Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2111

ciclosporin 1mg/mL (0.1%) eye drops emulsion (Verkazia®)

Santen GmbH

9 November 2018

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

ciclosporin 1mg/mL (0.1%) eye drops emulsion (Verkazia®) is accepted for use within NHSScotland.

Indication under review: treatment of severe vernal keratoconjunctivitis (VKC) in children from 4 years of age and adolescents.

Ciclosporin eye drops compared with vehicle improved the signs and symptoms associated with VKC, as measured by improvements in keratitis, requirement for rescue medication and development of corneal ulcers.

Chairman
Scottish Medicines Consortium

Indication

Treatment of severe vernal keratoconjunctivitis (VKC) in children from 4 years of age and adolescents.

Dosing Information

The recommended dose is one drop four 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.

Treatment must be initiated by an ophthalmologist or a healthcare professional qualified in ophthalmology.[1]

Product availability date

24 October 2018.

Ciclosporin has been designated as an orphan medicine by the European Medicines Agency (EMA) and meets SMC orphan criteria for this indication.

Summary of evidence on comparative efficacy

Vernal keratoconjunctivitis (VKC) is a rare type of ocular allergy condition which is characterised by conjunctival inflammation, corneal involvement (keratitis, ulceration, plaques and scars) and tissue remodelling including papilla formation. Ciclosporin has anti-inflammatory properties by inhibiting the development of cell-mediated reactions and production and/or release of proinflammatory cytokines as well as up-regulating the release of anti-inflammatory cytokines.[2] It has been licensed for the treatment of severe VKC in children and adolescents (aged 4 to 18 years).

Evidence to support the use of ciclosporin eye drops in the treatment of severe VKC comes from the pivotal, phase III study (VEKTIS). This comprised a four month, randomised, 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) and severe keratitis (grade 4 or 5 according to the modified Oxford scale). They had a mean visual analogue scale (VAS) score (range 0 to 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 were randomised equally to receive one drop of study medication into each eye morning, noon, afternoon and evening of (i) ciclosporin eye drops four times daily (high dose) , (ii) ciclosporin eye drops twice daily (morning and evening) plus vehicle eye drops twice daily (noon and afternoon) (low dose) or (iii) vehicle eye

drops four times daily.[2, 3] Rescue medication (dexamethasone 0.1% eye drops four times daily for five days) could be used if the patient had worsening keratitis or symptoms up to a maximum of two courses between two, monthly, scheduled visits during the treatment period and of four courses between the two-monthly visits during the follow-up period. Patients were not allowed to use topical anti-histamine and mast-cell stabilisers during the study.[2]

The primary outcome was the mean penalty-adjusted corneal fluorescein staining (CFS) score, measured monthly, over four months based on:

- keratitis assessed by CFS using the modified Oxford scale (7-point ordinal scale from 0, 0.5 and 1 to 5). Higher scores are associated with greater severity of keratitis.
- 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. This was assessed in the full analysis set (FAS), comprising all randomised patients who used at least one dose of study medication and who had post-baseline data but excluding those who withdrew during the first week, unrelated to study medication.[2]

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. Details are presented in table 1 below. 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 was found.[2]

A key secondary outcome was CFS responder rate. Response was defined as CFS score ≤50% of baseline without withdrawing from the study due to treatment and without rescue medication or corneal ulceration. Over the four month treatment period, the responder rate was significantly higher in both ciclosporin groups than in the vehicle group: details are presented in table 1. 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 to 4), found responder rates of 20%, 9.3% and 8.6% in the ciclosporin four times daily, twice daily and vehicle groups respectively. The comparisons of high and low dose ciclosporin with vehicle did not reach statistical significance: odds ratio 2.61 (95% CI: 0.84 to 8.10) and 1.18 (95% CI: 0.32 to 4.34) respectively.[2]

Table 1: Primary and key secondary outcomes for the VEKTIS study[1, 2]

	Ciclosporin eye drops four times daily (n=56)	**Ciclosporin eye drops twice daily (n=54)**	**Vehicle (n=58)**
Primary composite outcome			
Penalty-adjusted CFS score; mean (SD) over 4 months	2.06 (1.44)	1.93 (1.37)	1.34 (1.22)
Least squares mean difference (95% CI) versus placebo	0.76 (0.26 to 1.27), p=0.007	0.67 (0.16 to 1.18), p=0.010	
Secondary outcomes			
CFS responder rate over 4 months	55%	50%	28%
Odds ratio (95% CI) versus vehicle	3.28 (1.50 to 7.16), p=0.005	2.80 (1.26 to 6.21), p=0.010	
Change from baseline in mean VAS symptoms score (mm)	-49.7	-36.6	-29.3
Difference versus vehicle (mm)	-19.4 (p<0.001)	-8.4 (p=0.103)	
Use of rescue medication	32% (18/56)	31% (17/54)	53% (31/58)

CFS: corneal fluorescein staining, SD: standard deviation, CI: confidence interval, VAS: visual analogue scale

Health related quality of life was assessed using the QUICK questionnaire, which was developed specifically to measure quality of life in children with VKC. It comprises two domains: the symptoms domain (twelve items) and the daily activities domain (four items), each of which scored on a three-point scale: 1=never; 2=sometimes and 3=always. Scores for each domain were linearly transformed and total scores ranged from 0 to 100% of maximum.[4] The QUICK scores reduced from baseline to month 4 in all three groups. The difference between ciclosporin and vehicle groups was statistically significant for both the symptoms and daily activities scores at all timepoints for the ciclosporin eye drops four times daily group only, except daily activities at month 1. The treatment effect size of 0.67 for symptoms and 0.44 for daily activities were considered clinically relevant.[1, 2]

After four months, patients in both ciclosporin groups 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 high or low dose ciclosporin eye drops.[2] This follow-up period was primarily designed to assess the safety of ciclosporin eye drops but some exploratory efficacy outcomes were assessed. During the follow-up, a proportion of patients used ciclosporin eye drops in an intermittent manner. However, 42 patients in the ciclosporin four times daily group (including 13 patients initially randomised to vehicle) and 42 patients in the ciclosporin twice daily group (including 17 patients initially randomised to vehicle) continued to use study medication for

eight months. Overall CFS scores 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.[2]

In a supportive phase II/III study (NOVATIVE), two strengths of ciclosporin eye drops (0.05% and 0.1%) administered four times daily were compared with vehicle for four weeks in 118 patients, aged at least 4 years, with active, moderate to severe VKC. No significant difference was found between the ciclosporin and vehicle groups in the primary outcome (change from baseline in ocular symptoms, assessed using the BenEzra scale). There were significant improvements between ciclosporin and vehicle groups in secondary outcomes and a post hoc analysis in patients with severe VKC found greater improvements than in the overall population. [2]

Summary of evidence on comparative safety

Vehicle-controlled safety data to four months from the VEKTIS study are only available from the clinical study report. In the VEKTIS study, at four months, an adverse event had been reported in 42% (24/57) of ciclosporin four times daily patients, 33% (18/ 54) of ciclosporin twice daily patients and 40% (23/58) of vehicle patients and these were considered treatment-related in 19% (11/57), 9.3% (5/54) and 16% (9/58) of patients respectively. Three patients experienced serious adverse events during the 4 month treatment period but these were not considered to be related to study medication. The most frequently reported in each respective group were: instillation site pain (11%, 5.6% and 3.4%); ulcerative keratitis (7.0%, 5.6% and 5.2%); headache (7.0%, 0% and 1.7%); nasopharyngitis (0%, 5.6% and 1.7%); instillation site pruritus (3.5%, 3.7% and 3.4%); corneal leukoma (3.5%, 0% and 1.7%); foreign body sensation in eye (3.5%, 0% and 0%); pharyngitis (3.5%, 0% and 0%) and cough (3.5%, 0% and 0%).[5]

The European Public Assessment Report (EPAR) presented results of a pooled safety analysis of the VEKTIS and NOVATIVE studies for the initial randomised vehicle-controlled periods. In the randomised period, adverse events were reported in 38% (36/96), 34% (32/93) and 38% (37/98) of ciclosporin high dose, low dose and vehicle groups respectively. The most commonly reported adverse events were instillation site pain (9.4%, 7.5% and 4.1% respectively), instillation site pruritus (6.3%, 7.5% and 3.1% respectively) and ulcerative keratitis (4.2%, 3.2% and 6.1% respectively).[2]

Summary of clinical effectiveness issues

VKC is a rare type of ocular allergy condition which is usually bilateral; unilateral cases are less common and occur early in the disease. Although VKC appears to be mainly seasonal, it can also be perennial or chronic with or without acute exacerbations. It is more common in boys than girls and starts in early childhood. VKC can be self-limiting and resolve spontaneously at puberty but in up to 12 % of patients, symptoms persist into adulthood. The symptoms include itching, tearing, burning, stringy mucous and/or serous discharge, photophobia and blepharospasm. The aim of

treatment is to control symptoms and to prevent sight threatening complications including corneal ulceration, scarring, opacities, and keratoconus in patients with severe disease. Topical anti-histamines may be effective in mild cases and are used with topical mast stabilisers in moderate cases. Topical corticosteroids are often used in moderate to severe disease and to control acute exacerbations but their long-term use is limited by adverse events. Specially manufactured formulations of ciclosporin and tacrolimus have been used as an alternative to corticosteroids for many years.[2, 6] An identical formulation of ciclosporin eye drops (Ikervis®) is available, licensed for the treatment of severe keratitis in adult patients with dry eye disease which has not improved despite treatment with tear substitutes.[7] This has been accepted for use by SMC.

VKC is more common in hot, dry environments eg Mediterranean, West Africa and India and the overall prevalence in the European population is approximately 3 in 10,000. Ciclosporin eye drops (Verkazia®) has been granted orphan designation in Europe and meets SMC orphan status. This is the first ophthalmic formulation of ciclosporin to be licensed for the treatment of children and adolescents with severe VKC. Clinical experts consulted by SMC considered that ciclosporin eye drops (Verkazia®) fills an unmet need in this therapeutic area, namely to provide a corticosteroid-sparing medicine.

The pivotal clinical study found that high and low dose ciclosporin eye drops improved penalty-adjusted CFS scores significantly more than vehicle in children with severe VKC.[2] The primary outcome, the composite of the CFS score, which assessed keratitis and ocular surface damage, adjusted by the use of rescue medication and development of corneal ulcers, was accepted by the EMA since there are no validated alternative outcomes. However the use of an arbitrary adjustment of 1 for each penalty and the low likelihood of corneal ulcers given that patients with progression would receive rescue medication may limit the interpretation of the treatment effect of this outcome.[2] The difference between ciclosporin and vehicle groups in terms of the primary composite outcome was mainly driven by the treatment effect on the CFS score (>70%). The effect of rescue medication was smaller (20 to 30%) but the development of corneal ulcers, since it was so rare, had no effect. Therefore the effect of ciclosporin on preventing corneal ulceration is unknown.[2]

Over the four-month treatment period, the CFS responder rates were significantly higher in both ciclosporin groups compared with vehicle and the EMA considered these results to be clinically meaningful. In addition, the improvement in VKC symptoms (photophobia, tearing, itching and mucous discharge) compared with vehicle were considered clinically relevant in both ciclosporin groups.[2]

The vehicle-controlled data from the VEKTIS study was limited to 4 months which represents a season. Follow-up, uncontrolled data to 12 months in patients for whom the VKC allergy season was ongoing or who still had or had recurrence of signs and symptoms of VKC suggest that the treatment effect was maintained.[2] The SPC therefore notes that if signs or symptoms persist after the end of the season, treatment can be maintained at the recommended dose (four times daily) or decreased to twice daily. There are no data on treatment after 12 months and the SPC notes

that efficacy and safety of ciclosporin eye drops (Verkazia®) have not been studied beyond 12 months.[1, 2]

VKC is more common in countries with hot, dry climates but 60% of patients enrolled in the VEKTIS study were from Europe and the results are likely to be generalisable to a Scottish population. Study patients had not received topical or systemic immunosuppressants in the previous 90 days and the results may not be generalisable to patients who had recently received such treatment. Study patients were not allowed to receive concomitant antihistamine and mast-cell stabilisers and the study results may not be generalisable to patients who continue to use routine anti-allergy topical treatments in clinical practice. Ciclosporin eye drops (Verkazia®) are licensed for the treatment of severe VKC in children and adolescents (aged 4 to 18 years) and this reflects the population in the VEKTIS study. However VKC can continue into adulthood and there are no data in patients over 18 years.

The number of patients in the VEKTIS study was small and there are limited long-term efficacy and safety data. The EMA noted that there are uncertainties about the risk of infections and malignancies as a result of a local immunosuppression especially when used over prolonged periods and because of the limited long-term safety data.[2]

There are no clinical data comparing ciclosporin eye drops (Verkazia®) with an active comparator. However this was accepted by the EMA since there are no other suitable comparators for this condition and the use of corticosteroids was not considered appropriate because of local long-term side effects.[2]

The introduction of ciclosporin eye drops (Verkazia®) would offer 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 ciclosporin eye drops may reduce the need for corticosteroid eye drops and this was supported by a retrospective review of the use of ciclosporin 0.1% eye drops in 50 children in a UK centre.[8] Clinical experts consulted by SMC considered that ciclosporin eye drops (Verkazia®) is a therapeutic advancement due to providing a licensed medicine which may reduce the long-term use of topical corticosteroids.

Summary of comparative health economic evidence

The company submitted a cost- minimisation analysis comparing ciclosporin 1mg/mL 0.1% eye drops emulsion (Verkazia®) to a weighted average comparator which included ciclosporin (Ikervis®), ciclosporin 0.5% (Restasis®), ciclosporin 0.2% eye ointment (Optimmune®), and special manufactured ciclosporin, for the treatment of VKC in children from 4 years of age and adolescents (until the age of 18). The predominant treatment assumed in the weighted average was ciclosporin (Ikervis®).

A Semi-Markov model was provided by the company which comprised of two key health states, symptomatic and asymptomatic, and patients were assumed to have either seasonal disease or perennial disease. Patients categorised as seasonal are assumed to be symptomatic for 5 months and asymptomatic for the remaining 7 months of the year. Perennial patients, however are assumed to remain symptomatic all year around. The base case results are presented for a pooled cohort i.e. seasonal patients are assumed to account for 52% of the cohort, whilst perennial patients are assumed to account for 48% of the cohort. The model assumes comparable efficacy and mortality between treatment arms i.e. the proportion of patients who are symptomatic/ asymptomatic is assumed to be the same for both treatment arms. The time horizon in the analysis was 9 years. A long term model component was included, however <1% of patients remained in the model after 18 years.

Verkazia® and Ikervis® have the same composition and strength, therefore efficacy and safety are considered to be comparable between these treatments. Due to the absence of comparative clinical data versus the other treatments within the weighted average comparison, the company has assumed comparable efficacy versus these comparators. The economic analysis accounts for adherence/compliance by assuming relative dosing intensity. A rate of 78% was applied to all treatments and was based on the average compliance rate across EU countries (Spain, Germany, UK, France and Italy).

Medicine costs were included in the analysis and were included within the model as cost per monthly cycle (estimated as a function of pack cost, number of packs per month and relative dosing intensity). A patient receiving Verkazia® was assumed to use one pack per month (one drop applied four times daily according the treatment's SPC), whilst a patient receiving Ikervis® was assumed to use four packs per month (one drop applied four time daily, ie assumed to be as per Verkazia® dosing). Ophthalmology visits were included in the analysis and the number of visits per year was assumed to be the same for all treatments. The cost associated with rescue medication, dexamethasone 0.1%, was included as well as sodium cromoglicate 2% and usage was assumed to be the same for all treatments. The preparation cost in terms of staff time for special manufactured ciclosporin was also included. No adverse event costs were considered.

The base case results are presented in table 2. It is worth noting that the medicine cost per monthly cycle was estimated to be £227.93 for Verkazia® and £292.30 for the weighted average comparator. The incremental savings associated with Verkazia® therefore 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 (as reported under 'monitoring costs' in table 2).

Table 2: Base case results over model duration

	Verkazia®	Weighted average comparator
Medicine costs	£15,232	£19,534
Rescue medication	£15.60	£15.60
Monitoring	£2,574	£2,639
Eye drops	£203	£203
Total	£18,024	£22,391
Incremental savings	-£4,367	

There were a number of weaknesses within the analysis, these were as follows

- The assumption of comparable efficacy between Verkazia® and comparators which underpins cost- minimisation analysis, is not supported by robust clinical data. However the committee was reassured that Verkazia® and Ikervis® contain the same formulation of ciclosporin and therefore comparable efficacy between these treatments is a reasonable assumption.
- The company has compared Verkazia® to a weighted average comparison, however several comparators within the weighted average basket may not be appropriate to include i.e. Restasis® and special manufactured preparations of ciclosporin. It is worth noting that cost neutrality between Verkazia® and Ikervis® is implied within the model as both treatments result in the same per cycle cost. As comparable efficacy is assumed, the annual cost per patient is likely to be the same for both treatments.

The Committee considered the benefits of ciclosporin eye drops (Verkazia®) in the context of the SMC decision modifiers that can be applied and agreed that the criterion for the emergence of a licensed medicine as an alternative to an unlicensed product that is established in clinical practice in NHS Scotland was satisfied. In addition, as ciclosporin eye drops (Verkazia®) is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and after application of the appropriate SMC modifiers, the Committee accepted ciclosporin for use in NHS Scotland.

Summary of patient and carer involvement

No patient group submission was received.

Additional information: guidelines and protocols

There are no UK or European guidelines on the management of VKC.

Additional information: comparators

There are no other medicines licensed specifically for the treatment of severe VKC in children and adolescents.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per 30 days Cost per 4 month season Cost per year (£)
Ciclosporin 0.1% eye drops emulsion (Verkazia®)	**One drop in each eye four times daily (reduced to twice daily)**	**30 days: 288 (144)** **120 day season: 1,152 (576)** **Continuous for 1 year: 3,494 (1,747)**

Costs for ciclosporin eye drops (Verkazia®) from MIMS online on 06 November 2018. The SPC notes that each single-dose container is sufficient to treat both eyes.

Additional information: budget impact

The submitting company estimated there would be 138 patients eligible for treatment with Verkazia® in year 1 rising to 140 patients in year 5. The estimated uptake rate was 35% in year 1 (48 patients) and 96% in year 5 (134 patients).

The gross impact on the medicines budget was estimated to be £96k in year 1 rising to £265k in year 5. The net medicine budget impact was estimated as being zero on the basis of displacement of alternative treatments at equivalent cost.

References

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This assessment is based on data submitted by the applicant company up to and including 14 September 2018.

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.