

Clinical Commissioning Policy Statement

Serum eye drops for the treatment of severe ocular surface disease (all ages) [200401P]

Commissioning Position

Summary

Serum eye drops are recommended to be available as a treatment option through routine commissioning for severe ocular surface disease within the criteria set out in this document.

Information about serum eye drops

The intervention

Serum eye drops (SED) contain a large number of factors that are present in tears, providing a nutritional tear film substitute that possesses biological properties that promote ocular surface renewal, immunological defence and restore tear film homeostasis. SED are currently the only nutritional tear film substitute available in the UK that possess both lubricating and nutrient properties. SED have been produced exclusively by NHS Blood and Transplant Tissue Services since 2002. Traditionally, SED have been produced from a patient's own blood (autologous) but more recently they have also been produced from healthy volunteer donors (allogeneic). Allogeneic SED make this intervention available to patients who require immediate treatment or who are unable to give blood. The SEDs are a Medicines and Healthcare Products Regulatory Agency (MHRA) regulated unlicensed hospital special medicine.

Committee discussion

The Clinical Panel considered that the evidence base supported the proposition.

Clinical Priorities Advisory Group members considered the proposition and supporting documentation.

See the committee papers ([link](#)) for full details of the evidence.

The condition

Ocular surface disease (OSD) is a global public-health problem affecting up to 20% of the population with significant debilitating symptoms including constant pain, grittiness and soreness that the patients experiences day and night that impact on quality-of-life. The ocular surface is the area that extends from the eyelid margin to the cornea and comprises the cornea, conjunctiva, lacrimal gland, meibomian gland, eyelid and tears. The tear film acts as the outer scaffold of the ocular surface (apical mucosa), it creates a smooth refractive surface to enable sight and provides lubrication, physical protection, immunological defence and nutrition to the ocular surface. OSD can be caused by conditions that lead to alteration in the production, composition, or distribution of the tear film. This includes many conditions, such as Sjögren's syndrome-related dry eye, other immune-related dry eye (such as ocular mucous membrane pemphigoid, Stevens–Johnson syndrome, graft-vs-host disease, and ulcerative keratitis), neurotrophic cornea, injury (mechanical, chemical, thermal, and surgery), and stem cell failure. The most severe manifestations of OSD can lead to blinding complications.

Dry eye disease can occur secondary to many of the conditions that cause OSD. It is defined as a multifactorial disease of the ocular surface characterised by a lack 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. Simply, dry eye disease arises when the protective layer of tears that covers the ocular

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surface becomes dysfunctional. There are approximately 1000 patients currently receiving treatment and an expected incidence of 4.5 per million.

This policy proposes the use of SED for: the treatment of OSD refractory to conventional therapy; acute management of ocular surface injury (chemical, mechanical, thermal, immunological); supportive therapy for specialised ocular surface surgical procedures; and specific clinical indications (inherited OSD, recurrent corneal erosions syndrome, persistent epithelial defects, limbal epithelial stem cell failure, corneal neuropathic pain).

Current treatments

There are many options for the treatment of OSD which vary dependent on the patient presentation, these include: dietary modifications, artificial tears, lubricants, punctal occlusion devices, moisture chamber devices, therapeutic contact lenses, and prescription drugs, such as topical antibiotics, corticosteroids, secretagogues or immunomodulatory drugs. The aim of most treatments is to stimulate, replace or conserve tears or to reduce underlying inflammation. Commercially available artificial tears alleviate biomechanical trauma caused by dry eye states. However, it is hard to pharmacologically replicate the composition of natural tears, so they lack biological properties such as nutrients that promote ocular surface renewal and proteins that assist immunological defence. Frequent application of artificial tears has also been shown to cause toxicity and allergic reactions. Similarly, lubricants that have improved ocular surface retention and can promote epithelial proliferation, lack the chemical composition of tears, and patients remain symptomatic. These treatments are limited in their capacity as biological tear substitutes because they lack either the required nutrient or lubricant properties.

SED are a well-established current treatment for patients with severe OSD refractory to conventional therapy.

Comparators

There are no alternative treatments for patients with severe OSD refractory to conventional therapy. Patients may continue treatment with ineffective conventional therapies or may require escalation to surgical interventions.

Clinical trial evidence

Three papers were identified and considered during the development of the policy.

Paper 1: Pan et al, 2017

Autologous serum eye drops for dry eye

Pan et al (2017) conducted a systematic review to evaluate the efficacy and safety of autologous SED given alone or in combination with artificial tears as compared with artificial tears alone, saline, placebo, or no treatment for adults with dry eye. The search was carried out for all relevant literature published up to 5th July 2016. Five eligible randomised controlled trials (RCTs), containing 92 participants, were identified. These trials compared autologous SED versus artificial tears or saline in individuals with dry eye of various origins (Sjögren's syndrome-related dry eye, non-Sjögren's syndrome dry eye, and postoperative dry eye induced by laser-assisted *in situ* keratomileusis (LASIK)).

Three trials compared autologous SED with artificial tears; however, only one trial reported quantitative data for analysis. Low-certainty evidence from one trial suggested that autologous SED might provide some improvement in participant-reported symptoms compared with artificial tears after two weeks of treatment; the mean difference in mean change in symptom score measured on a visual analogue scale (range 0 to 100, with higher scores representing worse symptoms) was -12.0 (95% confidence interval (CI) -20.16 to -3.84; 20 participants). This same trial found mixed results with respect to ocular surface outcomes; the mean difference in mean change in scores between autologous SED and artificial tears was -0.9 (95%CI -1.47 to -0.33; 20 participants; low-certainty evidence) for fluorescein staining and -2.2 (95%CI -2.73 to -1.67; 20 participants; low-certainty evidence) for Rose Bengal staining. Both staining scales range

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from 0 to 9, with higher scores indicating worse results. The mean change in tear film break-up time was 2.00 seconds longer (95% CI 0.99 to 3.01; 20 participants; low-certainty evidence) in the autologous SED group than in the artificial tears group. Investigators reported no clinically meaningful differences in Schirmer's test scores between groups (mean difference -0.40 mm, 95% CI -2.91 to 2.11; 20 participants; low-certainty evidence). None of these three trials reported tear hyperosmolarity and adverse events.

Two trials compared autologous SED versus saline; however, only one trial reported quantitative data for analysis of only one outcome (Rose Bengal staining). Trial investigators of the two studies reported no differences in symptom scores, fluorescein staining scores, tear film breakup times, or Schirmer's test scores between groups at two to four weeks' follow-up. Very low-certainty evidence from one trial suggested that autologous SED might provide some improvement in Rose Bengal staining scores compared with saline after four weeks of treatment; the mean difference in Rose Bengal staining score (range from 0 to 9, with higher scores showing worse results) was -0.60 (95% CI -1.11 to -0.09; 35 participants). Neither trial reported tear hyperosmolarity outcomes.

Paper 2: Franchini et al, 2019

Serum eye drops for the treatment of ocular surface diseases: a systematic review and meta-analysis

Franchini et al (2019) carried out a systematic search of the literature to evaluate the use of SED in ocular surface disorders. 19 RCTs were included, investigating the use of SED in 729 patients compared to controls. For the quantitative synthesis, 10 RCTs were included, which were conducted in patients with dry eye syndrome comparing autologous SED to artificial tears.

At 2-6 weeks, no clear between-group differences in Schirmer test (MD 1.05; 95% CI: -0.17-2.26) and in fluorescein staining (MD -0.61; 95% CI: -1.50-0.28) were found (very low-quality evidence, down-graded for inconsistency, serious risk of biases, and serious imprecision). Slightly higher increase in tear film break-up time (TBUT) scores in autologous SED compared to control (MD 2.68; 95% CI: 1.33-4.03), and greater decrease in ocular surface disease index (OSDI) in autologous serum compared to control (MD -11.17; 95% CI: -16.58 - -5.77) were found (low quality evidence, down-graded for serious risk of bias, and for inconsistency). For the Schirmer test, fluorescein staining and TBUT, data were also available at additional follow-up timing (2-12 months): no clear between-group differences were found, and the quality of the evidence was graded as low/very-low.

Paper 3: Noble et al, 2004

Comparison of autologous serum eye drops with conventional therapy in a randomised controlled crossover trial for ocular surface disease

Noble et al (2004) carried out a prospective randomised crossover trial in north east England to compare the efficacy of autologous SED against conventional treatment in ocular surface disorders refractory to normal treatments. Patients fulfilling ophthalmological and haematological entry criteria were randomised to either 3 months of autologous SED 50% followed by 3 months of their conventional treatment, or 3 months of conventional treatment, followed by 3 months of autologous SED. Clinical assessments, including Schirmer's test, rose Bengal, and fluorescein staining, were carried out on entry and at monthly intervals. Impression cytology was performed at entry, 3 and 6 months. Grading was carried out on degrees of squamous metaplasia and goblet cell density. Subjective comfort was recorded daily using the "faces" scale. These categorical scores were converted to linear measurement using Rasch analysis. Statistical analysis was carried out using Wilcoxon's signed rank test and ANOVA.

16 patients were recruited with 31 eyes studied. The ocular surface diseases chiefly included Sjögren's syndrome (n = 6) and keratoconjunctivitis sicca (n = 5). Impression cytology available in 25 of 31 eyes showed significant improvement on SED treatment, $p < 0.02$. Rasch weighted faces scores were statistically significantly better with SED, $p < 0.01$.

Adverse events

One trial included in Pan et al (2017) reported adverse events; 2 of 12 participants had signs of conjunctivitis with negative culture that did resolve. No patients in the Noble et al (2004) trial experienced any adverse events or secondary infections related to SED treatment. Other trials did not report outcomes for adverse events.

Implementation

Criteria

Eligibility criteria

Patients of all ages* will be eligible to receive autologous SED if they have any of the following¹:

- **Severe ocular surface disease:** most common in Sjögren's syndrome (both primary and secondary to rheumatic diseases typically rheumatoid arthritis and systemic lupus erythematosus), acute or chronic immunobullous disorders usually ocular mucous membrane pemphigoid, Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, or Graft-versus-Host Disease.
- **Persistent and recurrent corneal epithelial defects:** caused by dry eye disease, as well as other inflammatory ocular surface conditions, commonly severe allergic eye disease, following corneal infections, limbal epithelial stem cell failure and neurotrophic keratitis. Defects must be present and persistent for >6 weeks duration refractory or partially responsive to all other appropriate licensed pharmacological interventions, outpatient or surgical procedures including medical or surgical tarsorrhaphy been used with no or an incomplete response. (**Neurotrophic keratitis** may be congenital, secondary to diabetic autonomic neuropathy, herpes zoster ophthalmicus, Vth cranial nerve tumours, and surgery leading to corneal anaesthesia with a persistent epithelial defect).
- **Supportive therapy:** for ocular surface reconstruction, patients in an intensive care setting with acute exposure keratopathy or toxic epidermal necrolysis, and those presenting acutely with severe ocular surface injury such as chemical, thermal, radiation or immunological injury including graft versus-host disease. Specialised ocular surface reconstruction is defined as reconstruction and replacement of the ocular surface with either or both human tissue or synthetic constructs).

*some patients may be too young to donate sufficient blood to create autologous serum eye drops - see below re restrictions for autologous serum eye drops.

In addition:

- Patients must be refractory or partially responsive to appropriate licensed pharmacological interventions, outpatient or surgical procedures including therapeutic contact lenses listed in Annex A
- Where early urgent intervention is required (chemical, mechanical, immunological injury) or scheduled intervention (supportive therapy for surgical intervention) treatment with serum eye drops may be considered earlier (see below re use of allogeneic SED).

¹ Rauz S, Koay S, Foot B, Kaye SB, Figueiredo F, Burdon MA, Dancey E, Chandrasekar A, Lomas R. The Royal College of Ophthalmologists Guidelines on serum eye drops for the treatment of severe ocular surface disease (Full Report) - *Eye (Lond)* Epub 2017 Nov 17. doi:10.1038/eye.2017.209

Starting criteria

All patients should meet clinically defined severity criteria according to the primary disease process and the doctor responsible for the management of the patient should have considered other available reversible causes/contributory factors and available treatment options.

Guidance scoring for disease severity. Any one of the following:

- Persistent ocular surface symptoms for > 1 year with a minimum ocular surface disease index score of >33
- Persistent epithelial defect unresponsive to standard treatment after 6 weeks
- Patients requiring acute supportive therapy for the indications outlined in eligibility criteria
- Abnormal corneal nerves using confocal microscopy in patients with corneal neuropathic pain
- Staining score of one of the following:
 - Van Bijsterveld score = 8-9
 - Ocular Surface Staining Score = 9-12
 - Oxford Staining Score = 11-15.

Allogeneic SED is recommended in patients:

- Who are unable to donate one unit of blood for the production of SED.
- Who require urgent treatment and the delay in production of the Auto-SED could have a negative impact on the clinical outcome of the patient e.g. acute chemical or immunological injury, or as supportive therapy for surgical interventions including ocular surface reconstruction, or acute presentations (such as ocular mucous membrane pemphigoid, Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, or Graft-versus-Host Disease).
- Where the composition of the Auto-SEDS may have potentially harmful serum constituents that could lead to severe ocular surface toxicity. E.g. patients with diabetes, immune-mediated diseases, those on cytotoxic drugs or with sepsis and those with underlying immune-mediated diseases such as graft-versus-host disease, acute toxic epidermal necrolysis or mucous membrane pemphigoid.

Dose

Autologous SED and allogeneic SED as a 50% dilution in 0.9% sodium chloride are recommended to be used. Frequency of use depends on individual circumstances. Patients typically initiated on 4-8 times per day and dosing tailored according to clinical response to treatment, up to every 15 minutes.

Monitoring

Patients should be assessed at 6 months to confirm an adequate response is attained for continuation of treatment, with trial of withdrawal of treatment to assess for remission in patients who have responded. Patients will be reviewed again at 1 year of treatment, and annually thereafter.

Stopping criteria

Withdrawal and stopping strategies should be considered in all patients commenced on SED treatment before committing patients to indefinite treatment. For example:

In all patients,

- Review of patients at 6 months to assess response to treatment
- Treatment to be stopped in patients who have no improvement in symptoms at this time
- Withdrawal should be trialled in all patients to assess for remission. Timing of withdrawal of treatment is dependent on patient eligibility category. For example:

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- **In severe ocular surface disease**, withdrawal of therapy for a minimum of 2 weeks up to 6 weeks after 12 months of treatment to define induction of remission and no relapse in ocular surface disease index score or ocular surface staining score.
- For patients with **previous acute ocular surface injury** (chemical, mechanical, thermal or immunological), discontinue treatment for 6 weeks after the acute event has resolved.
- For **persistent epithelial defects**, withdrawal of treatment 3 months after complete healing of an epithelial defect.
- In patients with **corneal neuropathic pain**, withdrawal of therapy for a minimum of 6 weeks after 12 months of treatment to define induction of remission by no relapse in ocular surface disease index score.
- Following specialised **ocular surface surgical reconstruction** procedures and supportive serum eye drops, therapy is withdrawn at 12 months post-surgery for 6 weeks.

Patients who have a relapse of symptoms following withdrawal of treatment (as defined in Annex B) will continue to be treated with serum eye drops: re-introduction of treatment can occur prior to end of planned minimum duration of treatment withdrawal if symptoms or signs reoccur.

Effective from

March 2019

Recommendations for data collection

Baseline clinical outcome data recorded should include: clinical indication, type of SED treatment (autologous or allogeneic), patient reported outcomes and the clinical outcome measures listed below. Patients should be followed up for a minimum three months after treatment initiation, 6 months and then annually. Patients must remain under a hospital service whilst on SED treatment. Follow-up outcome measures recorded should include the baseline measures in addition to: the frequency of treatment, duration of treatment, whether treatment has been discontinued, adverse local reactions or events. These data should be recorded and reported through a national registry and audit.

- Patient reported outcomes
 - Either Ocular Surface Disease Index (OSDI) or Dry Eye Questionnaire-5 (DEQ-5)
- Clinical Outcome measures including:
 - Visual acuity
 - Meniscus height
 - Presence of filaments
 - Tear film break-up time
 - Ocular Staining Score
 - Epithelial defect measurements
 - Schirmer's test
 - Confocal microscopy for corneal nerve morphology imaging.

Mechanism for funding

SED for the treatment of OSD within the criteria in this document will be commissioned and funded by NHS England Specialised Commissioning under existing arrangements for the

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provision of Specialised ophthalmology services. All associated activity should be recorded to the following lines:

- NCBPS37Z Ophthalmology (Adults)
- NCBPS23N Ophthalmology (Children).

Policy review date

This is a policy statement, which means that the full process of policy production has been abridged: a full independent evidence review has not been conducted; and public consultation has not been undertaken. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

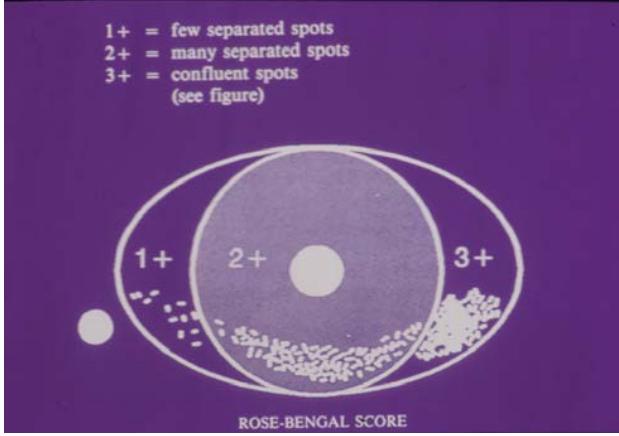
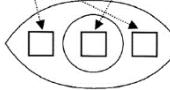
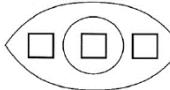
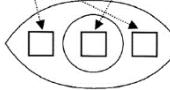
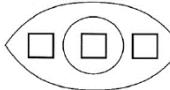
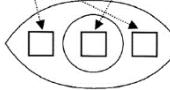
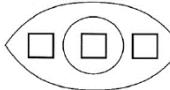
Definitions

Allogeneic	Serum collected from a healthy male donor
Autologous	Serum collected are from the individual
Ocular Surface Disease Index (OSDI)	Developed by the Outcomes Research Group at Allergan Inc. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease: <ul style="list-style-type: none">• normal - 0–12• mild dry eye -13–22• moderate dry eye - 23–32• severe dry eye - 33–100²
Persistent epithelial defect	A non-healing, or persistent, epithelial defect occurs when there is a failure of the mechanisms promoting corneal epithelialisation within the normal two-week time frame ³
Refractory	A disease or condition which does not respond to attempted forms of treatment
Unlicensed	The MHRA, the government body that regulates medicines and medical devices, classifies SED treatment as an unlicensed medicine. This means all licensed medical

² Amparo F, Schaumberg DA, Dana R. Comparison of Two Questionnaires for Dry Eye Symptom Assessment: The Ocular Surface Disease Index and the Symptom Assessment in Dry Eye. *Ophthalmology*. 2015;122(7):1498-503.

³ Shipra Gupta, MD, Pankaj Gupta, MS, MD, and Rony Sayegh, MD, Healing a Persistent Corneal Epithelial Defect 2014

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	<p>options should be considered by the doctor responsible for the patient or have been unsuccessful before they are able to prescribe SED</p>																																																		
<p>Van Bijsterveld score⁴</p>	<p>Is an ocular grading scale scoring the entire cornea and the nasal and temporal conjunctiva using a 0–3 grading system for each of the 3 areas based on increasing staining intensity. 1% Rose Bengal dye is used to stain both the cornea and conjunctiva</p> <div style="text-align: center;"> <p>1+ = few separated spots 2+ = many separated spots 3+ = confluent spots (see figure)</p>  <p>ROSE-BENGAL SCORE</p> </div>																																																		
<p>Ocular Surface Staining (OSS) Score⁵</p>	<p>OSS is the sum of a 0–6 score for fluorescein staining of the cornea and a 0–3 score for lissamine green staining of both nasal and temporal bulbar conjunctivae, yielding a total score ranging from 0 to 12. An abnormal OSS is defined as being a score of 3 or above</p> <div style="text-align: center;"> <p>SICCA Ocular Staining Score</p> <table border="0" style="width: 100%;"> <tr> <td style="width: 50%;"> <p>Right Eye</p> <p>Staining pattern score:</p> <table border="1" style="margin-left: auto; margin-right: auto;"> <tr> <td colspan="2" style="text-align: center;">Lissamine Green (conjunctiva only)</td> <td colspan="2" style="text-align: center;">Fluorescein (cornea only)</td> </tr> <tr> <td style="text-align: center;">Grade</td> <td style="text-align: center;">Dots</td> <td style="text-align: center;">Grade</td> <td style="text-align: center;">Dots</td> </tr> <tr> <td style="text-align: center;">0</td> <td style="text-align: center;">0-9</td> <td style="text-align: center;">0</td> <td style="text-align: center;">0</td> </tr> <tr> <td style="text-align: center;">1</td> <td style="text-align: center;">10-32</td> <td style="text-align: center;">1</td> <td style="text-align: center;">1-5</td> </tr> <tr> <td style="text-align: center;">2</td> <td style="text-align: center;">33-100</td> <td style="text-align: center;">2</td> <td style="text-align: center;">6-30</td> </tr> <tr> <td style="text-align: center;">3</td> <td style="text-align: center;">>100</td> <td style="text-align: center;">3</td> <td style="text-align: center;">>30</td> </tr> </table>  <p>Extra points–fluorescein only: (Mark all that apply and add to fluorescein score)</p> <ul style="list-style-type: none"> <input type="checkbox"/> +1 - patches of confluent staining <input type="checkbox"/> +1 - staining in pupillary area <input type="checkbox"/> +1 - one or more filaments <p>Total Ocular Staining score: <input style="width: 20px; 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<p>Oxford Staining Score⁶</p>	<p>A series of panels, labelled A-E, in order of increasing severity, reproducing the staining patterns encountered in dry eye, are used as a guide to grade the degree of staining seen in the patient. Staining is represented by punctate dots on a series of panels (A-E). Staining ranges from 0-5 for each are of the exposed surface (nasal, centre, temporal)</p>																																																		

⁴ van Bijsterveld OP. (1969). Diagnostic tests in the sicca syndrome. Arch Ophthalmol 82: 10-14.

⁵ Whitcher et al. (2010). A simplified quantitative method for assessing keratoconjunctivitis sicco from Sjogren's Syn from International Registry. Am J Ophthalmol 149:405-415

⁶Bron A, Evans VE, Smith JA. (2003). Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea 22(7): 640-50

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giving a total score ranging from 0-15

PANEL	GRADE	CRITERIA
A	0	Equal to or less than panel A
B	I	Equal to or less than panel B, greater than A
C	II	Equal to or less than panel C, greater than B
D	III	Equal to or less than panel D, greater than C
E	IV	Equal to or less than panel E, greater than D
>E	V	Greater than panel E

Annex A

Refractory or partially responsive Interventions

The interventions are as follows:

- Conservative:
 - Humidifiers
 - lid hygiene
 - moist-chamber goggles
 - All associated eye disease (blepharitis, Meibomianitis, lid malposition, trichiasis, blapharospasm) treatment optimised.
 - Regular, frequent (at least every hour and waking through the night to put in lubricants) high grade non-preserved ocular lubricants without significant relief (hyaluronates, liposomal sprays), and has tried different lubricant preparations.
- Topical anti-inflammatories:
 - non-preserved topical glucocorticoids
 - topical calcineurin inhibitors including Ikervis (ciclosporin 1mg/ml) (NICE TA369 December 2015)
 - Metallomatrix proteinase inhibitors
- Punctal occlusion (i.e., cauterity and/or punctal plugging)
- Where possible, therapeutic contact lenses, amniotic membrane, medical or surgical tarsorrhaphy.

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Annex B

Defining relapse of symptoms and signs following withdrawal of treatment

- Increase in ocular surface disease index by 25% that is refractory or partially responsive to appropriate licensed pharmacological interventions, outpatient or surgical procedures including therapeutic contact lenses with no or an incomplete response.

OR

- Increase of ocular surface staining by 25% refractory or partially responsive to addition of appropriate licensed pharmacological interventions, outpatient or surgical procedures including therapeutic contact lenses with no or an incomplete response.

OR

- Recurrence in epithelial defects of duration >2 weeks not responsive to appropriate licensed pharmacological interventions, outpatient or surgical procedures including therapeutic contact lenses with no or an incomplete response.

OR

- Regression in corneal nerve anatomy as measured by confocal microscopy by 20%.