NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Ciclosporin for treating dry eye disease ID665

Dear Frederic

The Evidence Review Group, Liverpool Reviews and Implementation Group (LRiG), and the technical team at NICE have now had an opportunity to take a look at the submission received on 13 January 2015 by Santen. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm**, **Thursday 19 February**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Pilar Pinilla-Dominguez, Technical Lead (pilar.pinilla-dominguez@nice.org.uk). Any procedural questions should be addressed to Lori Farrar, Project Manager (Lori.Farrar@nice.org.uk) in the first instance.

Yours sincerely

Frances Sutcliffe
Associate Director – Appraisals
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Section A: Clarification on effectiveness data

Literature searching:

A1. **Priority question: Previously published systematic reviews.** Two systematic reviews by Sacchetti 2014 [British Journal of Ophthalmology; 98(8):1016-22] and Zhou 2014 [Cornea; 33(7):760-7] have been recently published. In total, these two reviews included 20 RCTs.

i. Please clarify if the company's search identified these systematic reviews.
ii. Please clarify if the company considered the studies included in these reviews for inclusion.
iii. Please provide the rationale for the exclusion of each trial included in these reviews in Table A1 below.

Table A1: Ciclosporin trials excluded from evidence synthesis in company's submission

Study	Source	Reason for exclusion
Altiparmak 2010	Eye; 24:1044-50 [Erratum appears in 26(12):1602]	
Baiza-Duran 2010	British Journal of Ophthalmology; 94:1312-5	
Chen 2010	Journal of Ocular Pharmacology & Therapeutics; 26:361-6	
Demiryay 2011	Eye and Contact Lens; 37:312-5	
Gündüz 1994	Acta Ophthalmologica; 72:438-42	
Guzey 2009	Clinical & Experimental Ophthalmology; 37:541-9	
Jain 2007	Annals Of Ophthalmology; 39:19-25	
Kim 2009	American Journal of Ophthalmology; 147:206-13.e3	
Laibovitz 1993	Cornea; 12:315-23	
Liew 2012	Ophthalmology; 119:1328-35	
Moon 2007	Korean Journal of Ophthalmology; 21:189-94	
Rao 2010	Journal of Ocular Pharmacology & Therapeutics; 26:157-64	
Rao 2011	Journal of Ocular Pharmacology & Therapeutics; 27:603-9	
Salib 2006	Journal of Cataract & Refractive Surgery; 32:772-8	
Sall 2000	Ophthalmology; 107:631-9 [Erratum appears in 107(7):1220]	
Sall 2006	Eye and Contact Lens; 32:21-6	
Schrell 2012	Klinische Monatsblatter fur Augenheilkunde; 229:548-53	
Stevenson 2000	Ophthalmology; 107:967-74	
Su 2011	Cornea; 30:1098-104	
Willen 2008	Eye and Contact Lens; 34:43-5.	

A2. Please clarify whether you have tried to contact the authors regarding the findings of the ongoing systematic review currently being conducted on behalf of the Cochrane Collaboration (protocol available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010051/abstract).

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A3. Pages 39 and 221 of the company's submission appear to imply only part of the Cochrane Library was searched (i.e. CENTRAL). Please confirm if this was the case and if so, clarify why the whole of the Cochrane Library was not searched.

Clinical-effectiveness data:

A4. **Priority question: Ciclosporin (Ikervis) formulation.** The company's submission notes that different formulations of ciclosporin in olive or castor oil exist and these may be administered up to four times daily.

i. Notwithstanding reasons for exclusion (see response to question A1), does the company consider that data from trials of different formulations and from different manufacturers of these ciclosporin formulations can be pooled?
ii. Please clarify why a once-daily oil-in water dose of 0.1% was the preferred formulation for Ikervis in the SANSIKA and SICCANOVE trials.
iii. Please clarify whether, in terms of its consistency, the Ikervis eye drop is similar to Restasis rather than Optimmune, i.e. is more liquid based than ointment/gel based.
iv. Please clarify why cetalkonium chloride (CKC) was preferred to benzalkonium chloride (BAK) as the excipient for Ikervis in SANSIKA.
v. Please clarify whether, as a consequence of using different excipients in the two trials, the Ikervis formulation in each trial should be considered to be similar or not.

A5. **Priority question: Relevant trials in the company's submission:** Table B2 of the company's submission lists 31 relevant RCTs, six of which included ciclosporin (and five of these six included a comparison of ciclosporin to vehicle).

i. Please clarify whether the company considers the comparator treatments in all studies in which a comparator arm is a vehicle to be of equal efficacy or whether vehicles may be considered to differ across studies.
ii. Only SANSIKA and SICCANOVE are considered to be "pivotal" or "supportive" and are used to derive evidence that is presented in the company's submission. Please provide a rationale for the exclusion of the other four trials which studied ciclosporin (Kim 2009, ORA 2009, Sall 2000 and Stevenson 2000).
iii. Figure B1 shows that 29 studies have been excluded because of "outcomes". Guidance recommends that studies are not excluded for this reason because of selective reporting (the outcome may have been measured but not reported). Please clarify if there were other reasons to support the exclusion of these studies.

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A6. Please clarify whether data were collected on whether patients had aqueous-deficient or evaporative dry eye disease (DED) in the SANSIKA and SICCANOVE trials? If so, please present the proportion of patients with each type of DED by treatment arm for both trials individually.

A7. Table B6 of the company's submission states a secondary outcome for SANSIKA was "CFS improvement ≥2 points and global ocular discomfort improvement (VAS) ≥30%". However, this outcome does not appear to be reported in the company's submission or clinical study report. Please could you clarify this discrepancy?

A8. Page 86 of the company's submission states that in SICCANOVE, "the rate of CFS-OSDI responders in the targeted population (patients with CFS grade 4 and OSDI ≥30%) was 5.6% with the vehicle and 30.8% with NOVA22007 (one drop per day), after 6 months of treatment." However, according to Table B6, CFS-OSDI response was not reported to be a primary or secondary outcome in SICCANOVE. Please could you clarify this discrepancy?

Meta-analysis:

A9. Page 139 of the company's submission describes a "pre-specified meta-analysis of the SICCANOVE and SANSIKA studies" but on page 102, results are presented only for patients with Sjögren syndrome (SS). Please provide more information on this pre-specified meta-analysis, in particular:

i. When was this analysis pre-specified?
ii. Was a fixed or random effects model used?
iii. Please provide the results from this meta-analysis.
iv. Please provide similar meta-analyses (in a table and forest plot similar to Table B14 and Figure B4 of the company's submission) for ALL FAS and Severe FAS patients without SS.
v. Please also provide similar meta-analyses (in a table and forest plot similar to Table B14 and Figure B4 of the company's submission) for ALL FAS and Severe FAS patients overall (i.e. with and without SS).

A10. There appear to be discrepancies in the presentation and/or interpretation of the evidence presented by the meta-analysis:

i. In Table B14, the data in the vehicle arm for SICCANOVE are identical to that for SANSIKA. Please clarify if this is correct or amend accordingly.
ii. Page 103 of the company's submission states: "There was no difference observed when analysing the Sjögren severe set in the severe FAS data as detailed in Table B15 below." However, the p-value in Table B15 is presented as 0.028 implying that there was a statistically significant difference. Please could you clarify this discrepancy?
iii. Please provide a forest plot for the findings reported in Table B15 (similar to Figure B4).

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Safety data:

A11. Page 133 of the company's submission states that safety data were pooled. Please could you clarify whether you conducted a meta-analysis when pooling the safety data?

A12. There appears to be discrepancies in the presentation of the safety data in Table B21. For example, the frequency of meibomianitis and lacrimal disorder in SICCANOVE (reported on page 135) exceed the number of pooled events for meibomianitis and lacrimal disorder reported in Table B21. Please could you clarify this?

A13. Serious adverse events (SAEs) are reported on page 136 of the company's submission for both SANSIKA and SICCANOVE. Please clarify how many SAEs were in each treatment arm in each trial. Please also clarify if the SAE that was considered to be definitely related to the study drug in SICCANOVE was in the ciclosporin or vehicle arm.

A14. Alongside SAEs, severe AEs are also described in the company's submission.

i. Please clarify the difference between a SAE and severe AE.
ii. Severe ocular AEs are reported for SICCANOVE on page 135 of the company's submission and severe AEs reported for the second phase of SANSIKA on page 137 but similar data are not reported for the first phase of SANSIKA. Please clarify and report these data if available.
iii. Page 138 states "with the change from the BAK formulation to the CKC formulation, ocular AEs decreased in severity from 27.5% to 6.2%." Please clarify what these proportions relate to (e.g. do they relate to an incidence of severe AEs and if so, in which population? Are they some type of measure of severity intensity?).

A15. Please could you provide further details on the difference between treatment emergent adverse events and treatment related adverse events (section 6.6 of the company's submission)?

Health-related quality of life data:

A16. Page 78 of the company's submission states that EQ-5D was used in SANSIKA to estimate health utility values. Please could you clarify which tariff you used when estimating the EQ-5D utility values?

Section B: Clarification on cost-effectiveness data

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Questions B1-B5 have been asked in order to check the validation of key issues in the economic model.

B1. **Priority question: Age/Sex Distribution.** Please provide a breakdown of patient numbers at baseline for all patients in the SANSIKA trial (Part 1) by Age in 5 year age bands and by Sex as follows:

Age band	Males	Females
20-24	m_1	f_1
25-29	m_2	f_2
30-34	m_3	f_3
35-39	m_4	f_4
….	…	…
….	…	…
85-89	…	…
90+	…	…
Totals		

B2. **Priority question: Mean EQ-5D scores at Baseline by Age & Sex.** Please provide an analysis of baseline EQ-5D utility values in the SANSIKA trial, analysed by 5 year age-bands and sex as in the sample table below. EQ-5D utility values should be estimated using the UK valuation social tariff (Dolan et al 1997, CHE Discussion Paper 138), and relate only to patients completing all 5 dimensions of the questionnaire (i.e. no imputation of missing values).

Age band	Males			Females		
	N	Mean	St devn	N	Mean	St devn
20-24						
25-29						
30-34						
35-39						
….	…			…		
….	…			…		
85-89	…			…		
90+	…			…		
Totals						

B3. **Priority question: Mean EQ-5D results by Response.** Please provide a revised and extended version of Table B33 in the company's submission (as per Table B1 and Table B2 below). Only patients with valid EQ-5D responses to all 5 dimensions at baseline and at 6 months should be included. EQ-5D utility values should be estimated using the UK valuation social tariff (Dolan et al 1997, CHE Discussion Paper 138), and utility increments (6 months – baseline) should be calculated pairwise for each patient.

Table B1: Definition of response in SANSIKA (primary endpoint)

	Responders	Non-responders
Patient numbers	N_1	N_2
Mean EQ-5D utility score at baseline	Q_1	Q_2

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Mean EQ-5D utility score at 6 months	R_1	R_2
Mean EQ-5D utility change (6 months–baseline)	$X_1 = R_1 - Q_1$	$X_2 = R_2 – Q_2$
Standard deviation of estimated utility change	D_1	D_2
Standard error of estimated utility change	E_1	E_2
Attributable difference in utility change: Mean	$M_{12} = X_1 - X_2$	
Standard deviation	$SD(M_{12})$	
Standard error	$SE(M_{12})$	

Table B2: Post-hoc definition of response in SANSIKA

	Responders	**Non-responders**
Patient numbers	N_1	N_2
Mean EQ-5D utility score at baseline	Q_1	Q_2
Mean EQ-5D utility score at 6 months	R_1	R_2
Mean EQ-5D utility change (6 months–baseline)	$X_1 = R_1 - Q_1$	$X_2 = R_2 – Q_2$
Standard deviation of estimated utility change	D_1	D_2
Standard error of estimated utility change	E_1	E_2
Attributable difference in utility change: Mean	$M_{12} = X_1 - X_2$	
Standard deviation	$SD(M_{12})$	
Standard error	$SE(M_{12})$	

B4. **Priority question: Treatment Discontinuation**. Please provide results of Kaplan-Meier analyses of the FAS data set from the SANSIKA clinical trial for Time to Treatment Discontinuation as follows:

i. For patients in the Ikervis arm, including time on allocated treatment from baseline to the end of Part 2 of the trial.

ii. For patients in the Vehicle arm, including time on allocated treatment in Part 1 of the trial only.

iii. For patients in the Vehicle arm, including time on Ikervis in Part 2 of the trial, beginning at the start of Part 2.

Patients withdrawing from the study, lost to follow-up or dying should be censored at the time of withdrawal/loss to follow-up/death.

All the above results should be provided in tabular form (see example from SAS below) showing for each event time:

- time of event from baseline (days)
- product-limit estimate of survival proportion
- standard error of survival proportion
- number of patients failed

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- number of patients remaining at risk

Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

B5. **Priority question: Response rate definition.** Please provide a table of response rates from SANSIKA clinical trial for all the response rate definitions in the following table.

Response definition	**Ikervis response at 3 months**	**Vehicle response at 3 months**	**Ikervis response at 6 months**	**Vehicle response 6 months**
CFS better by 4, OSDI change ≥ -30%	%	%	%	%
CFS better by 3, OSDI change ≥ -30%	%	%	%	%
CFS better by 2, OSDI change ≥ -30%	%	%	%	%
CFS better by 1, OSDI change ≥ -30%	%	%	%	%
CFS unchanged, OSDI change ≥ -30%	%	%	%	%

B6. The company reports that a systematic review carried out by the Cochrane collaboration found limited evidence on the efficacy of punctual plugs (company's submission, page 154). Please provide a reference for this publication.

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B7. There appears to be some inconsistency in the marking of confidential data in Table B41 and that in Table B46 in the company's submission. Please could you clarify these discrepancies?

B8. Figures in Table B44 appear to not compute. Please could you clarify this?

Section C: Textual clarifications, references and additional points

The ERG appreciates that the company has provided cited references on a separate disk. However, in addition:

C1. **Priority request:** On page 51 of the company's submission it is stated that a full systematic review report is available on request. Please could you provide this?

C2. **Priority request:** Please also provide the full documents for the trial protocols and statistical analysis plans for SANSIKA and SICCANOVE.

C3. Not all references listed in the company's submission from page 210 onwards have an accompanying PDF/Word document. Please provide the relevant documents for the following reference:

34. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. American Journal of Ophthalmology. [http://dx.doi.org/10.1016/S0002-9394%2803%2900218-6]. 2003;136(2):01.

C4. In addition to the query raised in B6, a number of other references are cited throughout the company's submission without either the full citation or PDF/Word document provided. Please provide these for the following:

Stern 1998 (see page 21 of company's submission)

Nicols 2011 (see page 21 of company's submission)

National Health Service 2008 (see page 24 of company's submission)

National Health Service 2014 (see page 24 of company's submission)

Nichols (see page 78 of company's submission)

Rajagopalan (referred to numerous times, e.g. page 79 of company's submission)

EMEA/CHMP/SAWP/445808/2006 (see page 91 of company's submission)

McDonald 2010 (see page 165 of company's submission)

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Koffler 2010 (see page 165 of company's submission)

Rajagopalan 2005 (see page 165 of company's submission)

Mertzanis 2005 (see page 165 of company's submission)

Data on file (see page 206 of company's submission)

C5. **Priority Question**: please provide a copy of the EPAR. If the EPAR is not yet finalised please provide the draft version.