eye itching, tearing, discharge, irritation, redness and sensitivity to light.[4] Visual loss may occur due to corneal complications such as ulcers and scarring.[1] The condition is frequently associated with other atopic diseases, such as asthma, allergic rhinitis, and eczema.[2]

It generally presents in early to mid-childhood, is more common in boys and most prevalent in hot, arid environments such as the Mediterranean basin.[4] It usually lasts four to ten years and resolves after puberty, although in some cases it can continue into early adulthood.[2] The condition mainly appears during the spring months (vernal season) which reflects the seasonal increase in allergens but can recur or persist all year round.

The management of vernal keratoconjunctivitis involves a step-wise approach based on disease severity.[4] At first, the condition may be managed with mast cell stabilisers and antihistamines. If symptoms persist, topical corticosteroids may be given, and if response is not adequate with corticosteroid treatment, immunomodulating agents (such as off-label ciclosporin and tacrolimus) may be given. The side effects associated with corticosteroids, such as cataracts and glaucoma, are a limitation for their long-term use.[4] Clinical expert opinion indicates that off-label and unlicensed ciclosporin has been used for many years as an alternative to long-term corticosteroids to treat severe forms of vernal keratoconjunctivitis.

If left untreated severe VKC can lead to permanent sight loss and blindness.[5]

Evidence is very limited for this rare condition, but it is expected that between 0.01% and 0.03% of the UK population has VKC,[6] of whom an estimated 30% have the severe form warranting treatment with ciclosporin.

Topical ciclosporin is considered as a treatment option in the American Academy of Ophthalmology (AAO 2016)[4] and the UK College of optometrists (2017) guidelines on VKC.[3]

The manufacturer anticipates that ciclosporin will be used as a long-term option for the treatment of severe vernal keratoconjunctivitis to reduce the steroid burden and in place of off-label and unlicensed ciclosporin products.

Summary of evidence

Summary of efficacy data in proposed use:

Evidence to support the use of ciclosporin eye drops in the treatment of severe VKC comes from the pivotal phase III study Vernal KeratoconjunctivitiTIs Study (VEKTIS).[7]

VEKTIS comprised of a four month, randomised, multicentre, double-masked, vehicle controlled treatment period designed to assess efficacy, followed by an eight month double-masked follow up period designed to assess safety.

Eligible patients were aged 4 to 18 years and had severe VKC (grade 3 or 4 according to the Bonini scale)[8] and severe keratitis (corneal fluorescein staining (CFS) grade 4 or 5 according to the modified Oxford scale)[9]

They had a mean visual analogue scale (VAS) score (range 0-100mm) of ≥ 60mm for four subjective symptoms (photophobia, tearing, itching and mucous discharge), had active symptomatic disease at the start of the vernal season and a history of at least one recurrence in the previous year.

Eligible patients (n=169) were randomised equally to receive one drop of study medication into each eye morning, noon, afternoon and evening of:

1. Ciclosprin eye drops four times daily (n=57)
2. Ciclosprin eye drops twice daily (morning and evening) plus vehicle eyedrops twice daily (noon and afternoon) (n=55)
3. Vehicle eyedrops four times daily (n=57)

Of these, 143 patients completed the four month treatment period. Overall, the most frequent reasons for discontinuation were lack of efficacy and patient decision unrelated to an adverse event. More patients in the Verkazia BD dosing and vehicle groups versus the Verkazia QDS dosing group withdrew early because of lack of efficacy (9.3% and 8.6% vs 1.8% respectively).

The primary outcome was the mean penalty adjusted CFS score measured monthly, over 4 months based on:

- Keratitis assessed by CFS using the modified Oxford scale
- Need for rescue medication
- Occurrence of corneal ulceration

At each month, the change in CFS score from baseline was adjusted by one point for each course of rescue medication used and by one point for each occurrence of corneal ulceration.

During the four month treatment period, there were significantly greater improvements from baseline in the penalty adjusted CFS score in both ciclosporin groups compared with vehicle. The change from baseline in CFS score was the main driver of the treatment effect on the primary outcome, accounting for a relative contribution of 70% and 78% of the treatment effect for ciclosporin four times daily and twice daily respectively versus vehicle. Rescue medication accounted for a lower relative contribution of 30% and 22% of the treatment effect versus vehicle respectively. There were few cases of corneal ulceration and no difference between active and vehicle groups were found.[2]

At baseline, all patients included in the VEKTIS trial had severe corneal damage as assessed by CFS score (≥ 4 on modified oxford scale). At the end of the four month randomised phase, two thirds of Verkazia patients on QDS dosing improved from CFS grade ≥4 to CFS 0-1.

The CFS responder rate was significantly higher in the Verkazia QDS and BD dosing groups versus the vehicle group (57.1% and 61.1% vs 34.5%). A CFS responder was defined as a patient who met all of the following criteria at month 4:

- CFS score ≤50% of baseline CFS
- Did not withdraw for a reason possibly due to treatment
- No corneal ulceration
- No use of corticosteroid rescue medication in the last 3 months of treatment

An additional, more stringent, CFS responder analysis, using a CFS graded as 0 (clear) instead of ≤ 50% of baseline, in addition to no ocular ulceration, and no use of rescue medication in the last three months of treatment (months 2-4), found responder rates of 20%,9.3% and 8.6% in the Verkazia QDS, Verkazia BD and vehicle groups respectively.[2]

Four subjective symptoms of VKC (photophobia, tearing, itching and mucous discharge) were evaluated using a patient self-administered visual analogue scale (VAS). Verkazia QDS showed improvements in mean VAS vs vehicle as early as month1, which was sustained vs baseline over 12 months.

After four months, patients in both ciclosporin groups i.e. QDS and BD could continue study treatment at the same dose during the eight month follow up period. Patients who continued from the vehicle group were re-randomised to receive Verkazia QDS or BD. This follow up period was primarily designed to assess the safety of Verkazia but some efficacy outcomes

were assessed. 42 patients in the Verkazia QDS group (including 13 patients initially randomised to vehicle) and 42 patients in the Verkazia BD group (including 17 patients initially randomised to vehicle) continued to use study medication for the further eight months. Overall CFS and VAS symptoms scores remained stable for these patients and improved for the first four months in those patients who had been re-randomised from vehicle.

Topical steroid rescue medication was used by more patients receiving vehicle compared with those in the Verkazia QDS dose regimen (53.4% vs 32.1%) and the mean number of courses was approximately 50% less with Verkazia QDS vs vehicle (1.10 vs 0.66 p=0.010). The number of Verkazia QDS patients who required corticosteroid rescue medication remained low over 12 months.

Results would suggest that Verkazia has the potential to reduce the use of rescue corticosteroids in young patients with severe VKC and therefore reduce the potential for associated corticosteroid serious adverse events.

The VEKTIS trial also assessed the efficacy of a twice daily (BD) dosing regimen. The positive efficacy results for Verkazia BD confirm it as an option for dose tapering in suitable patients after the end of the season once adequate control of signs and symptoms is achieved.

Patients Health Related Quality of Life (HRQoL) was assessed using the QUICK questionnaire. The QUICK questionnaire is the only HRQoL tool developed specifically for paediatric patients with VKC.[2] Verkazia QDS treated patients reported a mean improvement from baseline of 55% for the QUICK symptoms domain and 83% for the QUICK daily activities domain. The QUICK scores remained low with Verkazia treatment to month 12.

Other efficacy data:

Supportive Phase II/III NOVATIVE study in moderate to severe VKC[2]

This was a multicentre, randomised, parallel group, dose ranging, controlled trial of efficacy and tolerance of ciclosporin A 0.05% and 0.1% ophthalmic cationic emulsion vs vehicle in patients with VKC.

It compared the efficacy, safety and tolerability of 2 dose regimens: 0.05% four times daily and 0.1% four times daily with vehicle in patients with active VKC.

The study duration was 4 months, divided into two treatment periods:

Period 1 was a 4 week three parallel groups, vehicle controlled treatment period where patients were randomised on a 1:1:1 basis to one of the three treatment groups ciclosporin 0.05%, ciclosporin 0.1% or vehicle one drop in both eyes four times a day.

Period 2 was a 3 month, two parallel group treatment period where all patients received ciclosporin 0.05% or 0.1% four time or twice daily (depending on tolerance) in both eyes.

Of 118 patients, 40 were randomised to receive vehicle, 39 to receive ciclosporin 0.05% and 39 to receive ciclosporin 0.1% four times daily. All patients were included in the safety analysis. At the end of Period 1, 111 (94.1%) patients were still in the study and all entered Period 2. Patients who received vehicle during Period 1 received ciclosporin 0.05% (19) and ciclosporin 0.1% (17), 39 patients remained in the 0.05% group and 36 remained in the 0.1% group.

The primary objective was to demonstrate superiority of ciclosporin 1mg / ml over vehicle. Change from baseline at month 1 in the overall rating of ocular symptoms was the primary endpoint. The study did not meet its primary objective with no statistically significant difference being shown for either of the active arms compared to vehicle. However, a significant benefit in favour of ciclosporin was shown in secondary endpoints evaluating objective ocular signs of VKC under the slit lamp.

At month 1, a statistically significant improvement in the overall rating of objective signs of VKC for patients in the two active groups was observed. Also, both doses of ciclosporin provided a statistically significant improvement in CFS assessed using the Oxford scale.

Results of a post-hoc analysis of the NOVATIVE study in 45 patients with active VKC and severe keratitis (CFS ≥4 on the modified Oxford scale) suggested a potential for greater benefit with the 0.1% dose over the 0.05% dose of ciclosporin. At month 1, mean improvement in CFS was greater with the higher dose with a reduction of 2.14 compared to a reduction of 1.94 with the low dose and a reduction of 1.14 with the vehicle. The effect size was greater for both high dose and low dose regimens compared to the entire study population (with moderate to severe VKC). Greater improvements over vehicle was also shown for both the 0.1% and 0.05% dose for the primary efficacy endpoint, the overall rating of objective symptoms and for the secondary endpoints improvement in CFS and the overall rating of objective VKC signs at month 1.

Summary of safety data:

Most treatment emergent adverse events were mild or moderate in severity and were similar in incidence across all three treatment groups, except for site instillation pain which occurred at a higher rate in the Verkazia QDS group.

The most common adverse reactions in the clinical trials with Verkazia were eye pain (11%) and eye pruritus (9%) which were usually transitory and occurred during instillation.

MedDRA system organ class	MedDRA frequency	Adverse reaction
Infections and infestations	Common	Upper respiratory tract infection.
	Uncommon	Keratitis bacterial, herpes zoster ophthalmic.
Nervous system disorders	Common	Headache.
Eye disorders	Very common	Eye pain.
	Common	Eye pruritus, ocular hyperaemia, eye irritation, ocular discomfort, foreign body sensation in eyes, lacrimation increased, vision blurred, erythema of eyelid, eyelid oedema.
	Uncommon	Blepharitis, conjunctival oedema.
Respiratory, thoracic and mediastinal disorders	Common	Cough.

Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100)

Contraindications

- Active or suspected ocular or peri-ocular infection.
- Ocular or peri-ocular malignancies or premalignant conditions

Efficacy and safety of Verkazia has not been studied beyond 12 months. Therefore, regular examination of the eyes is recommended every 3 - 6months, when Verkazia is used for more than 12 months.

Strengths and limitations of the evidence:

Strengths

Supported by multi centre, randomised double blind phase III study

The choice of the patient population in VEKTIS was based on the post hoc subgroup analysis in NOVATIVE which showed more promising results in the subset of patients with severe keratitis – appropriate patient cohort for licence

Appropriate patient cohort – well defined and representative of intended target population

Appropriate primary and secondary endpoints –for both Verkazia QDS and BD dosing vs vehicle were met

Demonstrated potential to reduce requirement for corticosteroid rescue medication

Limitations

Patient number small, but justified given rarity of disease

Limited long term safety and efficacy data

No active comparator – this was accepted by EMA as use of corticosteroids were not considered appropriate due to local long term side effects and in the absence of a licensed active ciclosporin comparator for severe VKC maintenance therapy, the Verkazia emulsion vehicle was used as a comparator. As the main ciclosporin treatment for severe VKC in the UK is Ikervis and Ikervis is essentially the same as Verkazia, it would not been appropriate to use Ikervis as the comparator. Furthermore, comparison of Verkazia with its vehicle was deemed necessary because eye drop vehicles are known to have a beneficial effect on their own.

Summary of evidence on cost effectiveness:

Verkazia has an equivalent cost to that of off label use of Ikervis and is less expensive than the unlicensed / special alternatives.

For SMC / AWMSG the company provided a cost minimisation analysis comparing Verkazia to a weighted average comparator which included Ikervis, Restatsis, Optimmune and special manufactured ciclosporin for the treatment of VKC in children from 4 years of age until the age of 18. The predominant treatment assumed in the weighted average was Ikervis. The incremental savings associated with Verkazia stem primarily from the difference in medicine costs over the duration of the model with a small contribution from the avoided costs of preparation time for special manufactured ciclosporin. The health economic evidence was accepted by both SMC and AWMSG.

Prescribing and risk management issues:

n/a

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Verkazia (Ciclosporin 0.1%)	QDS	£288 (120)	£3,456
Ikervis (Ciclosporin A 0.1%)	QDS	£72 (30)	£3,456
Restasis (Ciclosporin 0.05%)	QDS	£501 (60)	£12,024
Optimmune (Ciclosporin 0.2% eye ointment)	QDS	£77.28 (3.5g)	£3709.44 (assuming 4 tubes / month)
Costs based on Drug Tariff list prices May 2019. This table does not imply therapeutic equivalence of drugs or doses.			

Innovation, need and equity implications of the intervention:

Given the possible irreversible sight threatening character of severe forms of VKC in the paediatric population and in light of the safety concerns with long term use of corticosteroids, there is a need for treatment options with demonstrated efficacy and an acceptable safety profile in this setting.

Verkazia is the only licensed medication for the treatment of severe VKC in children. It offers a licensed treatment option for children and adolescents with severe VKC who would otherwise be managed by use of off label or specially manufactured formulations of ciclosporin or other immunosuppressants. The reduced proportion of patients requiring rescue medication suggests that Verkazia may reduce the need for corticosteroid eye drops.

Financial implications of the intervention:

The estimated population of Lancashire and South Cumbria is 1.7million.

Assuming between 0.01% and 0.03% of the population will suffer from VKC [6] there are potentially 170 – 510 patients. Around 30% of this population will suffer from severe VKC and therefore eligible for treatment with Verkazia, 51-153 in Lancashire and South Cumbria.

If Verkazia used QDS for 12 months the maximum cost for 51 patients = £176,256

for 153 patients = £528,768

In practice the potential cost could be less as patients can be maintained on BD dosing once adequate control of signs and symptoms is achieved.

If Verkazia used BD for 12 months the cost for 51 patients = £88,128

for 153 patients = £264,384

Treatment should be discontinued after signs and symptoms are resolved and reinitiated upon their recurrence – clinical opinion suggests that most patients are likely to need treatment for 8 months in a year.

From EPACT data, in the last 12 months, the 8 CCGs within Lancashire and South Cumbria spent £32,425.70 on ciclosporin 0.1% unit dose eyedrops (Ikervis) and £1,848.57 on ciclosporin 0.2% eye ointment (Optimmune). No Restasis was prescribed.

Ciclosporin 0.1% eyedrops (Ikervis) currently have a NICE TA (TA369) for treating severe keratitis in adult patients with dry eye disease that has not improved despite treatment with tear substitutes.

It is probable that a small proportion of the currently prescribed ciclosporin is being used to treat VKC off label. However, as the Ikervis license is for a different indication in a different cohort of patients (adults vs children), then it is difficult to determine the proportion of current use in VKC.

If the current Ikervis usage includes patients with VKC prescribed the four times a day dosage, as suggested by the requesting clinician and the SMC/AWMSG reviews, there should be no increase in expenditure if Verkazia is prescribed instead (cost neutral). If Verkazia were to be prescribed in place of Optimmune this would result in a small cost saving.

It is worth noting that the current total annual expenditure on ophthalmic ciclosporin across Lancashire and South Cumbria, is significantly less than the above population based estimates.

Service Impact Issues Identified:

N/A

Equality and Inclusion Issues Identified:

Cross Border Issues Identified:

GMMMG review out for consultation recommending that Verkazia be added to the paediatric RAG list as GREEN (following specialist initiation) for treatment of vernal keratoconjunctivitis in patients aged 4 to 18 years old and who are subject to active follow-up (e.g. reviewed every 6 months).

Pan Mersey APC currently have a GREY RAG rating for Verkazia – this medicine is still being evaluated according to local processes and a decision on whether to commission their use has not yet been made.

Legal Issues Identified:

N/A

Media/ Public Interest:

N/A

References

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