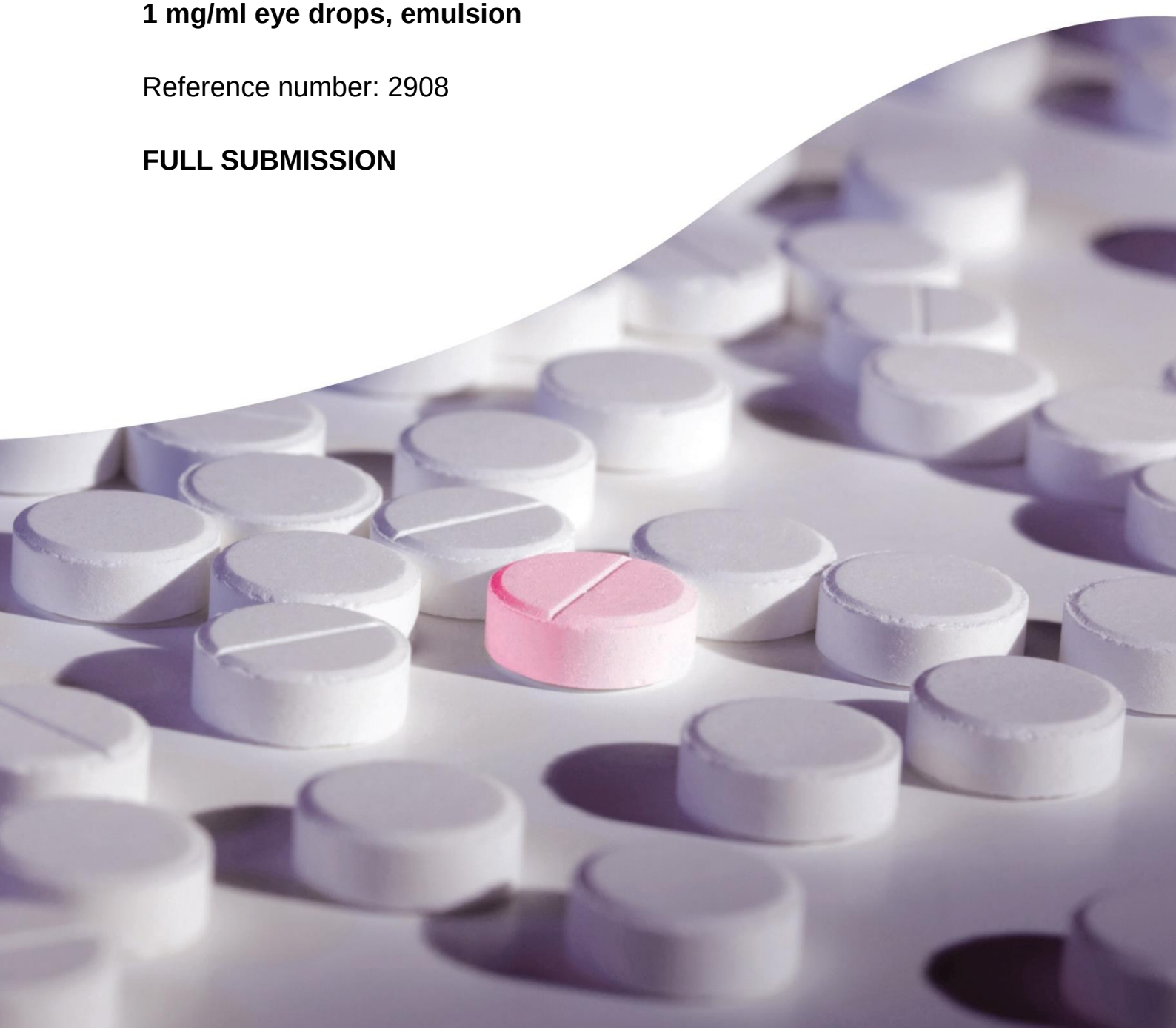
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Ciclosporin (Verkazia®)
1 mg/ml eye drops, emulsion

Reference number: 2908

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

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AWMSG Secretariat Assessment Report
Ciclosporin (Verkazia®) 1 mg/ml eye drops, emulsion

1.0 KEY FACTS

Assessment details	Ciclosporin (Verkazia®) for the treatment of severe vernal keratoconjunctivitis in children from 4 years of age and adolescents (until the age of 18).
Current clinical practice	Topical antihistamines and mast cell stabilisers may be used in the first instance, followed by topical corticosteroids. If symptoms persist after corticosteroid treatment, immunomodulating agents (e.g. ciclosporin) may be used. Verkazia® is the first licensed topical ciclosporin product for this indication. The applicant company anticipates that Verkazia® will be used to reduce the topical steroid burden and in place of unlicensed and off-label ciclosporin products. Clinical expert opinion indicates that topical ciclosporin is recognised as established practice. Experts suggest off-label Ikervis® (identical formulation to Verkazia®) is most frequently used in Wales when long-term corticosteroid treatment is required.
Clinical effectiveness	There are no efficacy or safety studies comparing Verkazia® with off-label or unlicensed ciclosporin products. Two randomised studies (phase II/III and phase III) compared Verkazia® with vehicle control in patients with vernal keratoconjunctivitis. Results of the pivotal phase III study showed that Verkazia® significantly improved the signs and symptoms of severe forms of the condition.
Cost-effectiveness	A cost-minimisation analysis compares Verkazia® with a weighted comparator of several other ciclosporin treatments for severe vernal keratoconjunctivitis in children and adolescents between 4 and 18 years of age. The company base case suggests cost savings of £5,033 per patient over a nine-year time horizon. AWTTC considers the most plausible cost savings to range between £1,254 to £11,613, given that these estimates take into account the uncertainty surrounding the model inputs. Using a cost-minimisation analysis is inappropriate because there are no well-designed equivalence and appropriate head-to-head trials. Due to this lack of data, the company's submission assumes equivalence in efficacy, patient preferences, patient-reported outcomes, medicine safety and adherence.
Budget impact	The company estimates that 79 patients are eligible to receive treatment with Verkazia® in Wales in Year 1, increasing to

	81 patients in Year 5, with uptake rates between 25% and 90%. The company base case suggests cost savings of £13,126 in Year 1, increasing to £45,150 in Year 5 however this is based on consumed medicines rather than dispensed. Taking into account the costs of dispensed medicines, the estimated budget impact suggests cost savings of £16,828 in Year 1 and £57,884 in Year 5. Due to the lack of Wales-specific data, patient numbers are based on a Norwegian prevalence survey funded by the company, and the opinion of one UK clinical expert. Clinical expert opinion sought by AWTTC indicates that these patient numbers are representative for Wales.
Additional factors to consider	AWTTC considers Verkazia® eligible to be appraised as an orphan medicine.

This assessment report is based on evidence submitted by Santen UK Limited[1] and an evidence search conducted by AWTTC on 3 and 8 October 2018.

2.0 BACKGROUND

2.1 Condition and clinical practice

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[2]. 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. Although no figures are available for the Welsh population, in the European union, prevalence is estimated at 1 to 3 per 10,000[2].

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 sought by AWTTC indicates that off-label and unlicensed ciclosporin has been used for many years in Wales as an alternative to long-term corticosteroids to treat severe forms of vernal keratoconjunctivitis.

2.2 Medicine

Verkazia® was granted marketing authorisation by the European Medicines Agency in July 2018 for the treatment of severe vernal keratoconjunctivitis in children and

adolescents from 4 to 18 years old[2]. Verkazia® 1 mg/ml eye drops contains ciclosporin as active ingredient and is the same formulation as Ikervis® which was approved in 2015 for the treatment of severe keratitis in adults with dry eye disease[5,6].

Verkazia® is supplied in single-dose containers and each container is sufficient to treat both eyes[5]. Verkazia® should be stored below 30°C. The recommended dose of Verkazia® is one drop four times a day (morning, noon, afternoon and evening) in each affected eye during the vernal keratoconjunctivitis season. If signs and symptoms persist after the end of the vernal season, Verkazia® can continue to be used at the recommended dose. Once signs and symptoms are under control the dose should be decreased to one drop twice daily. Treatment should be discontinued after signs and symptoms are resolved, and restarted if they recur[5]. The applicant company anticipates that Verkazia® 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[1].

2.3 Comparators

The comparators included in the company's submission are:

- off-label ciclosporin 1 mg/ml eye drops (Ikervis®)
- unlicensed ciclosporin 0.05% eye drops (Restasis®)
- unlicensed special manufactured ciclosporin A
- unlicensed ciclosporin 0.2% eye ointment (Optimmune®)
- unlicensed ciclosporin 0.06% eye drops (PADciclo)[1,7].

Optimmune® is licensed for veterinary use[8].

2.4 Guidance and related advice

In NHS England several clinical commissioning groups accept use of off-label ciclosporin (Ikervis®) eye drops as a third-line treatment option for vernal keratoconjunctivitis in children[9].

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, ciclosporin (Verkazia®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

3.0 CLINICAL EFFECTIVENESS

The company's submission includes two studies (VEKTIS AND NOVATIVE) comparing the efficacy and safety of Verkazia® to vehicle control in children and adolescents with vernal keratoconjunctivitis[1]. Vehicle control was the same formulation as Verkazia® but excluded the active substance[2]. VEKTIS was a pivotal phase III study in patients with severe vernal keratoconjunctivitis and NOVATIVE was a supportive phase II/III study in patients with moderate to severe vernal keratoconjunctivitis. The choice of the patient population and dose of Verkazia® in the VEKTIS study was based on a post-hoc subgroup analysis in the NOVATIVE study[2].

3.1 VEKTIS study

This double-blind, multicentre study had two parts: a four-month treatment phase which was designed as a superiority study and an eight-month safety follow-up phase[2]. The study evaluated the safety and efficacy of two different dosing regimens of Verkazia® in patients aged 4 years to < 18 years (mean age 9 years) with severe vernal keratoconjunctivitis in comparison with vehicle control. Patient enrolment happened

during the vernal season to allow the four-month treatment period. Patients were eligible to enrol in the study if: they had active, severe vernal keratoconjunctivitis (grade 3 or 4 on the Bonini scale) with severe keratitis (defined as corneal fluorescein staining grade 4 or 5 on the modified Oxford scale); and had a mean score of four subjective symptoms (photophobia, tearing, itching and mucous discharge) ≥ 60 mm using a 100 mm visual analogue scale. Patients were recruited in 11 countries, excluding the UK; a total of 101 patients were included in Europe[2].

In the four-month treatment phase, 169 patients were randomly assigned (1:1:1) to receive Verkazia® (1 mg/ml) four times daily, Verkazia® (1 mg/ml) twice daily plus vehicle control twice daily, or vehicle control four times daily in each eye[2]. During the eight-month follow-up phase, patients were allowed to continue on one of the two Verkazia® regimens. Patients who received vehicle control during the four-month phase and who continued in the eight-month phase were switched (1:1 randomisation) to Verkazia® four times daily or twice daily plus vehicle control twice daily. If patients experienced worsening symptoms they could receive rescue treatment. Rescue treatment was dexamethasone 0.1% eye drops and a maximum of two courses between two scheduled visits during the four-month treatment period were allowed. During the eight-month follow-up phase, a maximum of four courses between two scheduled visits were allowed[2].

The primary efficacy endpoint was the penalty-adjusted corneal fluorescein staining score at four months of treatment[2]. This was a composite score with a focus on signs, based on the change from baseline in keratitis (measured by corneal fluorescein staining to assess corneal health) and adjusted by penalties for the use of rescue medication and the occurrence of corneal ulcers (see Glossary). The key secondary efficacy endpoints in the four-month phase were:

- changes in the four most common symptoms of vernal keratoconjunctivitis (itching, photophobia, tearing and mucous discharge) measured by the visual analogue scale
- response analysis: each patient was classified as either a responder or non-responder. A responder was defined as a patient with a corneal fluorescein staining score at Month 4 ≤ 50% of baseline, who did not withdraw from the study for a reason possibly due to treatment, no corneal ulceration and no use of rescue treatment in the last three months of treatment.
- health-related quality of life, assessed by the QUICK questionnaire (see Glossary)[2].

Of the 169 patients enrolled, 168 (the full analysis set) were included in the four-month randomised phase[2]. A total of 142 patients were included in the eight-month phase (follow-up total set). The study results are shown in Table 1 and Table 2. After four months of treatment, there was a greater improvement in the average penalty-adjusted corneal fluorescein staining score in the Verkazia® groups compared with the vehicle control group (Table 1). The relative contribution of the three components of the primary endpoint to the size of the treatment effect in the four-month phase are shown in Table 1[2].

An improvement in patients' quality of life, assessed by the QUICK questionnaire, was shown for both treatment groups from baseline to Month 4[2]. A statistically significant difference compared with vehicle control was reported at each month for the Verkazia® four times daily group for both domains (symptoms and activities of daily life), except for daily activities at Month 1. For the low-dose Verkazia® group, statistically significant differences were only shown at Month 2[2]. Treatment benefits were sustained in the

eight-month follow-up phase; corneal fluorescein staining score, symptom and QUICK scores remained low and use of rescue medication was low[1].

Table 1. Key endpoints of the VEKTIS study[2]

	Verkazia® four times daily (n = 56) versus vehicle control (n = 58)	Verkazia® twice daily (n = 54) versus vehicle control (n = 58)
Penalty-adjusted CFS score at Month 4*		
Difference in least square mean	0.76	0.67
95% CI	0.26 to 1.27	0.16 to 1.18
p value	0.007	0.010
Mean change from baseline of mean CFS score per month†		
Least square mean (absolute contribution)	0.523	0.528
95% CI	0.109 to 0.937	0.113 to 0.943
Adjusted p value§	0.014	0.014
Relative contribution (%)	70.3	77.6
Mean number of rescue medication courses per month†		
Least square mean (absolute contribution)	0.220	0.149
95% CI	0.068 to 0.372	−0.003 to 0.301
Adjusted p value§	0.010	0.055
Relative contribution (%)	29.6	21.9
Mean number of ulcer occurrences per month†		
Least square mean (absolute contribution)	0.001	0.003
95% CI	−0.036 to 0.038	−0.033 to 0.040
Adjusted p value§	0.966	0.966
Relative contribution (%)	0.1	0.5
VKC symptoms as measured by VAS (average of the four symptom scores at Month 4)		
Difference in least square mean	−19.411	−8.355
95% CI	−29.307 to −9.515	−18.402 to 1.693
p value	< 0.001	0.103

* Primary endpoint
† Component of primary endpoint
§ Hochberg procedure
CFS: corneal fluorescein staining; CI: confidence interval; VAS: visual analogue scale; VKC: vernal keratoconjunctivitis

Table 2. Responder rate at Month 4 from the VEKTIS study[2]

	Verkazia® four times daily (n = 56)	Verkazia® twice daily (n = 54)	Vehicle control (n = 58)
Responder rate	32 (57.1%)	33 (61.1%)	20 (34.5%)
Odds ratio versus vehicle control	2.583	3.486	-
95% CI	1.207 to 5.531	1.576 to 7.713	-
p value	0.013	0.003	-
CI: confidence interval			

3.2 NOVATIVE study

This multicentre, dose-ranging study was divided in two parts: a one-month, three parallel groups, vehicle-controlled treatment phase, and a three-month, two parallel

group treatment phase[2]. Patients aged between 4 and 21 years (mean age 8.5 years) with moderate to severe, active vernal keratoconjunctivitis were recruited. Patients (n = 118) were randomised (1:1:1) to receive Verkazia® 1 mg/ml four times daily, Verkazia® 0.5 mg/ml four times daily or vehicle control. The primary efficacy endpoint was the overall rating of subjective symptoms (redness, itching, photophobia, tearing, mucous discharge and the ability to participate in normal daily activities) of vernal keratoconjunctivitis at Month 1 compared to baseline. These were measured using a five-point, semi-quantitative, visual analogue scale. Corneal fluorescein staining score was a secondary endpoint[2].

The study did not meet its primary efficacy endpoint[2]. Patients who received Verkazia® showed improvements in the primary endpoint, but these were not statistically significant compared with vehicle control. Post-hoc analyses in 45 patients with severe keratitis suggested a potential for a greater benefit with Verkazia® 1 mg/ml over the 0.5 mg/ml dose. At Month 1, Verkazia® 1 mg/ml showed a statistically significant improvement in corneal fluorescein staining score compared with vehicle control ($p = 0.009$)[2]. Therefore, it was decided to test Verkazia® 1 mg/ml in the VEKTIS study to support its use in patients with severe disease.

3.3 Safety

There are no safety data comparing Verkazia® with off-label and unlicensed ciclosporin products. The clinical studies outlined in Sections 3.1 and 3.2 did not highlight any specific safety concerns[2]. The majority of adverse events reported were infections and eye disorders that were mild to moderately severe[1]. In the VEKTIS study, the rates of treatment-emergent adverse events were similar in the control and active treatment groups. Most of these events were instillation site pain and pruritus. These events were reported during administration but usually resolved shortly after[1].

The Committee for Medicinal Products for Human Use (CHMP) highlighted that uncertainties remain in relation to the risk of infections and malignancies as a result of local suppression of the immune response[2]. Due to the lack of long-term data (limited to 12 months), further characterisation of the long-term safety profile of Verkazia® is needed. As required by CHMP, the marketing authorisation holder will explore the feasibility of performing a case-control study linked to existing cancer registries to generate additional data post-marketing[2].

The Summary of Product Characteristics advises regular monitoring of the eye when Verkazia® is used long term (> 12 months)[5]. In the NOVATIVE and VEKTIS studies, systemic exposure to ciclosporin was very low[2].

3.4 AWTTC critique

- Clinical expert opinion sought by AWTTC highlighted a definite unmet need for children and adolescents with severe vernal keratoconjunctivitis which requires long term topical corticosteroid treatment. Verkazia® is the first licensed topical ciclosporin formulation for this indication.
- Clinical expert opinion sought by AWTTC indicated that off-label Ikervis® is currently widely used in clinical practice as an alternative to long-term corticosteroid to treat severe vernal keratoconjunctivitis. However, the dose of Ikervis® would be one or two drops a day which is less than the licensed dose of Verkazia®.
- The company's submission included studies which support the superiority of Verkazia® to the vehicle control. No evidence is available that directly compares the clinical effectiveness and safety of Verkazia® with off-label and unlicensed ciclosporin. The European Medicines Agency considers that vehicle-controlled

studies are acceptable and it has been discussed in the CHMP scientific advice[2].

- The company conducted a systematic literature review but did not submit any indirect comparisons or mixed treatment evidence due to limited comparative studies.
- VEKTIS was the key study supporting the marketing authorisation of Verkazia®. The patient population was small (n = 169) which was considered acceptable by the European Medicines Agency given the rarity of the disease[2]. No patients from the UK were included in the study. This is not surprising given the geographical variation of the disease and its rarity[4].
- Given that the use of rescue treatment was allowed in cases of corneal progression, the development of corneal ulcers could be expected to be rare. Therefore, the CHMP highlighted the importance of analysing the relative contribution of each of the subcomponents of the primary endpoint. The VEKTIS study showed that reduction in corneal fluorescein staining score was the main driver of the observed treatment effect, with rescue medicine contributing to a lesser degree.
- The primary endpoint in the VEKTIS study was accepted by the CHMP given that there is no validated endpoint to assess efficacy in vernal keratoconjunctivitis[2]. However, the CHMP noted that the choice of penalty score of one was arbitrary and therefore requested sensitivity analyses modifying the weighting of the penalty. The outcome of post-hoc sensitivity analyses remained in favour of Verkazia® although uncertainties in the clinical relevance remained. The CHMP considered the significant improvement in responder rate to be more clinically meaningful in understanding the actual benefits of treatment[2].
- The CHMP highlighted that Verkazia® four times a day administration may not be feasible for children going to nursery or school[2]. In the VEKTIS study beneficial effects were also seen with the twice daily dose and the CHMP noted that a less frequent instillation (morning and evening only) would be expected to be more convenient[2].
- The NOVATIVE study included patients aged over 18 years, which is outside the licensed population.
- Direct safety and clinical efficacy data are limited to 12-month analyses[2]. The number of patients in the VEKTIS study who received the licensed dose intended for commercial use for at least 12 months is limited (n = 49); therefore, uncertainties on the long-term safety of Verkazia® must be considered[2].
- Clinical expert opinion sought by AWTTC suggests that the choice of comparators was appropriate for this submission, and indicated that Restasis®, Optimmune® and PADciclo are used infrequently in practice because they are poorly tolerated or unavailable.

4.0 COST-EFFECTIVENESS

4.1 Context

The company's submission includes a cost-minimisation analysis (CMA) comparing Verkazia® 1 mg/ml emulsion, administered topically as eye drops, with a weighted comparator of all other ciclosporin eye drop treatments identified in a survey conducted by the company, in patients with severe vernal keratoconjunctivitis between four years of age and adolescence[1,10]. The weighted comparator comprises of unlicensed and off-label ciclosporin including Ikervis® 0.1% [commercial in confidence data removed], Restasis® 0.05% [commercial in confidence data removed] and Optimmune® 0.2% [commercial in confidence data removed], special manufactured preparations 0.2%

[commercial in confidence data removed] and PADciclo [commercial in confidence data removed][10].

A Markov model with one-month cycle length is used to estimate the difference in treatment costs between Verkazia® versus the ciclosporin weighted comparator. The model adopts a nine-year time horizon and an NHS Wales/Personal and Social Services perspective. Patients start the model at a mean age of nine years as observed in the pivotal study[2] and either remain in the symptomatic stage if their vernal keratoconjunctivitis is persistent or transition between symptomatic and asymptomatic for patients with seasonal vernal keratoconjunctivitis.

Treatment acquisition costs are based on eye drop administration four times a day with the option to reduce to twice a day if symptoms improve (based on data from the pivotal study[2]). Cost of Verkazia® was provided by the company, cost of Ikervis®, Restasis®, Optimmune® and PADciclo were taken from published sources[7] and cost of special manufactured preparations was assumed to be the average of the two cheapest ciclosporin formulations. Compliance rate was assumed to be [commercial in confidence data removed]for all ciclosporin treatments based on European market research[11]. The analysis also includes costs of anti-allergic eye drops (either daily or every other day in perennial patients only), sodium cromoglicate (either two or four times a day)[7], and ophthalmologist appointments[12]. Preparation and dispensing costs of special manufactured ciclosporin included in the mixed comparator are derived from Personal Social Services Research Unit costs for the UK[13]. Rescue corticosteroid medication was assumed to be one course of topical corticosteroids (dexamethasone 0.1%) four times daily for five days based on the VEKTIS study[2]. All costs are discounted at 3.5%.

The company provided basic sensitivity analyses taking into account medicine dispensing rather than consumption.

4.2 Results

The results of the base case analysis are detailed in Table 3. When compared with the mixed, weighted comparator, Verkazia® is £5,033 less costly per patient over the time horizon in the base case. This cost saving increased to £6,434 when medicine dispensing rather than consumption was taken into account in sensitivity analysis. The cost differences are predominantly attributed to higher cost components of the mixed comparator.

Table 3. Results of the base case analysis and scenario/sensitivity analyses[1]

Scenario	Costs	Verkazia®	Comparator	Difference	Plausibility
Base case: Cost of consumed medicines rather than dispensed					
Verkazia® versus mixed ciclosporin comparator	Medicine acquisition costs	£15,232	£20,200	−£4,967	
	Monitoring costs*	£2,574	£2,639	−£65	
	Other costs†	£218	£218	£0	
	Total costs	£18,024	£23,057	−£5,033	
Scenario analysis: Cost of dispensed medicines rather than consumed					
Verkazia® versus mixed ciclosporin comparator	Medicine acquisition costs	£19,529	£25,897	−£6,368	e.g. more plausible than base case as it reflects true costs to the NHS.
	Monitoring costs*	£2,574	£2,639	−£65	
	Other costs†	£275	£275	£0	
	Total costs	£22,378	£28,812	−£6,434	
Sensitivity analysis: Assuming 2 drops a day for all formulations					
Verkazia® versus mixed ciclosporin comparator	Medicine acquisition costs	£9,764	£13,199	−£3,434	e.g. less plausible than base case as pivotal trial has shown higher efficacy for 4 drops.
	Monitoring costs*	£2,574	£2,639	−£65	
	Other costs†	£275	£275	£0	
	Total costs	£12,613	£16,113	−£3,499	
Sensitivity analysis: Assuming 2 drops a day for all unlicensed formulations but 4 drops for Verkazia®					
Verkazia® versus mixed ciclosporin comparator	Medicine acquisition costs	£19,529	£13,199	£6,330	Less plausible than base case as pivotal trial has shown higher efficacy for 4 drops which would also violate the basic assumption of equivalence required for CMA.
	Monitoring costs*	£2,574	£2,639	−£65	
	Other costs†	£275	£275	£0	
	Total costs	£22,378	£16,113	£6,265	

* Including ophthalmologist appointments and dispensing costs for special manufactured ciclosporin component of mixed comparator.
† Rescue medication (dexamethasone 0.1%) and eye drops (sodium cromoglicate 2%)
CMA: cost-minimisation analysis

4.3 AWTTC critique

The reliability of the CMA depends on the extent to which Verkazia® is considered to be therapeutically equivalent to the comparator. The company justified using a CMA, as opposed to a cost-utility analysis, on the basis that the main component of the mixed comparator (Ikervis®) has the same composition and strength as Verkazia® and can therefore be assumed to be of equal efficacy and safety, producing equal utility.

However, no head-to-head study data are available to corroborate this assumption. Furthermore, all other ciclosporin components of the mixed comparator are also assumed to be of equal efficiency, despite differences in composition and strength. The results of the CMA show that Verkazia® is cost-saving compared with the mixed, weighted comparator.

In the absence of well-designed equivalence studies and/or evidence of close comparability of other effects (impact on health-related quality-of-life, adverse events, patient preference, adherence and survival), AWTTC considers a CMA to be inappropriate in this instance.

The submission is characterised by strengths and limitations:

Strengths:

- The model reflects the correct patient population and adopts an appropriate perspective and time horizon.
- The company provides a transparent and detailed account of all methods and data inputs.

Limitations:

- The company's justification for using a CMA is not convincing, given that no head-to-head studies are available to infer equivalence. The company suggests that a systematic literature review did not yield any direct comparisons of different treatment options due to the rare nature of the condition. They therefore assume equal benefits and utility for all ciclosporin products. While this assumption might be more conceivable for Ikervis® as it has the same composition and strength, it is questionable for all other ciclosporin products included in the analysis. This uncorroborated assumption will therefore introduce bias of unknown proportion, and any difference in efficacy, utility or safety between the treatment options will contradict the principle of a CMA.
- The analysis adjusts acquisition costs assuming 78% compliance based on estimated compliance figures for Ikervis® suggested by 30 physicians in 5 European countries. This underestimates medication costs as the cost to the NHS will have occurred at the point of dispensing. However, this is likely to underestimate cost savings of Verkazia®.
- The company did not include a sensitivity analysis based on the acquisition cost of Verkazia® or the mixed comparator. Considering the high uncertainty based around the assumptions made to estimate some of the comparator component costs, this will affect the results. AWTTC calculations show that 20% variability in the comparator cost leads to a range of net cost differences between Verkazia® and the mixed weighted comparator of −£1,254 to −£11,613 based on dispensed (rather than consumed) medicines.
- The Markov model used for the CMA appears overly complex considering the scarcity of available data, requiring information on healthcare resource use, rescue medication and mortality. While all parameters other than medication cost are equal in the model, this violates the assumption of equivalence between products and a series of data assumptions is needed to populate the model. This will increase bias and uncertainty around the results.
- Because no other ciclosporin treatment is licensed for vernal keratoconjunctivitis in children and adolescents, there is uncertainty around whether the weighted comparators chosen by the company (based on a UK survey of ophthalmologists[10]) is most reflective of current practice in Wales. Furthermore, the percentage of patients receiving ciclosporin formulations and the costs of some of these treatments in Wales were unknown and therefore

based on assumptions, which will introduce bias. No sensitivity or scenario analyses are provided by the company to explore this uncertainty around the comparator and its cost.

- Removing Restasis®, Optimmune® and PADciclo from the mixed comparator and adding the share to either Ikervis® or special manufactured ciclosporin, results in incremental costs for Verkazia® versus the comparators between -£144 and -£419. These lower savings are caused by the price neutrality between Verkazia® and Ikervis® and the fact that special manufactured ciclosporin are assumed to have a price close to the Ikervis® price.
- Welsh prescribing data indicate that all mixed comparator components are stocked in some health board pharmacies in small quantities but it is unknown whether they are used for vernal keratoconjunctivitis. It is therefore impossible to verify the applicability and generalisability of the mixed comparator to Welsh clinical practice.
- Clinical expert opinion sought by AWTTC suggests that the dose of Ikervis® used in clinical practice is less than the licensed dose of Verkazia®. Halving the dose of the main component of the comparator will have cost implications which are not taken into account by the company.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC did not identify any studies relevant to the cost-effectiveness of Verkazia® compared with other ciclosporin options in the treatment of vernal keratoconjunctivitis in children and adolescents.

5.0 BUDGET IMPACT

5.1 Context and methods

The company has estimated that there will be 471 people of all ages with vernal keratoconjunctivitis in 2018 in Wales. This estimate is based on Office for National Statistics population statistics[14] and vernal keratoconjunctivitis prevalence data for Norway based on a European survey[15]. Due to a lack of available incidence data, prevalence is assumed to remain constant over time, taking into account population growth but excluding mortality and discontinuations[16]. Based on extrapolation from Norwegian published evidence[15], the company assumes that 25% of these cases are severe with [commercial in confidence data removed] of them paediatric according to a survey undertaken by the company[11]. The company estimates that 75% of severe vernal keratoconjunctivitis cases are treated with ciclosporin products based on expert opinion. Considering that no other treatment options are licensed in Wales, all eligible patients are assumed to be prescribed Verkazia®. Uptake rates are assumed to be 25% in Year 1 increasing to 90% in Year 5. The company provides a breakdown of how comparator medicines are likely to be displaced as a result.

5.2 Results

The budget impact is presented in Table 4. The company estimates that introducing Verkazia® would lead to an overall saving of £13,126 in Year 1, increasing to £45,150 in Year 5 however this is based on consumed medicines rather than dispensed. This estimate incorporates cost differences resulting from the equal displacement of all components of the mixed, weighted ciclosporin comparator. The company carried out sensitivity analyses changing ciclosporin uptake rates and cost, as well as daily dose, percentage of paediatric patients and the composition of the mixed comparator. Results remained cost saving throughout the analyses with overall cost reductions between £6,452 and £18,810 in Year 1, increasing to between £23,275 and £65,613 in

Year 5. Taking into account the costs of dispensed medicines rather than consumed, the estimated budget impact was −£16,828 in Year 1 and −£57,884 in Year 5.

Table 4. Company-reported costs associated with use of Verkazia® for the treatment of severe vernal keratoconjunctivitis in children and adolescents[1]

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (all licensed indications)	79	80	80	80	81
Sub-population of eligible patients (indication under consideration)	79	80	80	80	81
Uptake of new medicine (%)	25%	50%	70%	80%	90%
Number of patients receiving new medicine allowing for discontinuations	20	40	56	64	72
Medicine acquisition costs in a market without new medicine	£206,250	£208,210	£208,210	£208,210	£210,170
Medicine acquisition costs in a market with new medicine	£193,124	£182,442	£172,477	£166,221	£165,020
Net medicine acquisition costs	−£13,126	−£25,768	−£35,733	−£41,989	−£45,150
Net supportive medicines costs	£0	£0	£0	£0	£0
Net medicine acquisition costs (savings/costs) - including supportive medicines where applicable	−£13,126	−£25,768	−£35,733	−£41,989	−£45,150

The company estimates that net resource implications arising from the introduction of Verkazia® will lead to a saving of £2,244 over five years. This is a consequence of reduced pharmacy costs required for displaced hospital ciclosporin formulations. These resource-type savings are included for potential planning purposes but may be difficult or impossible to realise in practice.

5.3 AWTTC critique

- The submission gives a detailed, transparent account of the methods and data sources used to estimate budget impact. The company has factored population

growth into the calculations. However, mortality and discontinuation are not considered.
- The budget impact considerations include acquisition costs and other resource use such as supportive medicines costs (that is, anti-allergic eye drops and rescue medication) and monitoring costs but do not take into account costs associated with potential adverse events.
- Uptake rate estimates for Verkazia® are based on assumptions made by the company and might underestimate actual uptake considering the lack of licensed treatments for severe vernal keratoconjunctivitis. However, the company provides sensitivity analysis to explore the impact of different Verkazia® uptake rates on the displacement of the other comparators.

6.0 ADDITIONAL FACTORS TO CONSIDER

6.1 AWMSG's policy for orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

The company suggests that the prevalence of the population for the full licensed indication of Verkazia® meets the AWMSG criteria for an orphan medicine.

Based on an estimated prevalence of vernal keratoconjunctivitis in Norway[15], a prevalence rate of 1.5 per 10,000 population was assumed, resulting in 471 people of all ages with vernal keratoconjunctivitis in Wales, of whom approximately 106 are thought to be paediatric and have severe vernal keratoconjunctivitis[10,17]. Clinical expert opinion sought by AWTTC are supportive of these figures.

AWTTC considers Verkazia® eligible to be appraised as an orphan medicine because the full population of the licensed indication does not exceed the threshold of ≤ 5 patients in 10,000 (≤ 1,500 patients in Wales).

The New Medicines Group (NMG) and AWMSG will consider additional criteria (see Table 5) if they consider Verkazia® is an orphan medicine.

Table 5. Evidence considered by NMG/AWMSG

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers	Severe vernal keratoconjunctivitis is a rare but serious, inflammatory disease that seasonally affects the eyes (usually both eyes) of children and teenagers[18] and poses a high risk of permanent sight loss and blindness if not diagnosed and treated correctly[3]. It usually resolves after puberty but may continue into adulthood[2]. Symptoms include severe itching, photophobia, stringy mucous discharge, redness, tearing and blurred vision especially in the mornings which can result in frequent lateness for school[19]. Severe vernal keratoconjunctivitis impacts on children's and their caregivers' daily lives and social interactions and results in loss of educational opportunity and decreased health-related quality-of-life[20].
Whether the medicine addresses an unmet need (e.g. no other licensed medicines)	While topical corticosteroids are widely used to treat severe vernal keratoconjunctivitis[21], some cases remain symptomatic or require longer-term maintenance. In order to reduce corticosteroid use and its complications, off-label and unlicensed topical ciclosporin is used to improve symptoms and is currently the preferred maintenance therapy in children with severe vernal keratoconjunctivitis[15]. Verkazia® is the first licensed ciclosporin product to treat severe vernal keratoconjunctivitis.
Whether the medicine can reverse or cure, rather than stabilise the condition	There is no evidence that Verkazia® can reverse or cure severe vernal keratoconjunctivitis.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy) and that this "definitive" therapy is currently in development	There is no evidence that Verkazia® bridges a gap to a 'definitive therapy'.
The innovative nature of the medicine	Verkazia® is not an innovative medicine.
Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity)	This criterion is not applicable as the company has submitted a cost-minimisation analysis not a cost-utility analysis.
Added value to the patient's family (e.g. impact on a carer or family life)	Severe vernal keratoconjunctivitis in children and teenagers will require family or carers to attend hospital appointments with them or look after them when they miss time from school, which could require time off work.
AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics and Toxicology Centre; NMG: New Medicines Group; QALY: quality-adjusted life-year	

GLOSSARY

Primary endpoint of the VEKTIS study

The primary endpoint of the VEKTIS study was the penalty-adjusted corneal fluorescein staining score at four months. This was defined as the mean of the four efficacy scores taken at each monthly visit, based on:

- keratitis assessed by corneal fluorescein staining using the modified Oxford scale (seven-point ordinal scale [0, 0.5 and 1 to 5])
- need for rescue medication
- occurrence of corneal ulceration[2].

The efficacy score was calculated as follows:
Patient's score at Month X = corneal fluorescein staining (baseline) – corneal fluorescein staining (Month X) + penalty(ies).

Penalty for rescue medication: −1 per course, with a maximum of 2 courses between 2 scheduled visits.

Penalty for corneal ulceration: −1 per occurrence[2].

QUICK questionnaire

A questionnaire to measure health-related quality of life in children with vernal keratoconjunctivitis[2]. The questionnaire contained 16 items allocated into two domains: symptoms (12 items including burning, light sensitivity, itchy eyes and blurred eyes) and impact of vernal keratoconjunctivitis on daily activity (4 items: trouble playing outdoors; trouble practising sports; trouble meeting friends; and trouble going to the swimming pool)[20]. Each item which relates to what the patient experienced in the past two weeks was scored according to a three-point scale where 1 = never, 2 = sometimes and 3 = always[2]. QUICK scores range from 0 to 100, with the highest score indicating a worse health-related quality of life[2].

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