

## 5.04 CICLOSPORIN, Eye drops 0.1%, single dose units 0.4 mL, Ikervis<sup>®</sup>, Seqirus (Australia) Pty Ltd

### 1 Purpose of submission

- 1.1 The submission requested an Authority Required (STREAMLINED) listing for ciclosporin for the treatment of patients with severe keratitis with dry eye disease (DED).
- 1.2 Listing was requested on the basis of a cost-utility analysis versus best supportive care (BSC), which included artificial tears.

**Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)**

Component	Description
Population	Patients with severe keratitis with dry eye disease (DED).
Intervention	Ciclosporin 1 mg/mL, 0.1% eye drops, emulsion with preservative free artificial tears, as needed.
Comparator	Best supportive care (BSC), consisting of preservative free artificial tears as needed.
Outcomes	Assessment of signs and symptoms of DED and keratitis: <ul style="list-style-type: none"> <li>• Corneal fluorescent staining (CFS)</li> <li>• Ocular Surface Disease Index (OSDI)</li> <li>• Tear break up time (TBUT)</li> <li>• Shirmer tear test</li> </ul> Adverse events
Clinical claim	In patients with severe keratitis with DED who have failed to achieve symptom control with artificial tears, ciclosporin eye drops is superior to placebo with respect to efficacy and non-inferior with respect to safety.

Source: Table 1.1.1, p26 of the submission.

### 2 Background

#### **Registration status**

- 2.1 Ciclosporin was registered by the TGA on 11 December 2020 for:

“Treatment of severe keratitis in adult patients with dry eye disease which has not improved despite treatment with tear substitutes.”

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

### 3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty (units)	No. of Rpts	Dispensed Price for Max. Qty (unit)	Proprietary Name and Manufacturer
Ciclosporin 1 mg/mL (0.1%) eye drops; 30 × 0.3 mL unit doses	30	5	\$ [REDACTED]	Ikervis® Seqirus

<b>Category/Program:</b>	GENERAL – General Schedule (Code GE)
<b>PBS indication:</b>	Treatment of patients with severe keratitis with dry eye disease
<b>Treatment phase:</b>	Initiation
<b>Restriction:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Must be treated by an ophthalmologist or an optometrist
<b>Clinical criteria:</b>	Patient must have severe dry eye disease with keratitis defined as corneal fluorescein staining (CFS) grade of 4 using the modified Oxford scale or equivalent, and ocular surface disease index (OSDI) greater than or equal to 23 AND Patient must have failed to achieve adequate symptom control using optimised treatment with preservative free tear substitutes.
<b>Population criteria:</b>	Patient must be 18 years or older

<b>Category/Program:</b>	GENERAL – General Schedule (Code GE)
<b>PBS Indication:</b>	Treatment of patients with severe keratitis with dry eye disease
<b>Treatment phase:</b>	Continuation
<b>Restriction:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Must be treated by an ophthalmologist or an optometrist
<b>Clinical criteria:</b>	The patient must have demonstrated an adequate response to treatment with this drug 6 months after initiation.
<b>Population criteria:</b>	Patient must be 18 years or older.
<b>Definitions:</b>	An adequate response to treatment is defined as: an improvement in corneal fluorescein staining (CFS) of at least 3 using the modified Oxford scale or equivalent, and ocular surface disease index (OSDI) of at least 30% when compared with the baseline values.

<b>Category/Program:</b>	GENERAL – General Schedule (Code GE)
<b>PBS Indication:</b>	Treatment of patients with severe keratitis with dry eye disease
<b>Treatment phase:</b>	Continuation after assessment of response
<b>Restriction:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Must be treated by an ophthalmologist, an optometrist or a general practitioner
<b>Clinical criteria:</b>	Maintenance treatment of drug in patients meeting adequate response criteria assessment at 6 months
<b>Population criteria:</b>	Patient must be 18 years or older

- 3.1 The pre-PBAC response applied a 28% price reduction to the approved ex-manufacturer price (AEMP) offered in the submission, resulting in an AEMP of \$ [REDACTED] (DPMQ = \$ [REDACTED]).
- 3.2 The initiation and first continuation restrictions were based on ocular signs of keratitis, as measured by CFS, and ocular symptoms, as measured by the ocular surface disease index (OSDI); the OSDI is subjective. Noting that the TGA approved ciclosporin eye drops on the basis of improvement in ocular signs and not ocular symptoms, the ESC

considered that the ODSI and other symptom scores were potentially relevant in the restriction.

- 3.3 Evidence also suggested that after an induction with ciclosporin there were lasting benefits in terms of keratitis<sup>1</sup>. The ESC, based on the limited evidence that a defined course of ciclosporin may provide a lasting benefit, considered that it may be reasonable for the restriction to limit treatment (i.e. to 24 months), after which, a patient may requalify for treatment if they again met the initial criteria. The ESC considered that this may serve to manage the potential concerns surrounding long term immunosuppression use and the lack of evidence that ciclosporin provides symptomatic benefits. The pre-PBAC response considered it reasonable that treatment be re-evaluated at 24 months, but considered that patients should not have to requalify for treatment based on the initiation criteria as this would require patients to return to a severe disease state.
- 3.4 It was noted that the use of CFS and OSDI by GPs was minimal in routine practice, and that GPs would likely require training in how to conduct the tests and assess the grades. This may not be practical given the small number of patients that present to GPs. The Advisory Committee on Medicines (ACM) “agreed that prescribing of [ciclosporin] should be restricted to ophthalmologists. Ophthalmologists are experienced in differentiating patients with severe disease from those with milder disease (for whom lubricants would be more appropriate)” (ACM Minutes on Item No 2.06 ciclosporin, Oct 2020). The Pre-Sub-Committee Response (PSCR) stated that the Sponsor was willing to exclude GPs from the subsequent continuation restriction. The ESC considered this appropriate as including GPs could increase the risk of leakage beyond the proposed clinical criteria. The pre-PBAC response advised that the Product Information for ciclosporin was amended after the ACM meeting to read that ‘Treatment should be initiated by an ophthalmologist or appropriately qualified healthcare professional with expertise in the diagnosis, assessment and treatment of keratitis associated with dry eye disease’. The pre-PBAC response stated that this would include optometrists. Noting that the majority of GPs would not have access to a split lamp to facilitate the required ongoing assessment of the condition, the PBAC considered that initial and continuing prescribing of ciclosporin should be limited to ophthalmologists and optometrists. The PBAC considered that the inclusion of optometrists would improve equity of access to ciclosporin, particularly for rural and remote patients.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

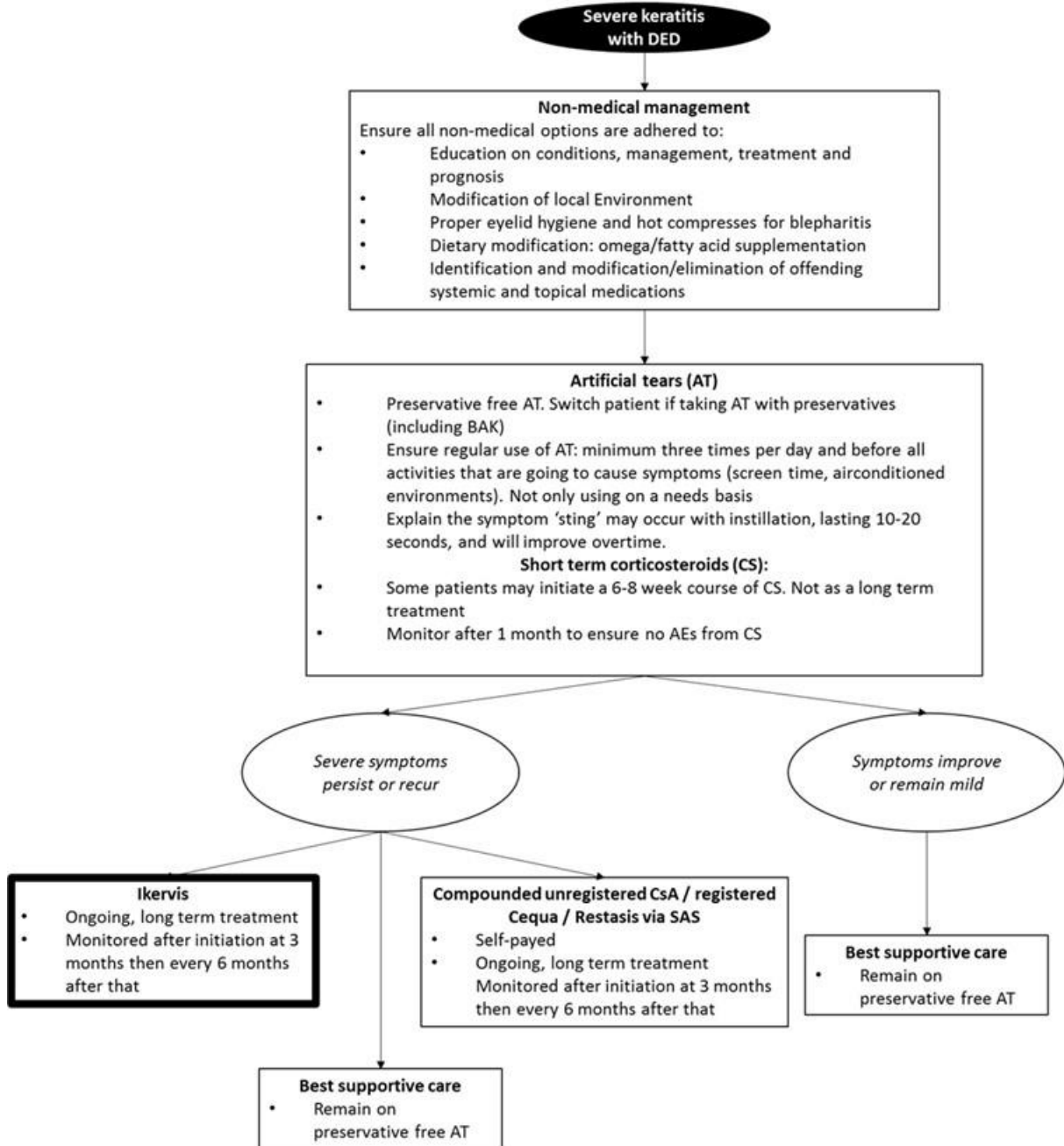
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<sup>1</sup> Straub M, Bron AM, Museller-Mathieu A, et al. Long-term outcome after topical ciclosporin in severe dry eye disease with a 10-year follow-up. *Br J Ophthalmol.* 2016;100(11):1547-1550.

## **4 Population and disease**

- 4.1 Keratitis is inflammation of the cornea and represents damage or lesions on the corneal surface; it predisposes the cornea to secondary infections and can result in sight-threatening sequelae (American Academy of Ophthalmology 2018). DED, or keratoconjunctivitis sicca, is a common ocular condition that is characterised by dryness of the conjunctiva and cornea. Patients with DED experience reduced tear production or tear film instability, which leads to discomfort and visual disability (American Academy of Ophthalmology 2018).
- 4.2 Ciclosporin is a calcineurin inhibitor immunosuppressant.
- 4.3 The submission presented a current and a proposed clinical management algorithm. The clinical management algorithm was based on local expert advice as there were no locally relevant treatment guidelines for severe keratitis with DED identified. The algorithm did not include the results of diagnostic tests (CFS on the Oxford Modified Scale and OSDI) or continuation treatment after achieving an adequate response. The comparator of BSC, which, in the clinical management algorithm consisted of preservative free artificial tears, was different to the comparator presented in the clinical trials, which was a vehicle of placebo cationic emulsion with no ciclosporin, with concomitant artificial tears.
- 4.4 Figure 1 presents the current and proposed clinical management algorithm.

Figure 1: Current and proposed treatment algorithm for treatment of severe keratitis with DED



AEs = adverse events; AT= artificial tears; CS = corticosteroid; CsA = ciclosporin; DED = dry eye disease; SAS = special access scheme. Source: Figure 1.2.1, p35 of the submission.

For more detail on PBAC’s view, see section 7 PBAC outcome.

## 5 Comparator

5.1 The submission nominated BSC, including preservative free artificial tears as needed, as the main comparator. The main argument provided in support of this nomination

was that there were no PBS listed treatment options for patients who continue to experience severe symptoms of DED despite use of artificial tears, and no ciclosporin eye drops were listed on the PBS. The only available treatment options included ongoing symptomatic control using artificial tears.

- 5.2 The ESC noted that the nominated comparator of BSC differed to the comparator presented in the clinical trials, which was a vehicle of placebo cationic emulsion with no ciclosporin in addition to artificial tears.
- 5.3 There were other ciclosporin eye drop formulations available in Australia; including extemporaneous preparations, an unregistered product, Restatis (0.05%), and the recently registered Cequa (0.09%). These may be potential future comparators.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease and how the drug would be used in practice. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this chronic condition.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from one health professional and one organisation via the Consumer Comments facility on the PBS website. The health professional described the symptoms related to severe dry eye disease and the quality of life benefits of treatment with ciclosporin for patients with severe disease.
- 6.3 The PBAC noted the advice received from Optometry Australia clarifying the likely use of ciclosporin in clinical practice. The PBAC specifically noted the advice that the use of ciclosporin may improve eye care and reduce eye pain. The PBAC noted that this advice was supportive of the evidence provided in the submission.

### ***Clinical trials***

- 6.4 The submission was based on two randomised controlled trials (RCTs):
  - SANSIKA: ciclosporin compared with a vehicle of placebo cationic emulsion with no ciclosporin in severe keratitis (CFS=4) patients with DED (N=245), and an extension open-label study of ciclosporin on severe keratitis patients (N=207).
  - SICCANOVE: ciclosporin compared with a vehicle of placebo cationic emulsion with no ciclosporin in moderate to severe keratitis (CFS= 2-4) patients with DED (N= 489).

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6.5 The submission also presented a meta-analysis of the SANSIKA trial and a subgroup of the SICCANOVE trial (patients with severe keratitis with DED as defined as CFS=4 and OSDI  $\geq$  23 (N=319) (Leonardi 2019).

6.6 Details of the trials presented in the submission are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

Study identifier	Protocol/Publication title	Publication citation
SANSIKA	A multicenter, randomized, double-masked, 2 parallel arm, vehicle-controlled, 6-month phase III trial with a 6 month open label treatment safety follow-up period to evaluate the efficacy and safety of cyclokat® 1 mg/ml (ciclosporin/cyclosporine) eye drops, emulsion administered once daily in adult patients with severe dry eye disease (DED).	Protocol no. NVG10E117, EudraCT no. 2011-000160-97
	Leonardi, A., et al. Efficacy and safety of 0.1% cyclosporine A cationic emulsion in the treatment of severe dry eye disease: a multicenter randomized trial.	European journal of ophthalmology 2016; 26.4: 287-296
	Leonardi, A., et al. (2016). Subgroup analysis of two phase III studies of 0.1% cyclosporine A cationic emulsion (CsA CE) in patients with dry eye disease.	Acta Ophthalmologica 2016; 94
	Baudouin, C., et al (2017). One-year efficacy and safety of 0.1% cyclosporine a cationic emulsion in the treatment of severe dry eye disease.	European Journal of Ophthalmology 2017; 27(6), 678-685.
	Leonardi, A., et al. (2015). The Effect of Ikervis® (1 mg/mL Ciclosporin cationic emulsion) on severe keratitis in patients with dry eye disease participating in a phase III study.	Acta Ophthalmologica 2015; 93
	Van Setten, G. B., et al (2016). Safety and efficacy of ciclosporin 1 mg/mL cationic emulsion (CsA CE) over 12 months in patients with severe dry eye disease (DED) in the SANSIKA Phase III trial.	Investigative Ophthalmology and Visual Science 2016; 57(12), 2865
SICCANOVE	A phase III, multicentre, randomised, controlled, double-masked trial of NOVA22007 (ciclosporin 0.1%) ophthalmic cationic emulsion versus vehicle in patients with moderate to severe dry eye syndrome	Protocol no. NVG06C103, EudraCT no. 2007-000029-23
	Baudouin, C., et al. A randomized study of the efficacy and safety of 0.1% cyclosporine A cationic emulsion in treatment of moderate to severe dry eye.	European journal of ophthalmology 2017; 27.5: 520-530
Meta-analysis of SICCANOVE and SANSIKA Leonardi (2019)	Efficacy meta-analysis for NOVA2007 studies NVG06C103 and Study NVG10E117. Statistical Tables and Figures. 7 August 2013.	August 2013
	Leonardi, A., et al. (2019). Efficacy and safety of 0.1% ciclosporin A cationic emulsion in dry eye disease: A pooled analysis of two double-masked, randomised, vehicle-controlled phase III clinical studies.	British Journal of Ophthalmology 2019; 103(1), 125-131
	Messmer, E., et al. (2016). Pooling of two randomized phase III clinical trials of ciclosporin 1 mg/mL cationic emulsion (CsA CE) as a treatment for severe keratitis in patients with dry eye disease (DED).	Investigative Ophthalmology and Visual Science 2016; 57(12), 2871.

CSR= clinical study report; RCT= randomised controlled trial; CAE= controlled adverse environment; NR= not reported.

Source: Table 2.2.2, p46 of the submission.

6.7 The key features of the trials included are summarised in Table 3.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Primary Outcomes	Use in modelled evaluation
<b>Ciclosporin vs. Vehicle</b>						
SANSIKA	245	R, DB 6 mths	Low	Severe keratitis with DED	CFS, VAS, CFS-OSDI response rate (Less stringent criteria: CFS improvement $\geq$ 2 grades and OSDI improvement of 30%) (More stringent criteria [post-hoc]: CFS improvement $\geq$ 3 grades and OSDI improvement of 30%)	Not used
SANSIKA Part 2	207	OL 6 mths	Low	Severe keratitis with DED	CFS, VAS, CFS-OSDI response rate	Not used
SICCANOVE	489	R, DB 6 mths	Low	Moderate to severe keratitis with DED	CFS, VAS	Not used
Meta- analysis	319	Included SANSIKA and SICCANOVE; subgroup analysis; assessed CFS-OSDI response (Less stringent criteria: CFS improvement $\geq$ 2 grades and OSDI improvement of 30%) (More stringent criteria [post-hoc]: CFS improvement $\geq$ 3 grades and OSDI improvement of 30%) in patients with severe keratitis with DED.				Used

CFS = corneal fluorescent staining; DB = double blind; DED = dry eye disease; OL = open label; OSDI= ocular symptom disease index; R = randomised; VAS= visual analogue scale.

Source: Table 2.3.1, Table 2.4.4, and Table 2.4.8, p49, 58, 66 of the submission.

### Comparative effectiveness

6.8 Table 4 presents the key efficacy results of mean change in CFS and Table 5 presents the CFS-OSDI response across the studies. CFS-OSDI response was used to support the claim of superior effectiveness of ciclosporin compared to BSC.

**Table 4: Results of mean change in CFS from baseline to 6 months across the studies**

Trial	Endpoint	Ciclosporin, Mean (SD)				Vehicle, Mean (SD)				Mean difference (95% CI)	P- value
		OR adjusted mean (95% CI)				OR adjusted mean (95% CI)					
		N	Baseline	Follow- up	Change	N	Baseline	Follow- up	Change		
<b>Total population</b>											
SANSIKA CFS=4 (FAS)	Secondary	154	4.00 (0.00)	2.19 (1.27)	-1.76 (-1.97, -1.56)	91	4.00 (0.00)	2.52 (1.08)	-1.42 (-1.68, -1.16)	-0.31 (-0.57, -0.06)	<b>0.017</b>
SICCANOVE CFS=2-4 (FAS LOCF)	Co-primary	241	2.83 (0.709)	1.78 (1.065)	-1.05 (0.983)	248	2.80 (0.720)	1.98 (1.172)	-0.82 (0.937)	-0.22 (-0.39, -0.06)	<b>0.009</b>
<b>Subgroup</b>											
Post-hoc SICCANOVE CFS=4 (SG)	Post-hoc	39	4.00 (0.00)	2.59 (1.141)	-1.41 (1.141)	36	4.03 (0.167)	3.36 (0.961)	-0.67 (0.986)	-0.74 (-1.24, -0.24)	<b>0.004</b>
<b>Meta-analysis (Leonardi 2019) of total trial population – SANSIKA and SICCANOVE</b>											
Meta-analysis	Post-hoc	-	-	-	-	-	-	-	-	-0.25 (-0.40, -0.11)	<b>0.0008</b>

CI = confidence interval; CFS = corneal fluorescent staining; FAS = full analysis set; LOCF = last observation carried forward; OR = odds ratio; SD = standard deviation; SG = subgroup. **Bold** indicates statistically significant results.

Source: Table 2.5.2, p69 and Table 2.6.4, p88 of the submission of the submission.

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Table 5: Results of CFS-OSDI response across the studies

Trial ID	Endpoint	Ciclosporin n/N (%)	Vehicle n/N (%)	Risk difference (95% CI)	Odds ratio (95% CI)	p-value
<b>Total population</b>						
<b>Improvement ≥ 2 grades (CFS) and 30% (OSDI)</b>						
SANSIKA	Primary	44/154 (28.6)	21/91 (23.1)	0.05 (-0.06, 0.17)	1.36 (0.74, 2.54)	0.326
SICCANOVE	NR	NR	-	-	-	-
<b>Improvement ≥ 2 grades (CFS)</b>						
SANSIKA	Secondary	80/154 (51.9)	41/91 (45.1)	0.07 (-0.06, 0.20)	1.288 (0.761, 2.185)	0.346
SICCANOVE	NR	NR	-	-	-	-
<b>Improvement ≥ 30% (OSDI)</b>						
SANSIKA	Secondary	61/154 (39.6)	36/91 (39.6)	0.00 (-0.13, 0.13)	1.021 (0.598, 1.755)	0.939
SICCANOVE	NR	NR	-	-	-	-
<b>Improvement ≥ 3 grades (CFS) and 30% (OSDI)</b>						
SANSIKA	Post-hoc	29/154 (18.8)	7/91 (7.7)	0.11 (0.03, 0.19)	2.95 (1.28, 7.68)	<b>0.016</b>
SICCANOVE	NR	NR	-	-	-	-
<b>PBS eligible subgroup – SICCANOVE (CFS=4; OSDI ≥ 23)</b>						
<b>Improvement ≥ 2 grades (CFS) and 30% (OSDI)</b>						
SICCANOVE CFS=4; OSDI ≥ 23 (SG)	Post-hoc	12/39 (30.8)	2/36 (5.6)	0.25 (0.09, 0.42)	7.56 (1.56, 36.68) <sup>a</sup>	<b>0.004</b>
<b>Improvement ≥ 2 grades (CFS)</b>						
SICCANOVE CFS=4; OSDI ≥ 23 (SG)	Post-hoc	16/39 (41.0)	6/36 (16.7)	0.24 (0.05, 0.44)	3.48 (1.18, 10.29) <sup>a</sup>	<b>0.013</b>
<b>Improvement ≥ 30% (OSDI)</b>						
SICCANOVE CFS=4; OSDI ≥ 23 (SG)	Post-hoc	16/39 (41.0)	9/36 (25.0)	0.16 (-0.05, 0.37)	2.09 (0.78, 5.61) <sup>a</sup>	0.106
<b>Improvement ≥ 3 grades (CFS) and 30% (OSDI)</b>						
SICCANOVE CFS=4 OSDI ≥ 23 (SG) <sup>a</sup>	NR	NR	-	-	-	-
<b>Meta-analysis (Leonardi 2019) of PBS eligible population – SANSIKA total population and SICCANOVE subgroup with severe keratitis CFS=4; OSDI ≥ 23)</b>						
Improvement ≥ 3 grades (CFS) and 30% (OSDI)	Post-hoc	34/193 (17.6)	7/126 (5.6)	0.12 (0.05, 0.19)	3.664 (1.639, 9.355)	<b>0.003</b>
Improvement ≥ 2 grades (CFS) and 30% (OSDI)	Primary	57/193 (29.5)	23/126 (18.3)	0.11 (0.02, 0.21)	1.803 (1.043, 3.192)	<b>0.038</b>
CFS response (improvement ≥ 2 grades)	Secondary	97/193 (50.3)	47/126 (37.3)	0.13 (0.02, 0.24)	1.557 (0.975, 2.501)	0.065
OSDI response (30% improvement)	Secondary	78/193 (40.4)	45/126 (35.7)	0.05 (-0.06, 0.16)	1.207 (0.753, 1.945)	0.436
Complete responders (CFS)	Secondary	11/193 (5.7)	4/126 (3.2)	0.03 (-0.02, 0.07)	1.823 (0.598, 6.775)	0.320

CI = confidence interval; CFS = corneal fluorescent staining; NR = not reported; OSDI = ocular disease surface index; SG = subgroup; **Bold** indicates statistically significant results.

<sup>a</sup> individual study data not reported in the SICCANOVE CSR or Leonardi 2019.

Source: Table 2.5.4, p73 of the submission and Table 2.6.2, p86 of the submission.

6.9 Ciclosporin was associated with a statistically significantly greater improvement in CFS at six months relative to baseline compared with vehicle in all trials and subgroups.

- 6.10 There was no significant difference in the co-primary responder rates (CFS improvement  $\geq 2$  and OSDI improvement  $\geq 30\%$ ) between the ciclosporin group (28.6%) and the vehicle group (23.1%) ( $p=0.326$ ) in the SANSIKA trial. The submission claimed this was due to the lack of correlation between signs and symptoms in DED (Baudouin 2014), and the beneficial effects of the vehicle itself. The ESC considered that the claim that the vehicle may bias the results against ciclosporin was reasonable.
- 6.11 In the post-hoc analysis for the SANSIKA trial, there was a significantly higher percentage of the co-primary endpoint of responders using the more stringent response definition (CFS improvement  $\geq 3$  and OSDI improvement  $\geq 30\%$ ) in the ciclosporin group (18.8%) versus the vehicle group (7.7%) ( $p=0.016$ ).
- 6.12 For the PBS eligible severe subgroup (CFS=4; OSDI  $\geq 23$ ) in the SICCANOVE post-hoc analysis, there was a significantly higher percentage of responders based on CFS improvement  $\geq 2$  grades and OSDI improvement 30% in the ciclosporin group (30.8%) versus the vehicle group (5.6%) ( $p=0.004$ ). However, this is the less stringent criteria for CFS-OSDI response rate and was not representative of the PBS restriction. The submission did not report the results for the more stringent response definition (CFS improvement  $\geq 3$  and OSDI improvement  $\geq 30\%$ ).
- 6.13 In the meta-analysis there was a significantly higher percentage of responders with ciclosporin versus the vehicle using the more stringent responder rate (CFS improvement  $\geq 3$  and OSDI improvement 30%) (17.6% and 5.6%,  $p=0.003$ ). The difference in CFS-OSDI responders was similar (17.6%) to the SANSIKA trial (18.8%).
- 6.14 When the CFS and OSDI components of the composite primary outcome were considered separately the available evidence did not support an improvement in the symptoms of DED, as measured by the OSDI, which could be attributed to the active ingredient, ciclosporin. The ESC noted that the evidence presented suggested that the symptomatic benefit of the product may be due to the cationic lipid based emulsion vehicle. This was acknowledged in the PSCR, which stated that symptom improvement has been shown to be superior with the use of a cationic lipid based emulsion compared with standard preservative free artificial tears. The pre-PBAC response acknowledged that the symptomatic benefit of ciclosporin is at least partly attributed to the cationic emulsion, but that it does not treat the underlying pathogenesis of the disease. The ESC considered that it was unclear whether the CFS-OSDI response results were clinically relevant for ciclosporin. The pre-PBAC response stated that patients achieving a CFS-OSDI response were almost free of the signs of dry eye disease, concurrent with significant symptomatic improvement and would have improved from severe to mild disease and reversed disease progression.
- 6.15 The ESC, noting the evidence presented in the PSCR with regards to the symptomatic benefit of the cationic lipid based emulsion, considered that there may be a clinical benefit to patients suffering from DED in having access to a product containing the

vehicle only (i.e. without the immunosuppressant agent), as no comparable product is currently available in Australia.

### Comparative harms

6.16 The summary of the adverse events from the pooled PBS eligible population of patients with severe keratitis with DED from the SANSIKA and SICCANOVE trials and the Leonardi 2019 meta-analysis is presented in Table 6.

**Table 6: Summary of key adverse events in the PBS eligible population from the pivotal trials and meta-analysis (Leonardi, 2019).**

Trial	Ciclosporin, n (%)	Vehicle, n (%)	Odds ratio (95% CI)
<b>SANSIKA trial</b>			
Any severe ocular TEAE	9 (5.8)	5 (5.6)	1.07 (0.35, 3.29)
Any TEAE	88 (57.1)	42 (46.7)	1.56 (0.92, 2.62)
Withdrawn due to an ocular TEAE	18 (11.7)	6 (6.7)	1.88 (0.72, 4.91)
Death	0	0	Not estimable
Instillation site pain	47 (30.5)	8 (8.9)	4.56 (2.04, 10.17)
Instillation site irritation	1 (0.6)	0	1.79 (0.07, 44.36)
<b>SICCANOVE trial</b>			
Any severe ocular TEAE	84 (34.7)	40 (16.0)	2.79 (1.82, 4.29)
Any TEAE	NR	NR	NR
Withdrawn due to an ocular TEAE	24 (9.9)	18 (7.2)	1.42 (0.75, 2.69)
Death	0	0	Not estimable
Instillation site pain	3 (1.2)	1 (0.4)	3.13 (0.32, 30.26)
Instillation site irritation	19 (7.9)	4 (1.6)	5.24 (1.76, 15.64)
<b>Meta-analysis (Leonardi 2019)</b>			
<b>Ocular TEAE</b>			
SANSIKA (N=250)	66 (42.9)	27 (30.0)	1.78 (1.02, 3.09)
SICCANOVE (N=242)	103 (42.6)	67 (26.8)	2.02 (1.39, 2.96)
Heterogeneity: $\text{Chi}^2 = 0.14$ , $\text{df}=1$ ( $p=0.70$ ); $I^2 = 0\%$			1.94 (1.42, 2.65)
Test for overall effect: $Z=4.17$ ( $p<0.0001$ )			
<b>Treatment related ocular TEAE</b>			
SANSIKA (N=250)	57 (37.0)	18 (20.0)	2.38 (1.29, 4.39)
SICCANOVE (N=242)	176 (78.9)	66 (58.9)	7.43 (4.99, 11.08)
Heterogeneity: $\text{Chi}^2 = 9.36$ , $\text{df}=1$ ( $p=0.002$ ); $I^2 = 89\%$			4.31 (1.41, 13.15)
Test for overall effect: $Z=2.57$ ( $p=0.01$ )			
<b>Instillation site pain</b>			
SANSIKA (N=250)	47 (30.5)	8 (8.9)	4.56 (2.04, 10.17)
SICCANOVE (N=242)	3 (1.2)	1 (0.4)	3.13 (0.32, 30.26)
Heterogeneity: $\text{Chi}^2 = 0.09$ , $\text{df}=1$ ( $p=0.76$ ); $I^2 = 0\%$			4.37 (2.05, 9.31)
Test for overall effect: $Z=3.82$ ( $p=0.0001$ )			
<b>Instillation site irritation</b>			
SANSIKA (N=250)	1 (0.6)	0	1.79 (0.07, 44.36)
SICCANOVE (N=242)	19 (7.9)	4 (1.6)	5.24 (1.76, 15.64)
Heterogeneity: $\text{Chi}^2 = 0.39$ , $\text{df}=1$ ( $p=0.53$ ); $I^2 = 0\%$			4.69 (1.66, 13.19)
Test for overall effect: $Z=2.93$ ( $p=0.003$ )			

CI = confidence interval; TEAE = treatment emergent adverse event. **Bold** indicates statistically significant results.

Source: Table 2.5.10, p81 of submission, 2.6.5, p89 of the submission.

- 6.17 Installation-site eye pain and eye irritation were higher with ciclosporin in the SANSIKA and SICCANOVE trials.
- 6.18 There were no deaths and no statistically significant difference in the proportions of patients discontinuing treatment due to ocular TEAEs in the SANSIKA and SICCANOVE trials.
- 6.19 In the meta-analysis there was a statistically significant higher proportion of patients with ocular TEAEs ( $p < 0.0001$ ), treatment related ocular TEAEs ( $p = 0.01$ ), instillation site pain ( $p = 0.0001$ ) and instillation site irritation ( $p = 0.003$ ) with ciclosporin than with the vehicle. However, there was statistically significant heterogeneity in the analyses of treatment related ocular TEAE ( $I^2 = 89\%$ ), eye disorders ( $I^2 = 61\%$ ), and eye irritation ( $I^2 = 63\%$ ). The proportions of patients experiencing these events in the SICCANOVE trial was markedly higher than in the SANSIKA trial. The submission claimed this was most likely due to the restricted artificial tears use in the SICCANOVE trial. This was uncertain.
- 6.20 Eye irritation and instillation site pain were more frequent with ciclosporin, however these events appeared to be mostly mild to moderate and transient.
- 6.21 The risk of peri-ocular skin cancer was noted in literature, as well as conjunctival neoplasia in a post-marketing source in France.

### ***Benefits/harms***

- 6.22 A summary of the comparative benefits and harms for ciclosporin compared to BSC is presented in Table 7.

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Table 7: Summary of comparative benefits of ciclosporin and BSC

Benefits							
Mean change in CFS from baseline to 6 months							
Trial	Ciclosporin			Vehicle			Mean difference*: Ciclosporin vs. Vehicle (95% CI)
	N	Mean Δ from baseline	SD	N	Mean Δ from baseline	SD	
<b>Patient population: severe keratitis with DED (CFS=4 and OSDI ≥ 23)</b>							
SANSIKA	154	-1.76	(-1.97, -1.56)	248	-1.42	(-1.68, -1.16)	<b>-0.31 (-0.57, -0.06)</b>
SICCANOVE <sup>a</sup>	39	-1.41	1.141	36	-0.67	0.986	<b>-0.74 (-1.24, -0.24)</b>
FAS							
SANSIKA	same as above						
SICCANOVE	241	-1.05	0.983	248	-0.82	0.937	<b>-0.22 (-0.39, -0.06)</b>
Meta-analysis	NR	NR	NR	NR	NR	NR	<b>-0.25 (-0.40, -0.11)</b>
CFS-OSDI response at 6 months							
Trial	Ciclosporin n/N	Vehicle n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)	
SANSIKA- Improvement ≥ 2 grades (CFS) and 30% (OSDI) (FAS)	44/154	21/91	1.24 (0.79, 1.94)	28.6	23.1	0.05 (-0.06, 0.17)	
SANSIKA- Improvement ≥ 3 grades (CFS) and 30% (OSDI) (FAS)	29/154	7/91	<b>2.45 (1.12, 5.36)</b>	18.8	7.7	<b>0.11 (0.03, 0.19)</b>	
Meta-analysis (Leonardi 2019) of PBS eligible population – SANSIKA total population and SICCANOVE subgroup CFS=4; OSDI ≥ 23; Improvement ≥ 2 grades (CFS) and 30% (OSDI)	57/193	23/126	<b>1.62 (1.05, 2.48)</b>	29.5	18.3	<b>0.11 (0.02, 0.21)</b>	
Harms							
Instillation-site pain							
SANSIKA	47/154	8/91	<b>3.47 (1.72, 7.01)</b>	30.5	8.8	<b>0.21 (0.12, 0.30)</b>	
SICCANOVE	3/241	1/248	3.09 (0.32, 29.47)	1.2	0.4	0.008 (-0.008, 0.02)	
Instillation site irritation							
SANSIKA	1/154	0/91	1.78 (0.07, 43.26)	0.65	0	0.006 (-0.007, 0.02)	
SICCANOVE	19/241	4/248	<b>4.89 (1.68, 14.16)</b>	7.88	1.61	<b>0.06 (0.02, 0.1)</b>	

CFS= corneal fluorescent staining; CI = confidence interval; DED = dry eye disease; FAS= full-analysis set; NR = not reported ;OSDI= ocular disease surface index; RD = risk difference; RR = risk ratio.

**Bold** indicates statistical significance

<sup>a</sup> Not full analytic set. Post-hoc analysis.

Source: Compiled and calculated during the evaluation based on Table 2.5.1, p68 of submission, Table 2.5.4, p73 of the submission, Table 2.5.10, p81 of submission, Table 2.6.2, p86 of the submission and Table 16, p96 of the SANSIKA CSR.

6.23 On the basis of the meta-analysis evidence presented by the submission in the full analysis set, the comparison of ciclosporin and vehicle resulted in:

- Approximately a 0.25 improvement in corneal fluorescein staining (CFS) score, which measures ocular signs of keratitis, over a maximum duration of follow-up of 6 months.
- 6.24 On the basis of the direct trial evidence (SANSIKA) presented by the submission, for every 100 patients treated with ciclosporin in comparison to vehicle over a maximum duration of follow-up of 6 months:
- No additional patients would show clinical improvement in terms of (i) corneal fluorescein staining (CFS) score, which measures ocular signs of keratitis, of greater than or equal to 2 grades and (ii) ocular surface disease index (OSDI), which measures the ocular symptoms of keratitis, by 30%.
  - Approximately 11 additional patients would show clinical improvement in terms of (i) CFS scores, which measures ocular signs of keratitis, of greater than or equal to 3 grades and (ii) OSDI, which measures the ocular symptoms of keratitis, by 30%.
  - Approximately 21 additional patients would experience instillation-site pain.
  - No additional patients would experience instillation-site irritation.
- 6.25 On the basis of the direct trial evidence (SICCANOVE) presented by the submission, for every 100 patients treated with ciclosporin in comparison to vehicle over a maximum duration of follow-up of 6 months:
- No additional patients would experience instillation-site pain.
  - Approximately 6 additional patients would experience instillation-site irritation.
- 6.26 On the basis of the meta-analysis evidence in the proposed PBS eligible population (Leonardi 2019) presented by the submission, for every 100 patients treated with ciclosporin in comparison to vehicle over a maximum duration of follow-up of 6 months:
- Approximately 11 additional patients would show clinical improvement in terms of (i) corneal fluorescein staining (CFS) score, which measures ocular signs of keratitis of greater than or equal to 2 grades and (ii) ocular surface disease index (OSDI), which measures ocular signs of keratitis, by 30%, as measured by the composite outcome.

***Clinical claim***

- 6.27 The submission described ciclosporin as superior in terms of effectiveness compared with BSC.
- 6.28 The therapeutic conclusion of the effectiveness based on ocular signs (as measured by CFS score) presented in the submission is supported by the clinical trial evidence; however, a benefit in OSDI was not supported when considered on its own (versus as part of the composite outcome).

- 6.29 The ESC noted that the evidence presented in the submission supported the claim of superior effectiveness in terms of the composite outcome of CFS-OSDI response; however, given the uncertainty around the impact on OSDI when considered separately from CFS, and the evidence that suggested that the symptomatic benefit of the product may be due to the cationic lipid based emulsion vehicle, it remained unclear whether these results are clinically relevant.
- 6.30 Notwithstanding the uncertainty around the appropriateness of the composite outcome, the ESC considered that the magnitude of benefit in terms of CFS-OSDI response was also uncertain because:
- There was no significant difference in the co-primary responder rates (CFS improvement  $\geq 2$  and OSDI improvement  $\geq 30\%$ ) between the ciclosporin group (28.6%) and the vehicle group (23.1%) ( $p=0.326$ ) in the SANSIKA trial.
  - Although the meta-analysis (Leonardi, 2019) of the key clinical trials (SANSIKA and SICCANOVE) found a significant difference in its primary outcome of CFS-OSDI response (CFS improvement  $\geq 3$  and OSDI improvement  $\geq 30\%$ ) in the PBS-eligible population (CFS=4; OSDI  $\geq 23$ ), this was based on a post-hoc analysis of the SANSIKA trial and a post-hoc subgroup analysis (15%) of the SICCANOVE trial.
  - The robustness of pooling and the exchangeability of the two trials within the meta-analysis was uncertain, given the differences in primary outcomes, cationic surfactant, treatment exposure, and use of concomitant treatment with artificial tears across the trials.
  - The sample sizes of the subgroups in the SICCANOVE (N=75), SANSIKA (N=245), SANSIKA Part 2 (N=177) trials, and meta-analysis (N=319) were small.
  - The treatment duration (6 months) and follow-up durations in the SICCANOVE and SANSIKA trials (6 months and 12 months respectively) were short, given that severe keratitis with DED is a chronic condition and treatment is ongoing. Consequently, the PBAC considered that the long-term effectiveness was uncertain. The submission provided an extension study, SANSIKA Part 2 (N= 177) (ciclosporin open label). SANSIKA Part 2 was an open label study that also had a small sample size, which increased the uncertainty of the results.
  - The ESC also noted that differences in factors such as the surfactants used, the mean number of days of exposure to treatment and the mean number of drops of artificial tears used between the trials could also affect the exchangeability of the trials.
- 6.31 The submission described ciclosporin as non-inferior in terms of safety compared to BSC. The ESC considered that this claim was adequately supported by the clinical evidence, although there is some uncertainty as:
- Installation-site eye pain and eye irritation were higher with ciclosporin.

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- The sample sizes of the subgroups in the SICCANOVE (N=75), SANSIKA (N=245), SANSIKA Part 2 (N=177) trials, and meta-analysis (N=319) were small.
  - The risk of peri-ocular skin cancer was noted in literature, as well as conjunctival neoplasia reported in a post-marketing source in France.
- 6.32 The TGA Clinical Evaluation Report stated that “despite the relative safety of the [ciclosporin] in treatment of adults with DED, the product can be unpleasant to use.” (Clinical Evaluation Report, Ciclosporin (2019)). However, the TGA considered while eye irritation and instillation site pain were more frequent with ciclosporin, that these “were mostly mild to moderate and always transient” (TGA Delegate’s Overview).
- 6.33 Overall, the PBAC considered that the claim that ciclosporin demonstrated superior comparative effectiveness and non-inferior comparative safety compared to BSC was reasonable.

***Economic analysis***

- 6.34 The submission presented a stepped economic evaluation based on direct randomised controlled trials (SICCANOVE and SANSIKA trials), a published meta-analysis (Leonardi 2019) and implemented a modelled evaluation.
- 6.35 The nominated comparator was ciclosporin + best supportive care (BSC) vs. BSC alone. BSC consisted of supportive care, including using artificial tear substitutes as required and periodical doctor consultations.
- 6.36 Table 8 presents the key components of the economic model.

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Table 8: Summary of model structure, key inputs and rationale

Component	Summary
Type of analysis	Cost-utility analysis
Outcomes	Quality-adjusted life years
Time horizon	5 years in the model base case vs. 6 months in key trials, plus 6 months, open-label extension follow-up study (Part 2 of SANSIKA trial).
Methods used to generate results	Cohort Markov model, which captured patients costs and outcomes over a 5-year time horizon
Health states	4 health states (Treatment initiation, In response, Not in response, Dead). The model presented was an adaptation of a model previously assessed by NICE (TA369, 2015) for the same indication ( submission). A similar model was also assessed by SMC (1089/15, 2015). The model NICE & SMC evaluated had 7 health states. The main differences were 3 additional health states related to punctal plugs. The submission noted that use of punctal occlusion is limited in Australia and its effectiveness has yet to be established, therefore these 3 health states were excluded. The impact of this exclusion on the ICER is unknown.
Cycle length	3 months
Transition probabilities	<p><u>Response rate at 6 months:</u> Severe keratitis subgroup from meta-analysis (meta-analysis CSR). The response rate applied in the model was based on data from the revised meta-analysis with a response definition of CFS improvement <math>\geq 3</math> &amp; OSDI improvement <math>\geq 30\%</math>. The definition of response differed from the primary outcome (CFS improvement <math>\geq 2</math> &amp; OSDI improvement <math>\geq 30\%</math>) of the SANSIKA trial and meta-analysis (Leonardi, 2019). The pre-PBAC response stated that the response definition used in the base case matched the continuation criteria in the proposed PBS listing.</p> <p><u>Treatment discontinuation:</u> SANSIKA trial. A pooled common rate of discontinuation was applied to both treatment and control arms post 90 days. Assumed discontinuations due to severe TRAEs were implicitly captured by the treatment discontinuation rate. Data to demonstrate and calculate these rates (daily discontinuation rate) could not be verified.</p> <p><u>Mortality:</u> Australian life table. Independent of treatment response</p>
Utilities	Utilities: Sourced from responders (defined as per PBS continuation rule) subgroup from SANSIKA. Same utilities for treatment initiation, responder and non-responder applied to both ciclosporin and BSC arms. The treatment effect (utility change) of 0.104 was based on the average pooled responder's change at 6 months. No adjustment for baseline utility was made. <sup>a</sup> It is likely that utility change was overestimated due to lower baseline value of the responder arm and the large change among responders in the vehicle arm. The applied utility increase for treatment response (0.1040) was much larger than the difference in utility values by treatment arms reported in SANSIKA trial (0.02 in the ciclosporin arm and 0.03 in the SOC arm).

<sup>a</sup> Due to unavailable patient-level data, adjustments could not be made during the evaluation.

BSC = best supportive care; CFS = corneal fluorescent staining; DED = dry eye disease; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; OSDI = ocular disease surface index; PBS = Pharmaceutical Benefits Scheme; SMC = Scottish Medicines Consortium; SOC = standard of care; TEAE = treatment emergent adverse event; TRAE = treatment related adverse event

Source: Table 3.1.1, p101of the submission and compiled during the evaluation.

6.37 Table 9 summarises the key drivers of the model.

**Table 9: Key drivers of the model**

Description	Method/Value	Impact Base case: \$ ██████ <sup>1</sup> /QALY gained
Utilities	Sourced from SANSIKA trial (based on post-hoc analysis of severe subgroup who responded as per proposed continuation rule). The applied utility increase for treatment response (0.1040) is much larger than the difference in utility values by treatment arms reported in SANSIKA trial (0.02 in in the ciclosporin arm and 0.03 in the BSC arm).	High, favours ciclosporin.  Applying a much smaller utility gain as reported in the SANSIKA trial increased the ICER to \$ ██████ <sup>2</sup> per QALY gained
Responder criteria	Based on revised meta-analysis with a response definition of CFS improvement ≥ 3 & OSDI improvement ≥ 30% and subgroup post-hoc analysis (response rates = 17.6% for the ciclosporin arm and 5.6% for the BSC arm). The response definition of the primary outcome of SANSIKA trial was CFS improvement ≥ 2 & OSDI improvement ≥ 30% (response rates = 28.60% for the ciclosporin arm and 23.10% for the BSC arm).	High, favours ciclosporin.  Applying rate from primary outcome of SANSIKA trial increased the ICER to \$ ██████ <sup>3</sup> per QALY gained

BSC = best supportive care; CFS = corneal fluorescent staining; ICER = incremental cost effectiveness ratio; OSDI = ocular surface disease index; QALY = quality adjusted life year

Source: Compiled during the evaluation

The redacted values correspond to the following ranges:

<sup>1</sup> \$15,000 to < \$25,000/QALY gained

<sup>2</sup> \$155,000 to < \$255,000/QALY gained

<sup>3</sup> \$75,000 to < \$95,000/QALY gained

6.38 Table 10 presents the results of the stepped economic evaluation.

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**Table 10: Results of the stepped economic evaluation**

Step and component	Ciclosporin + BSC	BSC	Increment
Step 1a: Trial-based analysis using the 6-month results of the severe keratitis subgroup (CFS=4 OSDI ≥ 23 at baseline) from the meta-analysis (Leonardi 2019).			
Outcome = CFS improvement ≥ 2 & OSDI improvement ≥ 30% (primary endpoint of SANSIKA)			
Costs	\$ [redacted]	\$624	\$ [redacted]
% responder	29.5	18.3	11.2
Incremental cost/extra responder at 6 months			\$ [redacted] <sup>1</sup>
Step 1b: Trial-based analysis using the 6-month results of post-hoc analysis of the severe keratitis subgroup (CFS=4 OSDI ≥ 23 at baseline) from the meta-analysis (meta-analysis CSR).			
Outcome = CFS improvement ≥ 3 & OSDI improvement ≥ 30% (proposed response rule)			
Costs	\$ [redacted]	\$624	\$ [redacted]
% responder	17.6	5.6	12.0
Incremental cost/extra responder at 6 months			\$ [redacted] <sup>1</sup>
Step 2a: Model-based analysis; based on outcome as per Step 1b with application of utilities to yield quality-adjusted life years as an outcome; discounted costs and outcomes at 5% p.a.; extrapolated to 1-year			
Costs	\$ [redacted]	\$1,181	\$ [redacted]
QALY	0.6523	0.6429	0.0094
Incremental cost/extra QALY gained			\$ [redacted] <sup>2</sup>
Step 2b: Model-based analysis; Step 2a; extrapolated to 2-year			
Costs	\$ [redacted]	\$2,298	\$ [redacted]
QALY	1.2711	1.2526	0.0185
Incremental cost/extra QALY gained			\$ [redacted] <sup>3</sup>
Step 2c: Model-based analysis; Step 2a; extrapolated to 3-year			
Costs	\$ [redacted]	\$3,363	\$ [redacted]
QALY	1.8546	1.8294	0.0253
Incremental cost/extra QALY gained			\$ [redacted] <sup>3</sup>
Step 2d: Model-based analysis; Step 2a; extrapolated to 4-year			
Costs	\$ [redacted]	\$4,375	\$ [redacted]
QALY	2.4054	2.3750	0.0304
Incremental cost/extra QALY gained			\$ [redacted] <sup>3</sup>
Step 2e: Model-based analysis; Step 2a; extrapolated to 5-year (base case)			
Costs	\$ [redacted]	\$5,336	\$ [redacted]
QALYs	2.9252	2.8911	0.0341
Incremental cost/extra QALY gained (base case)			\$ [redacted] <sup>4</sup>
<b>Pre-PBAC response – DPMQ reduced from \$108.79 to \$81.90; utility gain for responders reduced from 0.104 to 0.078</b>			
Costs	\$ [redacted]	\$5,336	\$ [redacted]
QALYs	2.9126	2.8871	0.0255
Incremental cost/extra QALY gained (base case)			\$ [redacted] <sup>4</sup>

BSC = best supportive care; CFS = corneal fluorescent staining; OSDI – ocular surface disease index; QALY = quality adjusted life year  
 Source: Table 3.8.1, p121; Table 3.8.4, p122 of the submission and compiled during the evaluation using estimates from Section 3 excel model (Ikervis PBAC Nov2020 – Section 3.xlsx).

The redacted values correspond to the following ranges:

<sup>1</sup> \$5,000 to < \$15,000/QALY gained

<sup>2</sup> \$55,000 to < \$75,000/QALY gained

<sup>3</sup> \$25,000 to < \$35,000/QALY gained

<sup>4</sup> \$15,000 to < \$25,000/QALY gained

6.39 The ESC considered that the results of the economic evaluation should be considered with caution because:

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- The response rate was informed from the revised meta-analysis with a response definition of CFS improvement  $\geq 3$  & OSDI improvement  $\geq 30\%$ , which differed from the primary outcome of the SANSIKA trial and meta-analysis (Leonardi, 2019). It was also based on a subgroup of severe DED identified for post-hoc analyses. The pre-PBAC response stated that the response definition applied in the model matched that in the proposed PBS listing.
- The applied utility gain for treatment response (0.1040) was larger than the difference in utility values by treatment arms reported in SANSIKA trial. Overall, utilities for patients in both the arms of the SANSIKA trial improved after 6 months by 0.02 (95% CI, -0.03; 0.06) in the ciclosporin arm and 0.02 (95% CI, -0.03; 0.07) in the BSC arm. The change from baseline at 6 months was not statistically significant in either arms and was not statistically significant different between the two arms ( $p=0.808$ ) (412 of the SANSIKA CSR). No adjustment for baseline utility was made to the value applied in the model and it is likely that the utility gain was overestimated due to the lower baseline value in the responder arm (0.624 compared to 0.673 in the non-responder arm) and the large change among responders in the vehicle arm. The PSCR acknowledged that the utility inputs were the key driver of the economic model, but considered that the application of the treatment arm utilities reported in the SANSIKA trial were not appropriate as they did not take into account the six month stopping rule for non-responders; rather, the relevant utility difference was between responders and non-responders. However, the ESC noted that this assertion did not take into account the issue of baseline correction nor adequately take into the account the likely range of disutility as informed by the literature. The ESC considered that, for the reasons outlined above, a utility gain of 0.104 likely represented a best-case or upper limit value, rather than an average, noting that the model submitted to NICE applied a utility gain of 0.08 to responders (see paragraph 6.43).

6.40 Table 11 presents the disaggregated health outcomes (QALYs) by health states, demonstrating the impact of utility inputs.

**Table 11: Summary of health outcomes included in the economic evaluation (discounted)**

Health state	Ciclosporin + BSC	BSC	Incremental outcome	% of total incremental outcome
Treatment initiation	0.329	0.325	0.004	12%
In response	0.327	0.104	0.223	656%
Not in response	2.270	2.462	-0.192	-565%
Total	2.925	2.891	0.034	100%

BSC = best supportive care

Source: Calculated and compiled during the evaluation using estimates from Section 3 excel model (Ikervis PBAC Nov2020 – Section 3.xlsx).

6.41 The 'In response' health state contributed the greatest proportion of incremental outcome observed.

6.42 The results of key univariate sensitivity analyses are summarised in Table 12.

Table 12: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
<b>Base case</b>	\$█	0.0341	\$█ <sup>1</sup>
<b>Utility inputs</b>			
SANSIKA, less stringent response criteria (0.738 and 0.660 for responder and non-responder)	\$█	0.0255	\$█ <sup>2</sup>
Messmer 2019 (0.759 and 0.638 for responder and non-responder)	\$█	0.0397	\$█ <sup>1</sup>
Schiffman 2003 (0.78 and 0.72 for responder and non-responder)	\$█	0.0197	\$█ <sup>3</sup>
Applying utility from SANSIKA part 1a Ciclosporin - response utility (0.68), no response (0.66) BSC - response utility (0.69), no response (0.66)	\$█	0.0051	\$█ <sup>4</sup>
Applying utility from SANSIKA part 2b Ciclosporin - no response (0.66), utility gain 0.05 BSC - no response (0.66), utility gain 0.01	\$█	0.0224	\$█ <sup>3</sup>
<b>Response rates at 6 months</b>			
Meta-analysis severe subgroup, CFS improvement ≥ 2 & OSDI improvement ≥ 30% (29.50% vs 18.30%)	\$█	0.0323	\$█ <sup>3</sup>
Meta-analysis severe Sjögren subgroup, CFS improvement ≥ 3 & OSDI improvement ≥ 30% (14.30% vs 3.80%)	\$█	0.0298	\$█ <sup>1</sup>
Meta-analysis severe Sjögren subgroup, CFS improvement ≥ 2 & OSDI improvement ≥ 30% (23.40% vs 9.40%)	\$█	0.0399	\$█ <sup>1</sup>
Meta-analysis all patients, CFS improvement ≥ 2 & OSDI improvement ≥ 30% (21.60% vs 13.10%)	\$█	0.0245	\$█ <sup>3</sup>
SANSIKA all patients, CFS improvement ≥ 3 & OSDI improvement ≥ 30% (18.80% vs 7.80%)	\$█	0.0314	\$█ <sup>2</sup>
SANSIKA all patients, CFS improvement ≥ 2 & OSDI improvement ≥ 30% (28.60% vs 23.10%)	\$█	0.0163	\$█ <sup>6</sup>
SICCANOVE mod to severe subgroup, CFS improvement ≥ 2 & OSDI improvement ≥ 30% (19.50% vs 10.20%)	\$█	0.0267	\$█ <sup>2</sup>
SICCANOVE severe subgroup, CFS improvement ≥ 2 & OSDI improvement ≥ 30% (30.80% vs 5.60%)	\$█	0.0715	\$█ <sup>5</sup>

BSC = best supportive care; CFS = corneal fluorescent staining; ICER = incremental cost effectiveness ratio; OSDI = ocular surface disease index; QALY = quality adjusted life year.

Source: Table 3.9.1, p122; Table 3.9.2, p123; Table 3.9.3, p124 of the submission and compiled during the evaluation

The redacted values correspond to the following ranges:

<sup>1</sup> \$15,000 to < \$25,000/QALY gained

<sup>2</sup> \$25,000 to < \$35,000/QALY gained

<sup>3</sup> \$35,000 to < \$45,000/QALY gained

<sup>4</sup> \$155,000 to < \$255,000/QALY gained

<sup>5</sup> \$5,000 to < \$15,000/QALY gained

<sup>6</sup> \$75,000 to < \$95,000/QALY gained

6.43 The pre-PBAC response noted that the utility gain applied to responders in the model submitted to NICE of 0.08 was similar to the utility gain of 0.078 applied in the ‘SANSIKA, less stringent response criteria’ sensitivity analysis presented above. This analysis resulted in an ICER of \$25,000 to < \$35,000 per QALY. Acknowledging the price reduction required to achieve the base case ICER of \$15,000 to < \$25,000 per QALY when a utility gain of 0.078 was applied and noting the presence of other potential uncertainties in the model, the Sponsor offered a 28% price reduction to the AEMP of

ciclosporin. This resulted in an AEMP of \$ [REDACTED] (DPMQ = \$ [REDACTED]) and an ICER of \$15,000 to < \$25,000 per QALY.

**Drug cost/patient/year**

6.44 The drug cost per patient is presented in Table 13. The expected cost per year of therapy with ciclosporin was estimated to be \$ [REDACTED] (calculated using the DPMQ).

**Table 13: Drug cost per patient for ciclosporin**

	<b>Trial dose and duration</b>	<b>Model</b>	<b>Financial estimates</b>
Mean dose	1 drop once daily at night (1 single-use container)	1 single-use container	1 single-use container
Mean duration	202.8 days (POST-SANSIKA study)	365 days per year. 17.6% continue after 6 months + discontinuation rate of 5.736% after day 90	365 days per year. 17.6% continue after 6 months + discontinuation rate of 11.19% end of Year 1 and 21.13% after Year 2
Cost/patient/month	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost/patient/year	Responders: \$ [REDACTED] <sup>a b</sup>	<u>Year 1</u> Responders: \$ [REDACTED] Non-responders: \$ [REDACTED] <u>Subsequent years</u> Responders: \$ [REDACTED]	<u>Year 1</u> Responders: \$ [REDACTED] Non-responders: \$ [REDACTED] <u>Subsequent years</u> Responders: \$ [REDACTED]

<sup>a</sup> Assuming 30.4 days in a month

<sup>b</sup> Assuming responders stay on treatment for 202.8 days (approximately 6.67 months)

Source: Compiled during the evaluation

**Estimated PBS usage & financial implications**

6.45 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the financial impact of listing ciclosporin on the PBS and RPBS for the treatment of severe keratitis with DED.

6.46 The submission assumed a prevalence of patients with CFS +4 of 0.75% (age 40+) and 0.06% (age 18-39) based on a linear extrapolation by age from the Melbourne Vision Impairment Project (McCarty, 1998) and made assumptions regarding the translation of CFS staining coverage to the modified Oxford scale. It was difficult to verify these estimates due to the ambiguity in DED and/or severe DED reported in the available literature.

6.47 Table 14 presents the key inputs for financial estimates.

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**Table 14: Key inputs for financial estimates**

Parameter	Value applied and source	Comment
Estimated prevalence of patients with CFS =4 & OSDI ≥ 23 and refractory on conventional care (artificial tears)	Prevalence of 0.06% (18-39 years) and 0.75% (40+ years) based on McCarty (1998).	Highly uncertain because of the age of the data and possible increasing prevalence of dry eye disease (Dana, 2019). Likely underestimated compared to estimates calculated from Farrand (2017): 0.27% (18-49 years) and 0.90% (50+ years).
Proportion of patients actively seeking medical care	60% based on Schaumberg (2003, 2009)	Likely underestimated because estimate was based on a study in the USA where clinical practice may vary. The study was also conducted before treatment was available.
Annual uptake rate	10% (assumption)	Likely underestimated based on growth from historical trends of artificial tears use on the PBS.
% responding to treatment at 6 months	17.6% based on severe subgroup from meta-analysis (Leonardi, 2019) with responder definition CFS improvement ≥ 3 & OSDI improvement ≥ 30%	Proportion applied as observed in key trials. However, the proportion likely to continue treatment may be underestimated because of leakage from use of CFS grading using modified Oxford scale by unfamiliar practitioners.
% discontinue treatment (due to any cause)	11.19% at end of first year; 21.13% in subsequent years	Uncertain as data used to demonstrate and calculate discontinuation rates could not be verified based on information provided in the submission. <sup>a</sup>
Artificial tear usage offset	19.53 prescriptions per patient per year	Likely overestimated as it is unclear if usage in a trial setting is applicable in a real-world setting. It was also assumed that artificial tears were applied to both eyes regardless if one or both eyes were treated with ciclosporin.

<sup>a</sup> Verification of sources was requested during the evaluation. However, the explanation of the data source was not sufficient for adequate verification.

CFS = corneal fluorescent staining; OSDI = ocular surface disease index ; PBS = Pharmaceutical Benefits Scheme

Source: Table 4.1.6, p132; Table 4.1.8, p134; Table 4.1.9; Table 4.1.10, p135; Table 4.1.13, p139 of the submission and Section 4 Excel workbook Tab Seqirus.

6.48 Table 15 presents the estimated use and financial implications. Updated financial implications accounting for the reduced price proposed in the pre-PBAC response are also presented.

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Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	1	1	1	1	1	1
Number of scripts dispensed <sup>a</sup>	2	3	4	5	5	6
<b>Estimated financial implications of ciclosporin</b>						
Cost to PBS/RPBS less copayments	\$7	\$7	\$7	\$7	\$7	\$7
<b>Estimated financial implications for artificial tears</b>						
Cost to PBS/RPBS less copayments	-\$7	-\$7	-\$7	-\$7	-\$7	-\$7
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$7	\$7	\$7	\$7	\$7	\$7
<b>Pre-PBAC response (DPMQ reduced from \$ to \$)</b>						
<b>Estimated financial implications of ciclosporin</b>						
Cost to PBS/RPBS less copayments	\$7	\$7	\$7	\$7	\$7	\$7
<b>Estimated financial implications for artificial tears</b>						
Cost to PBS/RPBS less copayments	-\$7	-\$7	-\$7	-\$7	-\$7	-\$7
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$7	\$7	\$7	\$7	\$7	\$7

<sup>a</sup> Assuming 12.17 prescriptions per year as estimated by the submission.

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

Source: Table 4.4.1. p142 of the submission and Table 1, p4 of the pre-PBAC response

The redacted values correspond to the following ranges:

<sup>1</sup> 5,000 to < 10,000

<sup>2</sup> 40,000 to < 50,000

<sup>3</sup> 50,000 to < 60,000

<sup>4</sup> 60,000 to < 70,000

<sup>5</sup> 70,000 to < 80,000

<sup>6</sup> 80,000 to < 90,000

<sup>7</sup> \$0 to < \$10 million

6.49 The total cost to the PBS/RPBS of listing ciclosporin was estimated to be \$0 to < \$10 million in Year 6, and a total of \$30 million to < \$40 million over the first 6 years of listing. Applying the new DPMQ proposed in the pre-PBAC response resulted in a total cost of listing ciclosporin to the PBS/RPBS of \$0 to < \$10 million in Year 6, and a total of \$20 million to < \$30 million over the first six years of listing.

6.50 The net cost to the PBS/RPBS may be underestimated due to uncertainty in the estimates of the prevalence of eligible patients, the proportion of patients seeking medical treatment, the assumed (constant) rate of uptake of ciclosporin, assumed (overestimated) reduction in usage of artificial tears and the potential for leakage relating to subjective assessments for continuing treatment. The PSCR and pre-PBAC response stated that the Sponsor would be willing to consider a risk sharing arrangement to assist in managing any financial uncertainty.

For more detail on PBAC's view, see section 7 PBAC outcome.

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the listing of ciclosporin for the treatment of severe keratitis with dry eye disease. The PBAC was satisfied that ciclosporin provides, for some patients, a significant improvement in efficacy over best supportive care (BSC). The PBAC considered that ciclosporin was cost effective at the price offered in the pre-PBAC response. The PBAC considered that the financial implication estimates were uncertain and recommended that a risk sharing arrangement (RSA) be implemented.
- 7.2 The PBAC considered there was a clinical need for treatments for severe keratitis with dry eye disease, noting the comments provided by one health professional and one organisation which were supportive of the evidence provided in the submission.
- 7.3 The PBAC noted that there are no Australian guidelines for the management of severe keratitis with dry eye disease, but that the treatment algorithm provided, which positioned ciclosporin eye drops in combination with preservative free artificial tears as a second line treatment after preservative free artificial tears as monotherapy was appropriate.
- 7.4 The PBAC considered that the proposed definition of severe keratitis with dry eye disease, which was based on ocular signs of keratitis (i.e. a corneal fluorescein staining (CFS) grade of 4) and ocular symptoms (i.e. an ocular surface disease index (OSDI) of greater than or equal to 23), was appropriate.
- 7.5 The PBAC considered that the nominated comparator of BSC, which included preservative free artificial tears as needed, was appropriate. The PBAC considered that the comparator in the clinical trials, which was a vehicle of cationic emulsion with no ciclosporin, would likely bias the results against ciclosporin.
- 7.6 The PBAC noted that the clinical evidence presented in the submission consisted of two randomised controlled trials comparing ciclosporin with the cationic emulsion, (i) SANSIKA, which enrolled patients with severe keratitis with dry eye disease (a CFS grade of 4); and (ii) SICCANOVE which enrolled patients with moderate to severe keratitis and dry eye disease (CFS grade of 2-4). The PBAC noted that patients in the SANSIKA trial could use preservative free artificial tears when required, but the patients in the SICCANOVE trial were allowed to use preservative free artificial tears up to six times a day only.
- 7.7 The PBAC noted that for the PBS eligible population, (i.e. those with a CFS grade = 4 and an OSDI  $\geq$  23 at baseline) there was a statistically significant improvement in ocular signs, as measured by change in CFS grade from baseline to six months, between the ciclosporin and cationic emulsion arms in both trials. The PBAC noted that neither trial demonstrated a benefit in terms of ocular symptoms, as measured by the OSDI.
- 7.8 In terms of the composite outcome of CFS improvement of  $\geq$  3 grades and a 30% improvement in OSDI (which matched the continuation criteria in the proposed PBS

restriction), the PBAC noted the results from a post hoc analysis of the SANSIKA trial were statistically significant (RD = 0.11; 95% CI: 0.03, 0.19). Results for the PBS eligible subgroup from the SICCANOVE trial were not reported, but a meta-analysis of both trials also resulted in a statistically significant outcome (RD = 0.12; 95% CI: 0.05, 0.19).

- 7.9 In terms of safety, the PBAC noted that the most commonly reported adverse events in both trials were eye irritation and installation pain, but that these were mostly mild to moderate and transient.
- 7.10 The PBAC noted that the efficacy and safety data were limited to 6 months in the randomised trials, with the SANSIKA trial including an open label extension to 12 months. The PBAC considered that the impact of long term ciclosporin use was unknown.
- 7.11 Overall, the PBAC considered that the claim that ciclosporin demonstrated superior comparative effectiveness and non-inferior comparative safety compared to BSC was reasonable.
- 7.12 The PBAC noted that the economic evaluation consisted of a cost utility analysis comparing ciclosporin with BSC.
- 7.13 The PBAC noted that the pre-PBAC response included a revised base case incremental cost effectiveness ratio (ICER) of \$15,000 to < \$25,000 per quality adjusted life year (QALY) which incorporated a reduced price for ciclosporin and a reduced utility gain for responders. The PBAC considered ciclosporin was cost-effective when these model inputs were applied.
- 7.14 The PBAC noted that the estimated financial impact of listing ciclosporin was uncertain due to the assumptions applied relating to the prevalence of eligible patients, the uptake rate of ciclosporin and the potential for continued use in patients who do not meet the continuation criteria or in patients with less severe disease. The PBAC also considered that the cost offsets due to an assumed reduction in preservative free artificial tear use would not be realised as patients would continue to use these products in combination with ciclosporin.
- 7.15 The PBAC considered that a RSA was appropriate to manage the risks of continued use in patients who do not meet the continuation criteria or use in patients with less severe disease. The PBAC advised that the financial estimates for ciclosporin, as presented in the pre-PBAC response (i.e. including the proposed price reduction) could be used as a basis for expenditure caps. The PBAC further advised that a rebate of 100% would be applicable for use beyond the expenditure caps.
- 7.16 In terms of the restriction, the PBAC:
- considered that the initial and continuing treatment restrictions should be Authority Required – immediate/real time assessment (telephone/online) to ensure use is in the intended severe keratitis patient population;

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- considered that the initial treatment restriction should be limited to 3 repeats, as the treatment algorithm states that monitoring should occur at 3 months after initiation;
  - noted that the majority of GPs would not have access to a split lamp to facilitate the required ongoing assessment of the condition, and therefore considered that initial and continuing treatment prescribing of ciclosporin should be limited to ophthalmologists and optometrists. The PBAC considered that the inclusion of optometrists would improve equity of access to ciclosporin, particularly for rural and remote patients; and
  - noting the lack of long term data, considered that a note should be included in the continuing treatment restriction stating that treatment should be re-evaluated after 24 months to manage the potential concerns regarding the long term use of ciclosporin and immunosuppression.
- 7.17 The PBAC advised that ciclosporin is not suitable for prescribing by nurse practitioners.
- 7.18 The PBAC advised that the Early Supply Rule should not apply to ciclosporin.
- 7.19 The PBAC advised that under Section 101(3BA) of the *National Health Act 1953* ciclosporin should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.20 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for ciclosporin:
- a) The treatment was not expected to provide a substantial and clinically relevant improvement in efficacy over standard of care as the improvement in ocular symptoms were not statistically significant;
  - b) The treatment is not expected to address a high and urgent unmet clinical need as treatment options are available;
  - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.21 The PBAC noted that this submission was not eligible for an Independent Review, as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

### 8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
CICLOSPORIN					
ciclosporin 0.1% eye drops, 30 x 0.3 mL unit doses	NEW	1	30	3	Ikervis®
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Optometrists					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Immediate/real time assessment (telephone/online) [new/existing code]					
<b>Episodicity:</b> Chronic					
<b>Severity:</b> Severe					
<b>Condition:</b> Dry eye disease with keratitis					
<b>Indication:</b> Chronic severe keratitis associated with dry eye disease					
<b>Treatment Phase:</b> Initial treatment					
<b>Clinical criteria:</b>					
Patient must have a corneal fluorescein staining (CFS) grade of 4 using the modified Oxford scale or equivalent					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must have an ocular surface disease index (OSDI) of at least 23					
<b>AND</b>					
<b>Clinical criteria:</b>					
The condition must not be adequately controlled by monotherapy with a preservative free artificial tear substitute					
<b>AND</b>					
<b>Clinical criteria:</b>					
The treatment must be in combination with a preservative free artificial substitute					
<b>Treatment criteria:</b>					
Must be treated by an ophthalmologist or an optometrist					
<b>Population criteria:</b>					
Patient must be 18 years or older					
<b>Prescribing Instructions:</b> The modified Oxford scale is a chart system that aims to facilitate consistent and objective grading of stain coverage, which involves a visual inspection of the patient's eye and comparing against the illustrations included in the chart to establish grade [include link here].					

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
CICLOSPORIN					
ciclosporin 0.1% eye drops, 30 x 0.3 mL unit doses	NEW	1	30	5	Ikervis®
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Optometrists					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code]					
<b>Episodicity:</b> Chronic					
<b>Severity:</b> Severe					
<b>Condition:</b> Dry eye disease with keratitis					
<b>Indication:</b> Chronic severe keratitis with dry eye disease					
<b>Treatment Phase:</b> Continuing Treatment					
<b>Clinical criteria:</b>					
Patient must have received PBS-subsidised treatment with this drug for this condition					
<b>AND</b>					
<b>Clinical criteria:</b>					
The patient must have demonstrated an improvement in corneal fluorescein staining of at least 3 from baseline, using the modified Oxford scale or equivalent					
<b>AND</b>					
<b>Clinical criteria:</b>					
The patient must have demonstrated an improvement in ocular surface disease index (OSDI) of at least 30% compared to baseline.					
<b>Treatment criteria:</b>					
Must be treated by an ophthalmologist or an optometrist					
<b>Population criteria:</b>					
Patient must be 18 years or older					
<b>Prescribing Instructions:</b>					
The modified Oxford scale can be found at [insert link here]					
<b>Note:</b>					
It is recommended that treatment should be re-evaluated after 24 months to manage the potential concerns regarding the long term use of ciclosporin and immunosuppression					

***This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

## 9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available

through the PBS. The PBAC welcomes applications containing new information at any time.

## **10 Sponsor's Comment**

Seqirus is pleased that Ikervis will soon be available on the PBS to meet the significant unmet clinical need in patients with severe dry eye disease inadequately treated with artificial tears.