

## 5.04 CICLOSPORIN, Eye drops 900 micrograms per mL single dose units 0.25 mL, Cequa<sup>®</sup>, Sun Pharma ANZ Pty Ltd.

### 1 Purpose of submission

- 1.1 The Category 2 submission requested Section 85 listing of ciclosporin 0.09% eye drops formulated as an aqueous nanomicellar solution (0.09% OTX-101) for the treatment of chronic severe dry eye disease (DED) with keratitis.
- 1.2 Listing was requested based on a cost-minimisation analysis versus ciclosporin 0.1% formulated as a cationic emulsion (0.1% CsA CE; Ikervis).

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

Component	Description
Population	Patients with chronic severe DED with keratitis equivalent to a CFS grade 4 on the modified Oxford scale and an OSDI $\geq$ 23 at baseline (treatment initiation), inadequately controlled by monotherapy with preservative free artificial tears.
Intervention	0.09% OTX-101 bid
Comparator	0.1% CsA CE qd
Outcomes	Change equivalent to an improvement in CFS of at least 3 from baseline (treatment initiation), using the modified Oxford scale, and an improvement in OSDI by at least 30% compared with baseline (treatment initiation).
Clinical claim	0.09% OTX-101 bid is non-inferior to 0.1% CsA CE qd with respect to efficacy and safety.

Source: Table 1, p8 of the submission. Abbreviations: bid = twice daily; CFS = corneal fluorescein staining; CsA CE = ciclosporin (Ikervis); DED = dry eye disease; OSDI = ocular surface disease index; OTX-101 = ciclosporin (Cequa); qd = once daily

### 2 Background

#### **Registration status**

- 2.1 0.09% OTX-101 was Therapeutic Goods Administration (TGA) approved on 31 January 2020. The registered indication for 0.09% OTX-101, “to increase tear production in patients with moderate to severe keratoconjunctivitis sicca (dry eye) where prior use of artificial tears has not been sufficient”, is similar to but not the same as the registered indication for the comparator, which is “Treatment of severe keratitis in adult patients with dry eye disease which has not improved despite treatment with tear substitutes”. The difference in registered indication is due to differences in the design of the trials that were performed to support the TGA registration and used as evidence for the submission.

#### **Previous PBAC consideration**

- 2.2 The PBAC recommended the listing of 0.1% CsA CE for chronic severe DED with keratitis in March 2021. The PBAC has not considered 0.09% OTX-101 previously.

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

### 3 Requested listing

3.1 The submission proposed the same restriction as that for 0.1% CsA CE.

Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
CICLOSPORIN ciclosporin 0.09% eye drops 60 x 0.25mL unit doses	1	5	\$81.97	Cequa	Sun Pharma ANZ Pty Ltd.
Category/Program:	General Schedule				
PBS indication:	Chronic severe dry eye disease with keratitis				
Treatment phase:	Initial				
Restriction:	Authority Required (telephone/online PBS Authorities system)				
Treatment criteria:	Patient must be undergoing simultaneous treatment with a preservative free artificial tears substitute AND Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist; OR Must be treated by an optometrist in accordance with Optometry Board of Australia guidelines				
Clinical criteria:	Patient must have a corneal fluorescein staining (CFS) grade of 4 at treatment initiation, using at least one of: (i) the Oxford scale, (ii) the modified Oxford scale, (iii) an equivalent scale to the Oxford scale as determined by the prescriber AND Patient must have an ocular surface disease index (OSDI) score of at least 23 at treatment initiation AND The condition must be inadequately controlled by monotherapy with a preservative free artificial tears substitute				
Population criteria:	Patient must be 18 years or older				
Prescriber criteria:	Medical Practitioners, Optometrists				

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Category / Program:	General Schedule
PBS Indication:	Chronic severe dry eye disease with keratitis
Treatment phase:	Continuing treatment
Restriction:	Authority Required (telephone/online PBS Authorities system)
Treatment criteria:	<p>Patient must be undergoing simultaneous treatment with a preservative free artificial tears substitute</p> <p>AND</p> <p>Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist; OR</p> <p>Must be treated by an optometrist in accordance with Optometry Board of Australia guidelines</p>
Clinical criteria:	<p>Patient must have received PBS-subsidised treatment with this drug for this condition</p> <p>AND</p> <p>The condition must have improved to an extent that corneal fluorescein staining, using the same scale used at the time of the first authority application, shows an improvement (reduction) by at least 3 grades from baseline (the grade stated in the first authority application) - the improvement need only be demonstrated by staining once only with the first Continuing treatment authority application</p> <p>AND</p> <p>The condition must have improved to an extent that the patient's ocular surface disease index score at the time of this authority application, has improved (reduced) by at least 30% compared to the value stated in the first authority application (i.e. baseline)</p>
Prescriber criteria:	Medical Practitioners, Optometrists

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

## 4 Population and disease

- 4.1 The submission stated that DED is defined as “a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles” by the Tear Film and Ocular Surface (TFOS) Dry Eye Workshop (DEWS) II (Craig et al, 2017). Keratitis is the inflammation of the cornea and may be associated with DED.
- 4.2 The submission stated that “Ciclosporin is a calcineurin inhibitor immunosuppressant agent. When administered systemically, it is able to inhibit the activation of transcription factors required for T-cell activation and inflammatory cytokine production. In patients whose tear production is presumed to be suppressed due to ocular inflammation associated with DED, topical administration of ciclosporin is thought to act as a partial immunomodulator”. However, deficient tear production is not the only pathological process in DED; not all patients with DED will have defective tear production, and it is not clear how many of those patients have an inflammatory process as the cause.<sup>1</sup> The therapeutic effect of ciclosporin in DED should not be assumed to be due to immunomodulation.

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<sup>1</sup> Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. *Ocul Surf.* 2017;15(3):276. Epub 2017 Jul 20.

- 4.3 The proposed target population for the PBS listing of 0.09% OTX-101 is the same as that for 0.1% CsA CE, which is defined by a corneal fluorescein staining (CFS) score of 4 or 5 on the modified Oxford scale, and an Ocular Surface Disease Index (OSDI) score of at least 23.
- 4.4 The submission proposed that 0.09% OTX-101 would be an alternative to 0.1% CsA CE based on the treatment algorithm accepted by the PBAC at its March 2021 consideration of 0.1% CsA CE.

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

## **5 Comparator**

- 5.1 The submission nominated 0.1% CsA CE as the comparator because it is the only PBS-listed ciclosporin product for this condition. The PBAC considered this comparator appropriate.

*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 described the natural history of the disease, and the impact of severe DED on quality of life and daily living. The clinician discussed the transitivity between the different scoring methods used in the 0.1% CsA CE and 0.09% OTX-101 trials, noting that clinical experts and consensus groups generally consider the OSDI and SANDE symptom scores, and Oxford and NEI CFS scales to be comparable. The clinician noted that these scales are not always used in clinical practice to assess DED and that clinicians are able to identify severe DED without the use of formal symptom scoring. The clinician stated that not all factors involved in the pathogenesis of DED are currently understood and noted that there was considerable variation in treatment tolerability and response to treatments between patients that was not predictable. The clinician indicated that there is currently no clear treatment algorithm for DED and that patients would usually try multiple treatments until an effective, tolerable treatment was identified. The clinician considered that having an additional formulation of ciclosporin would be useful given that patients can have a variable tolerability to different formulations. The PBAC noted the information presented in the hearing.

### ***Consumer comments***

- 6.2 The PBAC noted that no consumer comments were received for this item.

### ***Clinical studies***

- 6.3 The submission was based on two randomised controlled trials (Study 2014 and Study 2016) comparing 0.09% OTX-101 to vehicle, and two trials (SANSIKA and SICCANOVE)

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comparing 0.1% CsA CE to vehicle. Results of Study 2014 and Study 2016, and of SANSIKA and SICCANOVE (previously considered by the PBAC) were used for an indirect comparison between 0.09% OTX-101 and 0.1% CsA CE with vehicle as the common reference. Post hoc subgroup analyses of pooled results from the trials for multiple endpoints were presented to align the populations in the trials with the proposed population for PBS listing.

6.4 Details of the trials presented in the submission are provided in the table below.

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

Trial ID	Protocol title/ Publication title	Publication citation
Study 2014	<p>A randomized, multicenter, double-masked, vehicle-controlled, dose-ranging study of the safety and efficacy of OTX-101 in the treatment of Keratoconjunctivitis Sicca. NCT02254265</p> <p>Tauber, J., Schechter, B. A., Bacharach, J., Toyos, M. M., Smyth-Medina, R., Weiss, S. L. &amp; Luchs, J. I. 2018. A Phase II/III, randomized, double-masked, vehicle-controlled, dose-ranging study of the safety and efficacy of OTX-101 in the treatment of dry eye disease.</p>	<p>Date: 09 March 2016</p> <p><i>Clin Ophthalmol.</i> 2018, 12, 1921-1929.</p>
Study 2016	<p>A randomized, multicentre, double-masked, vehicle-controlled study of the safety and efficacy of OTX-101 in the treatment of Keratoconjunctivitis Sicca. NCT02688556</p> <p>Goldberg, D. F., Malhotra, R. P., Schechter, B. A., Justice, A., Weiss, S. L. &amp; Sheppard, J. D. A Phase 3, Randomized, Double-Masked Study of OTX-101 Ophthalmic Solution 0.09% in the Treatment of Dry Eye Disease. <i>Ophthalmology</i>, 126, 1230-1237.</p> <p>Sheppard, J., Bergmann, M., Schechter, B. A., Luchs, J., Ogundele, A. &amp; Karpecki, P. Phase 3 Efficacy (Worse-Eye Analysis) and Long-Term Safety Evaluation of OTX-101 in Patients with Keratoconjunctivitis Sicca.</p>	<p>Date: 19 July 2017</p> <p><i>Ophthalmology</i>, 2019.126, 1230-1237.</p> <p><i>Clin Ophthalmol</i>, 2021 15, 129-140.</p>
Pooled analyses of Study 2014 and 2016	<p>Malhotra, R., Devries, D. K., Luchs, J., Kabat, A., Schechter, B. A., Shen Lee, B., Shettle, L., Smyth-Medina, R., Ogundele, A., Darby, C., Bacharach, J. &amp; Karpecki, P. Effect of OTX-101, a Novel Nanomicellar Formulation of Cyclosporine A, on Corneal Staining in Patients With Keratoconjunctivitis Sicca: A Pooled Analysis of Phase 2b/3 and Phase 3 Studies.</p> <p>Sheppard, J., Kannarr, S., Luchs, J., Malhotra, R., Justice, A., Ogundele, A., Darby, C. &amp; Bacharach, J. Efficacy and Safety of OTX-101, a Novel Nanomicellar Formulation of Cyclosporine A, for the Treatment of Keratoconjunctivitis Sicca: Pooled Analysis of a Phase 2b/3 and Phase 3 Study.</p> <p>Smyth-Medina, R., Johnston, J., Devries, D. K., Jasper, A., Kannarr, S. R., Schechter, B. A., Shen Lee, B., Varghese, G., Ogundele, A., Darby, C. H., Karpecki, P. &amp; Luchs, J. Effect of OTX-101, a Novel Nanomicellar Formulation of Cyclosporine A, on Conjunctival Staining in Patients with Keratoconjunctivitis Sicca: A Pooled Analysis of Phase 2b/3 and 3 Clinical Trials.</p>	<p><i>Cornea</i>, 2019. 38, 1259-1265.</p> <p><i>Eye Contact Lens</i>, 2020. 46 Suppl 1, S14-S19.</p> <p><i>J Ocul Pharmacol Ther</i>, 2019. 35, 388-394.</p>

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Trial ID	Protocol title/ Publication title	Publication citation
	Toyos, M., Gupta, P. K., Mitchell, B. & Karpecki, P. The Effect of OTX-101 on Tear Production in Patients with Severe Tear-deficient Dry Eye Disease: A Pooled Analysis of Phase 2b/3 and Phase 3 Studies.	<i>Curr Eye Res</i> , 2021. 1-5.
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 Cyclokot® 1 mg/ml (ciclosporin/cyclosporine) eye drops, emulsion administered once daily in adult patients with severe dry eye disease (DED)	2011-000160-97 (Protocol no. NVG10E117)
	Leonardi, A., Van Setten, G., Amrane, M., Ismail, D., Garrigue, J. S., Figueiredo, F. C. & Baudouin, C. Efficacy and safety of 0.1% cyclosporine A cationic emulsion in the treatment of severe dry eye disease: a multicenter randomized trial.	<i>Eur J Ophthalmol</i> , 2016. 26, 287-96.
	Baudouin, C., De La Maza, M. S., Amrane, M., Garrigue, J. S., Ismail, D., Figueiredo, F. C. & Leonardi, A. 2017. One-Year Efficacy and Safety of 0.1% Cyclosporine a Cationic Emulsion in the Treatment of Severe Dry Eye Disease.	<i>Eur J Ophthalmol</i> , 2017. 27, 678-685.
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	<i>EudraCT</i> 2007-000029-23 (Protocol no. NVG06C103)
	Baudouin, C., Figueiredo, F. C., Messmer, E. M., Ismail, D., Amrane, M., Garrigue, J. S., Bonini, S. & Leonardi, A. 2017. A randomized study of the efficacy and safety of 0.1% cyclosporine A cationic emulsion in treatment of moderate to severe dry eye.	<i>Eur J Ophthalmol</i> , 2017. 27, 520-530.
Meta-analysis of SICCANOVE and SANSIKA	Leonardi, A., Messmer, E. M., Labetoulle, M., Amrane, M., Garrigue, J. S., Ismail, D., Sainz-De-La-Maza, M., Figueiredo, F. C. & Baudouin, C. 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.	<i>Br J Ophthalmol</i> , 2019. 103, 125-131.

Source: Table 2.2.1, pp31-32 of the submission.

- 6.5 The key features of the included evidence are summarised in Table 3 below.
- 6.6 Although ‘vehicle’ was nominated as the common comparator, the vehicle of the intervention (aqueous nanomicellar ophthalmic solution) and the comparator (cationic lipid-based emulsion) were different. In its previous consideration of the 0.1% CsA CE trials, the PBAC considered that the cationic lipid-based emulsion vehicle showed superior efficacy compared to artificial tears (paragraph 6.14 and 7.5, ciclosporin, Public Summary Document (PSD), March 2021 PBAC meeting).
- 6.7 The post hoc subgroup analyses were used as the basis for the claim of non-inferior effectiveness. The details of the populations and outcomes used for this comparison are shown in Table 4.

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Table 3: Key features of the evidence – indirect comparison

Trial	N	Design/duration	Risk of bias	Eligibility Criteria	Primary Outcome(s)	Notes
<b>0.09% OTX-101 vs vehicle</b>						
Study 2014 (NCT 02254265)	455	R, DB, MC, 12 wk	Low	DED for > 6 mo <b>and</b> lissamine green staining score $\geq 3$ and $\leq 9$ (maximum score 12) <b>and</b> SANDE score $\geq 40^a$	Change in lissamine green conjunctival staining; change in SANDE Score	-
STUDY 2016 (NCT 02688556)	745	R, DB, MC, 12 wk	Low	DED for > 6 mo <b>and</b> lissamine green staining score $\geq 3$ and $\leq 9$ (maximum score 12) <b>and</b> SANDE score $\geq 40$	Schirmer's Test increase $\geq 10$ mm from baseline	-
Study 2016 (NCT 02688556) Open label continuation phase	258 (129 continuing 0.09% OTX-101, 129 switching to 0.09% OTX-101 from vehicle)	OL, MC, 40 wk	High	Completion of DB phase	Adverse events	-
<b>0.1% CsA CE vs vehicle</b>						
SICCANOVE	496	R, DB, MC, 26 wk	Low	Moderate to severe symptoms <b>and</b> Tear Break-Up Time $\leq 8$ sec <b>and</b> moderate to severe corneal fluorescein staining <b>and</b> impaired tear production by Schirmer's Test <b>and</b> marked conjunctival lissamine green staining	Change in corneal fluorescein staining; change in global symptom score	Randomisation stratified by Sjogren Syndrome (177 patients)
SANSIKA	246	R, DB, MC, 26 wk	Low	Severe corneal fluorescein staining <b>and</b> impaired tear production <b>and</b> moderate or worse symptoms by OSDI.	Proportion with corneal fluorescein staining improved $\geq 2$ grades <b>and</b> 30% reduction in OSDI.	-

Source: Created from listings at <https://clinicaltrials.gov/> accessed 30 November 2021. Abbreviations: DB = double blind; MC = multi-centre; OL = open label; R = randomised, DED = Dry Eye Disease.

<sup>a</sup> SANDE score was calculated as follows: frequency of dry eye/irritation was rated from 0 = rarely to 100 = all the time, and severity of dry eye/irritation was rated from 0 = very mild to 100 = very severe; the Score was the square root of the product of the frequency score and the severity score.

Table 4: Key features of the subgroups used for the indirect comparison<sup>a</sup>

Trial	N (N for parent trial)	Design/duration	“PBS Equivalent” Eligibility Criteria	PBS Continuation or Equivalent Outcome	Notes
Study 2014 NCT 02254265	77 (304)	R, DB, MC, 12 wk	CFS score $\geq 2.5$ on NEI scale <b>and</b> SANDE score $\geq 40$	Proportion with NEI score $\leq 0.5$ <b>and</b> change in SANDE $\geq 30\%$	DED for > 6 mo <b>was</b> required for entry but is <b>not</b> a PBS criterion.
Study 2016 NCT 02688556	167 (744)	R, DB, MC, 12 wk	CFS score $\geq 2.5$ on NEI scale <b>and</b> SANDE score $\geq 40$	Proportion with NEI score $\leq 0.5$ <b>and</b> change in SANDE $\geq 30\%$	DED for > 6 mo <b>was</b> required for entry but is <b>not</b> a PBS criterion.
Pooled	244	-	-	-	-
SICCANOVE	75 (489)	R, DB, MC, 26 wk	CFS (Oxford Scale) $\geq 4$ <b>and</b> OSDI $\geq 23$ .	Corneal fluorescein staining improved $\geq 3$ Oxford Scale grades <b>and</b> $\geq 30\%$ reduction in OSDI.	Tear Break-Up Time $\leq 8$ sec <b>and</b> impaired tear production by Schirmer’s Test <b>and</b> marked conjunctival lissamine green staining <b>were</b> required for entry but are <b>not</b> PBS criteria.
SANSIKA	245 (245)	R, DB, MC, 26 wk	CFS (Oxford Scale) $\geq 4$ <b>and</b> OSDI $\geq 23$ .	Corneal fluorescein staining improved $\geq 3$ grades <b>and</b> $\geq 30\%$ reduction in OSDI.	Impaired tear production by Schirmer’s Test <b>was</b> required for entry but is <b>not</b> a PBS criterion.
Pooled	320	-	-	-	-

Source: Table 2.2-2 and Figure 2.2-2, p34.

Abbreviations: DB = double blind; DED = dry eye disease; MC = multi-centre; OL = open label; OSDI= Optical Surface Disease Index, R = randomised. CFS = corneal fluorescein staining, NEI = National Eye Institute, SANDE = Symptom Assessment in Dry Eye. <sup>a</sup>PBS criteria: patient must have a CFS grade of 4 at treatment initiation, using at least one of: (i) the Oxford scale, (ii) the modified Oxford scale, (iii) an equivalent scale to the Oxford scale as determined by the prescriber AND Patient must have an ocular surface disease index (OSDI) score of at least 23 at treatment initiation.

6.8 It was uncertain how the submission derived the PBS-eligible subgroups. As stated in the submission, Study 2014 and Study 2016 used different CFS and symptom grading methods to SANSIKA and SICCANOVE. These methods are not comparable. The scale for CFS changes used in the trials of 0.09% OTX-101 was the Expanded National Eye Institute / Industry Workshop Scale (NEI) rather than the modified Oxford Scale previously accepted by the PBAC. The symptom scale used in the trials of 0.09% OTX-101 was the Symptoms Assessment in Dry Eye (SANDE) scale. For the trials of 0.1% CsA CE, the symptom scale used was the Ocular Surface Disease Index (OSDI).

6.9 The submission nominated ‘the proportion of patients achieving an improvement from baseline to a maximum CFS score of 1.5 in the worst eye (NEI scale) and  $\geq 30\%$  improvement in SANDE scores’ as ‘equivalent composite outcomes’ to the primary outcomes (improvement  $\geq 2$  grades for CFS (modified Oxford Scale) and  $\geq 30\%$  for OSDI) of SANSIKA, based on feedback from key opinion leaders. For ‘CFS (modified Oxford grade)  $\geq 3$  and OSDI  $\geq 30\%$  response rate’, the submission proposed the ‘proportion of patients achieving an improvement from baseline to a maximum CFS

score of either 0.5 (base case) or 1.0 (sensitivity analysis) in the worst eye and  $\geq 30\%$  improvement in SANDE scores' as the equivalent outcome.

- 6.10 The submission proposed a CFS score of  $\geq 2.5$  on the Expanded National Eye Institute (NEI)/ Industry Workshop Scale (NEI) scale to be equivalent to a CFS score of 4 on the modified Oxford scale.
- 6.11 The validity of this equivalence is central to the assessment of comparative effectiveness. The Oxford Scale is graded between 0 and 5 based on the observer counting the fluorescein-stained dots in the eye as a whole, with each grade defined as a half-log increase in the number of dots: Grade 1 has more than 1 dot but fewer than 10, Grade 2 has more than 10 but fewer than 32, Grade 3 has more than 32 but fewer than 100, Grade 4 has more than 100 but fewer than 320, and Grade 5 has more than 320 (Bron, 2003, Figure 1). For clinical use, a simplified scale was proposed which did not require dots to be counted, but instead matched the grades to drawings (Bron, 2003, Figure 4); this was used in the 0.1% CsA CE trials. Notably, the Oxford Scale does not account for the possibility that some parts of the eye may be more severely affected than others.
- 6.12 The NEI Scale divides the cornea into five zones where CFS is graded in each zone and the final score is the sum of the scores for all zones. In the most recent version of the scale, each zone is graded from 0-4, giving a range of 0-20 (Wolffsohn, 2017). Notably, it is inherent in the NEI scale, in contrast to the Oxford Scale, that severity may vary across the cornea, though the NEI score is the total score for the cornea as a whole.
- 6.13 It was not clear how the submission has used the NEI scale to define keratitis equivalent to an Oxford Scale score of 4 or greater for the purposes of the subgroup analyses. The submission states at several points that a zone grading of 2.0 (sensitivity analysis) or 2.5 (base case) on the NEI scale corresponds to an Oxford Scale score of 4. However, a grading of 2.0 or 2.5 in each of the five corneal zones would equate to a total CFS score of 10-12.5 for that eye on the NEI scale. That would be a reasonable equivalent to an Oxford Scale score of 4 or greater, however, a total CFS score of 10-12.5 was not the score used to define the PBS-eligible population in the subgroup analyses of the 0.09% OTX-101 trials and it was unclear what score was used. The submission made references to marked central corneal staining (which represents severe keratitis according to DEWS (2007b)) with a central corneal zone score of at least 2 or 2.5. Although there is no threshold for 'marked' in the NEI scale, the submission had nominated a score of either  $\geq 2.0$  or  $\geq 2.5$  to be equivalent to the stringent criteria of 'severe keratitis'. The submission also referred to a score of at least 2 or 2.5 in any corneal zone, although using a score for a single zone rather than the summed score for all zones has not been validated. Further, counting only a single zone means that improvement to a score of  $\leq 1.5$  in what was the worst zone at baseline could be associated with worsening in all other zones but the patient would be counted as successfully treated. This not consistent with the design of the NEI scale, which incorporates heterogeneity both at baseline and in response.

- 6.14 The uncertainty concerning how the PBS-eligible subgroups were defined made interpretation of the data presented difficult. It was also difficult to align changes in the Oxford Scale scores to changes in the NEI scores because of the logarithmic nature of the Oxford Scale. For example, the submission presented data for the proportion of the PBS-eligible population with “Improvement to CFS  $\leq$  1.5 (NEI) however, it was not clear which zone the improvement had to be in, or whether the total NEI score, the sum of all five zones, must be  $\leq$  1.5. The Pre-Sub-Committee Response (PSCR) stated that for the subgroup analyses of the 0.09% OTX-101 trials, the CFS was only assessed in the one zone with the highest CFS score at baseline (i.e. the worst zone) and only in the eye with the worst zone. The PSCR noted that the use of only one single zone of the cornea to define keratitis in the PBS population excludes other areas of the eye which may also be affected. The PSCR noted that feedback from clinical experts indicated that worsening in other zones is unlikely when there is improvement in the worst zone.
- 6.15 The SANDE scale combines the self-reported severity and self-reported frequency of eyes being “dry and/or irritated. The OSDI considers only the frequency of symptoms, not their severity, and asks separately about a wider range of symptoms (light sensitivity, grittiness, soreness, blurred vision, and poor vision), functional impairment, and environmental precipitants. The effect is that a patient with infrequent, severe symptoms will record a similar SANDE score to a patient with frequent, mild symptoms, but those patients would have quite different OSDI scores. For example, of 16 patients with an OSDI score between 20 and 35 (i.e., around the PBS-eligibility threshold) seven (44%) had SANDE scores below 40. Conversely, of 13 patients with OSDI scores below 20, six (46%) had SANDE scores over 40. Using the SANDE score of 40 as equivalent to an OSDI score of 23 does not produce the same “PBS-eligible” subgroups.
- 6.16 Given the differences between the scales described above, the PBAC considered that the outcomes were not sufficiently comparable to allow any assessment of comparative effectiveness by means of an indirect comparison.

### ***Comparative effectiveness***

- 6.17 The results of the trials of 0.09% OTX-101, for the full trial populations, are shown in Tables 5 and 6 below. The results for the subgroup analyses are discussed below, in paragraphs 6.18-6.20.

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**Table 5: Results of mean change in CFS assessed by NEI Scale from baseline to 3 months across the studies of 0.09% OTX-101**

Trial	Endpoint	0.09% OTX-101, Mean (SD)				Vehicle, Mean (SD)				Mean difference (95% CI)	p-value
		N	Baseline	Follow-up	Change	N	Baseline	Follow-up	Change		
<b>Total population</b>											
Study 2014 <sup>1</sup>	Secondary	152	4.5 (3.1)or 4.5 (3.05) <sup>2</sup>	Not reported	-1.4 (2.87)	152	4.6 (2.8)	Not reported	-0.6 (2.76)	-0.9 (-1.4, -0.3)	<b>p=0.0015</b>
STUDY 2016 <sup>3</sup>	Secondary	371	4.06 (2.374)	Not reported	-1.44 (1.976)	373	4.30 (2.650)	Not reported	-1.17 (2.181)	-0.36 (-0.56, -0.15)	<b>p=0.0007</b>

Source: compiled from <sup>1</sup>Tauber et al, although follow-up results were only shown graphically; <sup>2</sup>TABLE 2.5.3 of the submission contains different data from the publication; <sup>3</sup>data from Table 2.5.5 in the submission, Total CFS score. 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.

**Table 6: Change in SANDE scores over 3 months**

Trial	Endpoint	0.09% OTX-101, Mean (SD)				Vehicle, Mean (SD)				Mean difference (95% CI)	p-value
		N	Baseline	Follow-up	Change	N	Baseline	Follow-up	Change		
<b>Total population</b>											
Study 2014 <sup>1</sup>	Co-primary	152	62.62 (14.557)	Not reported	-17.93 (22.686)	152	61.49 (14.337)	Not reported	-18.40 (23.021)	0.74 (-4.33, 5.80);	p=0.7755
STUDY 2016	Secondary	371	63.1 (15.71)	Not reported	-18.8 (24.08)	373	62.2 (16.12)	Not reported	-19.1 (23.14)	-0.05 (-2.9, 4.0)	p=0.7528

Source: compiled from Table 2.5.2, p 82 and Table 2.5.5 pp 87-88 of the submission.

6.18 The results of the SANSIKA and SICCANOVE trials are presented below from the March 2021 ciclosporin PSD.

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Table 7: Results of mean change in CFS assessed by the Oxford Scale from baseline to 6 months across the 0.1% CsA CE studies

Trial	Endpoint	0.1% CsA CE, Mean (SD) OR adjusted mean (95% CI)				Vehicle, Mean (SD) OR adjusted mean (95% CI)				Mean difference (95% CI)	p- value
		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>

Source: Table 4, March 2021 ciclosporin PSD.

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

Table 8: Results for CFS-OSDI response across the 0.1% CsA CE studies

Trial ID	Endpoint	0.1% CsA CE 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	-	-	-	-

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Trial ID	Endpoint	0.1% CsA CE n/N (%)	Vehicle n/N (%)	Risk difference (95% CI)	Odds ratio (95% CI)	p-value
<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

Source: Table 5, March 2021 ciclosporin PSD

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.

- 6.19 The submission provided multiple post hoc subgroup analyses as the whole-of-trial population did not align with the current PBS listing of 0.1% CsA CE. This approach was consistent with the PBAC Guidelines and consistent with the approach in the submission for 0.1% CsA CE.
- 6.20 The submission presented results for the subgroup analyses as categorical outcomes for different grades of response rather than continuous outcomes as for the total trial population, using standard statistical approaches to calculate pooled estimates of effect sizes with different metrics. The submission also presented meta-analyses of the results of SANSIKA and SICCANOVE, from the PSD for 0.1% CsA CE and the publication by Leonardi et al. (2019).

- 6.21 The results of the subgroup analyses were difficult to interpret. The populations in the trials of 0.09% OTX-101 were, overall, much less severely affected, even allowing for the difference in measures of severity: over the two OTX-101 trials, 2014 and 2016, a total of 244/1049 (23.3%) of patients had marked corneal fluorescein staining (i.e. severe keratitis) and moderate to severe symptoms, compared to 320/620 (51.6%) of patients in the SICCANOVE and SANSIKA trials. It was not possible to compare the baseline characteristics of the patients included in the subgroup analyses. Only the baseline characteristics of the whole-of-trial population were presented, and the submission stated that “The baseline characteristics for the post hoc specified PBS population in Study 2014, Study 2016 and SICCANOVE were unavailable”.
- 6.22 Because of the uncertainty about the definition of severe keratitis for the subgroup analyses of the 0.09% OTX-101 trials, it was difficult to reconcile the numbers included in the PBS-eligible subgroup with the reported baseline characteristics of the trials. For example, for Study 2016, the PBS-eligible subgroup was reported to be 167/744 (35% of the total Study 2016 population). However, the submission provided data for baseline central CFS scores for the whole study and specified that the mean (SD) score for patients randomised to 0.09% OTX-101 was 0.6 (0.6), and for the vehicle-treated patients it was 0.7 (0.7). Based on this data, only a small percentage of patients would be expected to have central CFS scores over 2. In Study 2014, the mean (SD) corneal staining scores for the study eyes were 0.8 (0.79) for the central zones, 1.4 (0.88) for the inferior zones, 0.9 (0.78) for the lateral zones, 1.1 (0.78) for the medial zones, and 0.5 (0.56) for the superior zones. These scores were similar to or less than those of the non-study eyes. For the worst zone, the inferior zone, only about 10% of patients had scores > 2.5.
- 6.23 The results of the subgroup analyses for various levels of response were presented in the submission. Only the pooled analyses resulted in statistically significant differences. Given the fundamental questions about the validity of the data, these results have not been re-presented. Similarly, the results of the indirect comparison of the PBS-eligible subgroups were also not re-presented.
- 6.24 The submission then used the pooled estimates of effect size for the subgroups from Study 2014 and 2016 and the estimates of effect from the pooled SANSIKA and SICCANOVE subgroup, to carry out a formal statistical indirect comparison using the Bucher method. The results of these comparisons for multiple different outcomes and composite outcomes (different changes in corneal fluorescein staining scores combined with symptom scores) were presented in the submission.
- 6.25 The submission presented a detailed discussion of the transitivity assumptions concerning the comparison of the 0.09% OTX-101 trials with the 0.1% CsA CE trials, noting that:
- The baseline characteristics of the populations in the trials were different;
  - The grading systems for disease characteristics were different between the 0.09% OTX-101 trials and the 0.1% CsA CE trials;

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- Different scoring methods were used across the 0.09% OTX-101 trials and the 0.1% CsA CE trials for the outcomes of interest;
- There were differences in eligibility criteria between the 0.09% OTX-101 trials and the 0.1% CsA CE trials;
- The treatment durations of the 0.09% OTX-101 trials and the 0.1% CsA CE trials were different;
- There were differences between the 0.09% OTX-101 trials and the 0.1% CsA CE trials with respect to use of artificial tears.

In addition, the vehicle in the trials of 0.09% OTX-101 was different to the vehicle in the trials of 0.1% CsA CE.

6.26 Given these significant differences between the trials together with the issues identified with the subgroup analyses, the transitivity assumptions for an indirect comparison were not satisfied.

### Comparative harms

6.27 Adverse events for the full trial populations as reported in the trials of 0.09% OTX-101 are summarised in Table 9. Table 10 presents the adverse events from the trials of 0.1% CsA CE.

Table 9: Adverse events in the randomised trials of 0.09% OTX-101

	0.09% OTX-101 n/N (%)	Vehicle n/N (%)	Odds Ratio (95% CI)
<b>Any TEAE</b>			
Study 2014	52/152 (34.2%)	51/152 (33.6%)	1.03 (0.64, 1.66) p=0.90
Study 2016	151/372 (40.6%)	91/372 (24.5%)	2.11 (1.54, 2.89) p<0.0001
Pooled	203/524 (38.7%)	142/524 (27.1%)	1.51 (0.75, 3.04) p=0.25
<b>Treatment-related Ocular TEAE</b>			
Study 2014	30/152 (19.7%)	12/152 (7.9%)	2.87 (1.41, 5.85); p=0.004
Study 2016	102/372 (27.4%)	33/372 (8.9%)	3.88 (2.54, 5.93); p<0.0001
Pooled	132/524 (25.2%)	45/524 (8.6%)	3.59 (2.49, 5.16); p<0.0001
<b>Instillation Site Pain</b>			
Study 2014	23/152 (15.1%)	5/152 (3.3%)	5.24 (1.94, 14.19); p=0.001
Study 2016	90/372 (24.2%)	16/372 (4.3%)	7.10 (4.08, 12.36); p<0.0001
Pooled	113/524 (21.6%)	21/524 (4%)	6.61 (4.07, 10.73); p<0.0001
<b>Instillation Site Reaction</b>			
Study 2014	0/152 (0)	1/152 (0.7%)	0.33 (0.01, 8.19); p=0.50
Study 2016	4/372 (1.1%)	2/372 (0.5%)	2.01 (0.37, 11.05); p=0.42
Pooled	4/524 (0.8%)	3/524 (0.6%)	1.35 (0.30, 6.09); p=0.69
<b>Withdrawal due to an AE</b>			
Study 2014	5/152 (3.3)	6/152 (3.9%)	0.83 (0.25, 2.77); p=0.76
Study 2016	17/372 (4.6%)	3/372 (0.8%)	5.89 (1.71, 20.27); p=0.0049
Pooled	22/524 (4.2%)	9/524 (1.7%)	2.20 (0.31, 15.37); p=0.43

Source: Table 2.6-19, pp134-5

CI = confidence interval; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk

Table 10: Adverse Events in Trials of 0.1% CsA CE

	0.1% CsA CE n/N (%)	Vehicle n/N (%)	Odds Ratio (95% CI)
<b>Any TEAE</b>			
SANSIKA	88/154 (57.1%)	42/90 (46.7%)	Not reported
SICCANOVE	54/252 (21.4%)	28/250 (11.2%)	
Pooled	142/396 (35.9%)	69/340 (20.3%)	
<b>Treatment-related Ocular TEAE</b>			
SANSIKA	57/154 (37.0%)	18/90 (20%)	Not reported
SICCANOVE	92/242 (38%)	41/250 (16.4%)	
Pooled	149/396 (37.6%)	59/340 (17.4%)	
<b>Instillation Site Pain</b>			
SANSIKA	Not reported	Not reported	Not reported
SICCANOVE	Not reported	Not reported	
Pooled	48/396 (12.1%)	9/340 (2.6%)	
<b>Instillation Site Reaction</b>			
SANSIKA	Not reported	Not reported	Not reported
SICCANOVE	Not reported	Not reported	
Pooled	20/396 (5.1%)	4/340 (1.2%)	
<b>Withdrawal due to an AE</b>			
SANSIKA	21/154 (13.6%)	9/90 (10.0%)	Not reported
SICCANOVE	24/242 (9.9%)	18/250 (7.2%)	
Pooled	45/396 (11.4%)	27/340 (7.9%)	

Source: Tables 2.5-16 and 2.5-17, pp104-5; Leonardi et al, 2016, Supplementary Appendix 2.

### **Clinical claim**

- 6.28 The submission described 0.09% OTX-101 as non-inferior in effectiveness and safety compared with 0.1% CsA CE.
- 6.29 The therapeutic conclusion presented in the submission was not adequately supported by the evidence presented in the submission because the post hoc subgroups used in the indirect comparison were inappropriate as the basis for a statistical analysis. The PBAC considered that a naïve comparison without statistical analysis was more appropriate as the basis of assessment. The pre-PBAC Response noted that in the naïve comparison of 0.09% OTX-101 and 0.1% CsA CE, a similar proportion of patients (17.8%) in the PBS population of the pooled 0.09% OTX-101 arm of Study 2014 and Study 2016, achieved the equivalent of the criteria for continuing treatment on the PBS, compared to the proportion of patients (17.6%) in the pooled 0.1% CsA CE arm of SANSIKA and SICCANOVE, who met the criteria for continuing treatment on the PBS.
- 6.30 Overall, the PBAC considered that the claim of non-inferior comparative effectiveness and safety were reasonable.

### **Economic analysis**

- 6.31 The submission presented a cost-minimisation analysis based on the claimed non-inferiority of 0.09% OTX-101 to 0.1% CsA CE. The key components and assumptions are shown below.

**Table 11: Key components and assumptions of the cost-minimisation analysis**

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in the submission, effectiveness is assumed to be non-inferior
Therapeutic claim: safety	Based on evidence presented in the submission, safety is assumed to be non-inferior
Evidence base	Indirect comparison of proposed medicine and main comparator
Equi-effective doses	0.09% OTX-101 bid $\equiv$ 0.1% CsA CE qd
Direct medicine costs	Costs of proposed medicine and comparator are equivalent
Other costs or cost offsets	None

Source: Table 3.1-1, p161 of the submission.

6.32 The equi-effective doses were estimated as 0.09% OTX-101 one drop twice daily and 0.1% CsA CE one drop daily, based on the dosing regimens used in the clinical trials and as recommended in the PIs.

6.33 No additional costs or cost-offsets were included in the analysis. The results of the cost-minimisation analysis are presented below.

**Table 12: Cost-minimisation analysis**

	0.09% OTX-101	0.1% CsA CE
Prescriptions		
Prescriptions per 30 days	1	1
Quantity per prescription		
Single dose units per pouch	10	5
Pouches per pack	6	6
Single dose units per pack	60 [6 x 10]	30 [6 x 5]
Single dose units per day	2	1
Days of treatment per pack	30 [60/2]	30 [30/1]
Cost of treatment per prescription		
AEMP per single dose unit	\$1.08 [\$65.00/60]	\$2.17 [\$65.00/30]
AEMP per day	\$2.17 [\$1.08 x 2]	\$2.17 [\$2.17 x 1]
AEMP per prescription	\$65.00	\$65.00
Difference in cost of treatment		\$0.00

Source: Table 3.3-2, p164 of the submission.

AEMP= approved ex-manufacturer price

### **Drug cost/patient/year**

6.34 The total cost per patient per year based on 12.18 scripts per year is \$990.20 (calculated using DPMQ).

### **Estimated PBS usage & financial implications**

6.35 This submission was not considered by the Drug Utilisation Sub-Committee.

6.36 The submission used an epidemiological approach to estimate use. The key inputs were the same as those from the March 2021 PSD for 0.1% CsA (see the Table below). The submission assumed that by year 6 of listing 0.09% OTX-101 would have 50% of the market share.

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Table 13: Key inputs for financial estimates

	Value	Source	Comments
<b>Epidemiology</b>			
Australian population aged 18-39 years	2022: 8,372,889 2023: 8,475,114 2024: 8,579,615 2025: 8,686,587 2026: 8,785,822 2027: 8,880,538	DoH utilisation and cost model workbook	-
Australian population aged 40+ years	2022: 12,385,028 2023: 12,607,357 2024: 12,832,237 2025: 13,057,915 2026: 13,287,398 2027: 13,512,563	DoH utilisation and cost model workbook	-
Prevalence of patients with CFS=4 and OSDI $\geq$ 23 and refractory on conventional care	Aged 18-39 years: 0.06% Aged 40+ years: 0.75%	ciclosporin PSD March 2021, Table 14 par. 6.47 p.23	Previously considered uncertain but accepted by the PBAC subject to an RSA.
% patients actively seeking medical care	60%	ciclosporin PSD March 2021, Table 14 p.23	Previously accepted
% patients responding to treatment at 6 months	17.60%	ciclosporin PSD March 2021, Table 14 p.23	Previously accepted
% patients discontinuing treatment	Year 1: 11.19% Year 2+: 21.13%	ciclosporin PSD March 2021, Table 14 p.23	Previously accepted
<b>Changes in utilization</b>			
0.1% CsA CE annual uptake rate	All years: 10%	ciclosporin PSD March 2021, Table 14 p.23	Previously accepted
0.09% OTX-101 uptake rates	Year 1: % Year 2: % Year 3: % Year 4: % Year 5: % Year 6: %	Sun Pharma Assumption	Assumption - cannot be verified
<b>Cost of medicines</b>			
0.1% CsA CE 30 x 0.3 mL	AEMP: \$65.00	Schedule of Pharmaceutical Benefits (item 12663L)	
0.09% OTX-101 60 x 0.25 mL	AEMP: \$65.00	SUN Pharma proposed	
<b>Patient co-payments</b>			
Beneficiary type distribution	General ordinary: 0.25% General safety net: 0.95% Concessional ordinary: 64.14% Concessional safety net: 34.66% RPBS ordinary: 60.52% RPBS safety net: 39.48%	Services Australia: Pooled services processed for preservative free ocular lubricant over the 12-month period September 2020 to August 2021	
Co-payments by beneficiary type	General ordinary: \$41.30 General safety net: \$6.60 Concessional ordinary: \$6.60 RPBS ordinary: \$6.60	DoH utilisation and cost model workbook	

Source: Table 4.1.1, p167 of the submission. RSA = risk sharing arrangement

6.37 The estimated use and financial implications are shown below in Table 14.

**Table 14: 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	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Number of scripts dispensed <sup>a</sup>	█ <sup>1</sup>	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>6</sup>
<b>Estimated financial implications of 0.09% OTX-101</b>						
Cost to PBS/RPBS less co-payments	\$█ <sup>2</sup>	\$█ <sup>2</sup>	\$█ <sup>2</sup>	\$█ <sup>2</sup>	\$█ <sup>2</sup>	\$█ <sup>2</sup>
<b>Estimated financial implications for 0.1% CsA CE</b>						
Cost to PBS/RPBS less co-payments	-\$█ <sup>2</sup>	-\$█ <sup>2</sup>	-\$█ <sup>2</sup>	-\$█ <sup>2</sup>	-\$█ <sup>2</sup>	-\$█ <sup>2</sup>
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$0	\$0	\$0	\$0	\$0	\$0

Source: Tables 4.2.1, 4.2.2, 4.2.5, 4.3.4, 4.4.1; p172-178.

<sup>a</sup> Assuming 12.18 per year as estimated by the submission.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 <5,000

<sup>2</sup> \$0 to <\$10 million

<sup>3</sup> 5,000 to <10,000

<sup>4</sup> 10,000 to <20,000

<sup>5</sup> 20,000 to <30,000

<sup>6</sup> 30,000 to < 40,000

6.38 The total cost to the PBS/RPBS of listing 0.09% OTX-101 was estimated to be \$0 to <\$10 million in Year 6, and a total of \$0 to <\$10 million in the first 6 years of listing.

6.39 If the assumption that 0.09% OTX-101 substitutes only for 0.1% CsA CE is correct, there would be no net cost to the PBS. The existing risk sharing arrangement (RSA) would manage any potential risk of market expansion with a second product.

### **Financial Management – Risk Sharing Arrangements**

6.40 The submission assumed an RSA exists for 0.1% CsA CE with a █% rebate for all use beyond the annual expenditure caps (based on the PBAC’s comments in the ciclosporin PSD March 2021 paragraph 7.15). The submission assumed 0.09% OTX-101 will join the RSA for 0.1% CsA CE.

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

## **7 PBAC Outcome**

7.1 The PBAC recommended the listing of 0.09% OTX-101 (0.09% ciclosporin) for the treatment of chronic severe dry eye disease with keratitis. The PBAC’s recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of 0.09% ciclosporin would be acceptable if it were cost-minimised against 0.1% ciclosporin.

7.2 The PBAC noted that the sponsor hearing indicated there was considerable variation between patients in terms of tolerability to treatment and treatment effectiveness

between different ciclosporin eye drop formulations. The PBAC considered it would be useful to have an additional formulation of ciclosporin eyedrops with a different vehicle (aqueous nanomicellar ophthalmic solution) to the currently listed 0.1% ciclosporin eyedrops (cationic lipid-based emulsion) which would provide an alternative for patients who may not tolerate 0.1% ciclosporin. The PBAC also considered that having a second supplier for ciclosporin eyedrops would be useful for managing any risks associated with a single supplier on the PBS.

- 7.3 The PBAC advised that the equi-effective doses are 0.09% ciclosporin one drop twice daily and 0.1% ciclosporin one drop once daily.
- 7.4 The PBAC noted that the submission was based on post hoc subgroup analyses of pooled results from Study 2014 and Study 2016 comparing 0.09% ciclosporin to vehicle, and pooled results from SANSIKA and SICCANOVE trials comparing 0.1% ciclosporin eyedrops to vehicle. The PBAC noted that the subgroup analyses were presented to better align the population in the 0.09% ciclosporin trials to the PBS-eligible population, which was based on the 0.1% ciclosporin trials.
- 7.5 The PBAC considered it was difficult to interpret the results of the indirect comparison of the PBS-eligible subgroups noting the considerable differences between the 0.09% ciclosporin and 0.1% ciclosporin trials outlined in paragraph 6.25. The PBAC considered that the 0.09% ciclosporin and 0.1% ciclosporin trials were not sufficiently transitive to support a formal statistical indirect comparison. However, based on a naïve indirect comparison, the PBAC accepted the submission's claim of non-inferior effectiveness, noting that the proportion of patients who responded to treatment (CFS  $\leq 0.5$  (NEI) and  $\geq 30\%$  SANDE) at 3 months in the pooled 0.09% ciclosporin arm of Study 2014 and Study 2016 was similar to the proportion of patients who responded to treatment (CFS  $\geq 3$  grades (Oxford) and  $\geq 30\%$  OSDI) in the pooled 0.1% ciclosporin arm of SANSIKA and SICCANOVE.
- 7.6 In terms of safety, the PBAC noted that the number of treatment emergent adverse events were similar between the pooled 0.09% ciclosporin arm of Study 2014 and Study 2016 and the pooled 0.1% ciclosporin arm of SANSIKA and SICCANOVE. The PBAC accepted the submission's claim of non-inferior safety compared to 0.1% ciclosporin.
- 7.7 The PBAC noted that the submission estimated no financial implications with the listing of 0.09% ciclosporin. The PBAC considered there was a risk of use outside the requested PBS population noting that clinicians may use different scoring methods for DED in clinical practice. The PBAC considered it was appropriate for 0.09% ciclosporin to join the existing RSA caps currently in place for 0.1% ciclosporin. The PBAC considered that the RSA would be appropriate to manage the risks of use outside the PBS population and continued use in patients who do not meet the continuation criteria.

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- 7.8 The PBAC advised that 0.09% ciclosporin should not be used concurrently with any other PBS-subsidised therapy for this condition and advised that this be reflected in the 0.1% CsA CE PBS restriction.
- 7.9 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because 0.09% ciclosporin is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over 0.1% ciclosporin, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.10 This submission does not meet the criteria 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 0.09% eye drops, 60 x 0.25 mL unit doses	NEW	1	60	5	Cequa
Restriction Summary / Treatment of Concept:					
Restriction Summary / Treatment of Concept:					

<b>Administrative Advice</b>	Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.
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<b>Category / Program</b>	GENERAL - General Schedule (Code GE)
<b>Prescriber Type(s)</b>	Medical Practitioners, Optometrist
<b>PBS Indication</b>	Chronic severe dry eye disease with keratitis
<b>Treatment phase</b>	Initial treatment for up to the first 180 days of treatment
<b>Restriction Level / Method</b>	Authority required
<b>Treatment criteria</b>	Patient must be undergoing simultaneous treatment with a preservative free artificial tears substitute AND Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist; or Must be treated by an optometrist in accordance with Optometry Board of Australia guidelines AND Patient must not be undergoing treatment with this drug under this treatment phase beyond day 180 of treatment

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<p><b>Clinical criteria</b></p>	<p>Patient must have a corneal fluorescein staining (CFS) grade of 4 at treatment initiation, using at least one of: (i) the Oxford scale, (ii) the modified Oxford scale, (iii) an equivalent scale to the Oxford scale as determined by the prescriber  AND  Patient must have an ocular surface disease index (OSDI) score of at least 23 at treatment initiation  AND  The condition must be inadequately controlled by monotherapy with a preservative free artificial tears substitute  AND  The treatment must be the sole PBS-subsidised therapy for this condition.</p>
<p><b>Population criteria</b></p>	<p>Patient must be at least 18 years of age</p>
<p><b>Prescriber Instructions</b></p>	<p>Prescribing instruction:  State in the first authority application for this drug, for the purpose of having a baseline measurement to assess response to treatment under the Continuing treatment listing, each of:  (i) the qualifying corneal fluorescein staining grade (a numerical value no less than 4),  (ii) the qualifying ocular surface disease index score (a numerical value no less than 23).</p>
<p><b>Administrative Advice</b></p>	<p>The Oxford scale, modified Oxford scale and Ocular Surface Disease Index (OSDI) were relied upon in the submission supporting initial PBS listing.  The Oxford scale uses a chart system consisting of a series of panels, labelled A to E in order of increasing severity. In each chart, staining is represented by dots. To grade staining, comparisons are made between the panels and the appearance of staining on the exposed interpalpebral conjunctiva and cornea of the patient. The details of the chart are presented in Figure 1 and, in a simplified form in Figure 4 (where the criteria, dot count and log columns are not displayed), in the following literature article: Bron A, Evans V, Smith, J. Grading of corneal and conjunctival staining in the context of other dry eye tests. <i>Cornea</i>. 2003;22(7):640-650.  The modified Oxford scale is as above, but with the first grade depiction (Grade 0), termed 'Grade 0.5'.  A list of equivalent scales to the Oxford scale is not provided. Prescribers should be satisfied that a scale other than the Oxford scale, if used, is equivalent to the Oxford scale.  The Ocular Surface Disease Index (OSDI) is a 12-item questionnaire created by the Outcomes Research Group at Allergan Inc, Irvine, CA, USA, to assess dry eye symptoms and the effects on vision-related function.  The questionnaire has 3 subscales: ocular symptoms, vision-related function, and environmental triggers. Patients rate their responses on a 0 to 4 scale with 0 corresponding to 'none of the time' and 4 corresponding to 'all of the time'. A final score is calculated which ranges from 0 to 100 with scores 0 to 12 representing normal, 13 to 22 representing mild dry eye disease, 23 to 32 representing moderate dry eye disease, and greater than 33 representing severe dry eye disease.  The OSDI questionnaire asks the following:  Presence of ocular symptoms - Have you experienced any of the following during the last week?  1. Eyes that are sensitive to light  2. Eyes that feel gritty  3. Painful or sore eyes  4. Blurred vision  5. Poor vision  Impact on daily activities - Have you had problems with your eyes limited you in performing any of the following during the last week?  1. Reading  2. Driving at night  3. Working with a computer or bank machine (ATM)  4. Watching TV</p>

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	<p>Environmental factors - Have your eyes felt uncomfortable in any of the following situations during the last week?</p> <ol style="list-style-type: none"> <li>1. Windy conditions</li> <li>2. Places or areas with low humidity (very dry)</li> <li>3. Areas that are airconditioned</li> </ol> <p>Rate responses on a scale of 0 to 4; 0 = none of the time, 1 = some of the time, 2 = half of the time, 3 = most of the time, and 4 = all of the time.</p> <p>Further information on this index is in the following literature article: Walt J, Rowe M, Stern K. Evaluating the functional impact of dry eye: the Ocular Surface Disease Index. Drug Information Journal. 1997;31:1436</p> <p>The 'Dry Eye OSDI 'Questionnaire' app developed by Allergan Inc is available to download for iPhone.</p> <p>If the maximum number of repeats stated in this listing is not requested in this application, further supplies can be obtained through this treatment phase listing to continue treatment for up to the first 180 days of treatment, but the OSDI score and CFS grade need not be re-stated. Alternatively, treatment may be continued under the 'Continuing treatment' phase listing, provided the patient meets all eligibility criteria specified in that treatment phase listing.</p>
<b>Administrative Advice</b>	<p>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a>) or by telephone by contacting Services Australia on 1800 888 333.</p>

<b>Category / Program</b>	GENERAL - General Schedule (Code GE)
<b>Prescriber Type(s)</b>	Medical Practitioners, Optometrist
<b>PBS Indication</b>	Chronic severe dry eye disease with keratitis
<b>Treatment phase</b>	Continuing treatment
<b>Restriction Level / Method</b>	Authority required
<b>Treatment criteria</b>	<p>Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist; or</p> <p>Must be treated by an optometrist in accordance with Optometry Board of Australia guidelines</p>
<b>Clinical criteria</b>	<p>Patient must have received PBS-subsidised treatment with this drug for this condition</p> <p>AND</p> <p>The condition must have improved to an extent that corneal fluorescein staining, using the same scale used at the time of the first authority application, shows an improvement (reduction) by at least 3 grades from baseline (the grade stated in the first authority application) - the improvement need only be demonstrated by staining once only with the first Continuing treatment authority application</p> <p>AND</p> <p>The condition must have improved to an extent that the patient's ocular surface disease index score at the time of this authority application, has improved (reduced) by at least 30% compared to the value stated in the first authority application (i.e. baseline)</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition.</p>
<b>Prescriber Instructions</b>	<p>Prescribing instructions:</p> <p>State in the first continuing treatment authority application for this drug:</p> <p>(i) an improved corneal fluorescein staining grade (a numerical value that has improved by 3 grades from that provided in the first Initial 1 treatment authority application).</p> <p>State in all continuing treatment authority applications:</p> <p>(ii) the ocular surface disease index score at the time of this authority application (a numerical value that is at least 30% lower than that stated in the first Initial 1 treatment authority application).</p>
<b>Cautions</b>	<p>It is recommended that the potential for immunosuppression with long term use of this drug be clinically reviewed after at least 24 months of treatment, if not already reviewed.</p>

- 8.2 Flow on changes to 0.1% ciclosporin restriction to include treatment criteria, “The treatment must be the sole PBS-subsidised therapy for this condition.”

***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**

The sponsor had no comment.