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Serum Eye Drops for the Treatment of Severe Ocular Surface Disease

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# Introduction

## Ocular Surface Disease and the Tear Film

Ocular surface disease (OSD) is a global public-health problem with significant impact on quality-of-life. The ocular surface is a specialised tissue extending from the mucocutaneous junction at the eyelid margin, into the natural gutter between the eyelid and eyeball (conjunctival fornix), to the limbus (housing the corneal stem cells) and the cornea (the transparent window in front of the eye). It comprises the surface and glandular epithelia of the cornea, conjunctiva, lacrimal gland, as well as the accessory lacrimal glands, meibomian glands, and their apical (tears) and basal (connective tissue) matrices and eyelids.1 All components of the system are linked functionally by continuity of the epithelia, their nerve and blood supply together with the endocrine and immune systems. The outer scaffold of the ocular surface, is the apical matrix, known as the tear film. All regions of the ocular surface epithelia produce constituents of the tear film: the corneal and conjunctival epithelia produce hydrophilic mucins that provide a platform for the aqueous component of the tear film; the lacrimal and accessory lacrimal glands secrete water and protective proteins, immunoglobulins, vitamins and nutrients vital for ocular surface health; and the meibomian gland provides the complex superficial tear lipid layer that prevents tear evaporation. These components not only maintain a smooth refractive surface on the cornea to enable sight, the tear film is critical in providing lubrication, physical protection, immunological defence and nutrition to the ocular surface that is regulated by and closely interacts with the neural, endocrine, vascular, and immune systems.

Failure of one or more of these complex components, result in OSD which in its severest form, may lead to blinding complications. These include chronic inflammation, stem cell failure, ulceration, infection, corneal perforation and scarring. Specifically, conditions that lead to alteration in the production, composition, or distribution of the tear film result in symptoms and signs of damage to the structures of the ocular surface. The consequence is noticeable irritation, reduction of visual function, severe sight-threatening complications such as infection and ocular perforation, and importantly, impairment of quality of life similar to that of severe angina, renal dialysis, and disabling hip fracture.2 A large number of clinical conditions lead to OSD. These conditions include: Sjögren's Syndrome related dry eye, other immune-related dry eye (such as ocular Mucous Membrane Pemphigoid, Stevens-Johnson-Syndrome, Graft Versus Host Disease, and Ulcerative keratitis), neurotrophic cornea, injury (mechanical, chemical, thermal, surgery) and stem cell failure.

## Current Practice

Commercially available artificial tears alleviate biomechanical trauma caused by dry eye disease states, but lack biological properties such as nutrients that promote ocular surface renewal and immunological defence. This is due to difficulty in synthetically replicating the complex nature of the tear-film architecture and chemical composition. Lubricants such as those containing carboxymethylcellulose have improved ocular surface retention and promote epithelial proliferation, whereas sodium hyaluronate preparations exploit the property that it is a ubiquitous naturally occurring extracellular matrix glycosaminoglycan found within the ocular tissues, that plays an important role in wound healing, inflammation and lubrication. Attempts to develop a biological tear substitute that has lubricating and nutrient properties promoting ocular surface renewal and immunological defence have been limited. Isolated reports of single compound topical agents such as Vitamin A, epidermal growth factor (EGF) and albumin have shown some *in vitro* and *in vivo* efficacy, but clinical response is equivocal and long-term clinical applications have not been developed. Current standard treatment is itemised below:

* Environmental advice
	+ Spectacles
	+ Increase humidity
	+ Omega 3 fish oils
	+ Omega 7
	+ Refrain from periocular cosmetics (minimum of 6 weeks trial)
* Non-preserved ocular lubricant eye drops
	+ Hypromellose
	+ Carbomers
	+ Ointments
	+ Hydroxypropylguar
	+ High Concentration Hyaluronate
	+ Hyaluronate with Xanthangum
	+ SoyBean with Phospholipids
* Lubricants with osmoprotectants
	+ Glycerine and L-Carnitine and /or erythritol
	+ (LOC Tears, Allergan Refresh Optive Advanced, Thealoz Duo, Hydramed Drops)
* Lubricants and lipids
	+ Systane Balance, Soothe VP, Emulstil
* Alternative non-preserved lubricants
	+ Non-preserved saline 0.9%
	+ Balanced Salt Solution
* Mucolytics for breakdown of filaments
	+ Acetylcysteine preserved
	+ Acetylcysteine non-preserved (UL-HOP)
* Topical anti-inflammatories
	+ Prednisolone 0.5% SDU 2-3x per day
	+ Dexamethasone 0.1% SDUs
	+ Topical ciclosporin (Optimmune (UL-HOP) veterinary preparation)
	+ Ikervis once daily at night (NICE TA269 December 2015)
* Metallomatrix proteinase inhibitors
	+ Doxycycline 50mg od minimum of 3 months
* Punctal occlusion
	+ Punctal plugs (removable not intracanicular after treating Meibomian gland disease)
	+ Punctal cautery
	+ Surgical closure - wounding and suture closure
* Secretagogues
	+ Oral Pilocarpine max 5mg 4x per day (start with 2.5mg od and build up)
* Contact lenses
	+ Silicone hydrogel contact lenses
	+ Therapeutic rigid gas permeable scleral contact lenses (if Schirmer’s I >5mm)
	+ Prosthetic replacement of the ocular surface ecosystem (PROSE)
* Blepharospasm
	+ Botulinum Toxin
* ‘Topical’ Biologics (currently not licensed in the UK and EU)
	+ NGF 10-20 ug/ml
	+ Lifitegrast 5% £3-500

A guide to tailoring symptoms and signs of dry eye disease stratified according to disease severity level with a hierarchy of suggested treatment for each level of severity has been proposed by the Dry Eye Workshop 2007 and are shown in **Tables 1 and 2** respectively.3 (NB DEWS II will be published during 2017 with a new section on management – this section is subject to change)

Table 1: Symptoms and signs of dry eye stratified according to disease severity\*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Severity Level | 1 | 2 | 3 | 4 |
| Discomfort | Mild +/or episodic; occurs under environmental stress | Moderate episodic or chronic; stress or no stress | Severe frequent or constant without stress | Constant, severe and/or disabling |
| Visual symptoms | None or episodic mild fatigue | Annoying +/or episodic; activity limiting  | Annoying, chronic +/or constant; limiting activity | Constant +/or possibly disabling |
| Conjunctival hyperaemia | None to mild | None to mild | Mild to moderate | Moderate to marked |
| Conjunctival staining | None to mild | Variable | Moderate to marked | Marked |
| Ocular surface staining  | None to mild | Variable | Marked central | Severe punctate erosions |
| Tear film signs and impact on cornea | None to mild | Mild debris, 🡫 meniscus | Filamentary keratitis; mucus clumping; ↑ tear debris | Filamentary keratitis; mucus clumping; ↑ tear debris; ulceration |
| Lid, Meibomian glands, and ocular surface failure\*\* | MGD variably present | MGD variably present | Frequent | Trichiasis, keratinisation, symblepharon |
| TFBUT (s) | Variable | <10 | <5 | Immediate |
| Schirmer’s I score (mm/5 min)† | Variable | <10 | <5 | <2 |

\* adapted from the Dry Eye Workshop 2007

\*\* ocular surface failure is defined as failure of mechanisms responsible for maintaining a healthy ocular surface characterised by persistent epithelial defects, keratinisation of the normally non-keratinised ocular surface epithelium, and progressive conjunctival scarring with formation of symblephara (adhesions tethering the tarsal (eyelid) and bulbar (eyeball) conjunctiva).

†Schirmer’s I rates are defined for strips-stimulated tear production performed without the use of topical anaesthetic.

Table 2: Dry eye severity level and a hierarchy of treatment\*

|  |  |
| --- | --- |
| Severity Level | Treatment |
| 1 | *Initiate conservative treatment*  |
| * Education and environmental/dietary modifications
 |
| * Elimination of offending systemic medications and preservatives
 |
| * Lubricants: drops/ gels/ointments
 |
| * Eye lid therapy
 |
| 2 | *If level 1 treatments are inadequate, add:* |
| * Anti-inflammatories (topical steroids and topical calcineurin inhibitors)
 |
| * Tetracyclines for meibomian gland dysfunction
 |
| * Punctal plugs
 |
| * Secretagogues
 |
| * Moisture chamber spectacles
 |
| 3 | *If level 2 treatments are inadequate, add:* |
| * Permanent punctal occlusion
 |
| * Contact lenses
 |
| * Serum eye drops
 |
| 4 | *If level 3 treatments are inadequate, add:* |
| * Systemic anti-inflammatory agents
 |
| * Surgery
	+ lid surgery: tarsorrhaphy
	+ Transplantation: salivary gland, amniotic membrane
 |

\* adapted from the Dry Eye Workshop 2007

## Serum Eye Drops

### Physiology

Serum eye drops (SED) are an adjunctive treatment for complex, often immune-mediated, OSD where the production and quality of the tear-film has been compromised leading to debilitating symptoms and severe sight-threatening damage of the surface of the eye; or as supportive therapy for surgical procedures or acute injury (chemical, thermal, immunological). Serum contains a large number of epitheliotrophic factors that are present in tears and are likely to be responsible for the therapeutic effects observed in patients with OSD over and above conventional commercially available lubricants. SED provide the only nutritional tear film substitute available in the United Kingdom that possesses biological properties promoting ocular surface renewal and immunological defence and aids therapeutics as well as patient satisfaction and subjective outcomes. This is due to the similarities between the constituents of and the natural (whole) tear film as shown in **Table 3**.

Table 3: Similarities of key constituents in whole tears and serum

|  |  |  |
| --- | --- | --- |
| **Parameter** | **WholeTears** | **Serum**  |
| pH | 7.4 | 7.4 |
| Osmolality | 298 | 296 |
| EGF (ng/ml) | 0.2-3.0 | 0.5 |
| TGF-β(ng/ml)  | 2-10 | 6-33 |
| NGF (pg/ml)  | 468.3 | 54.0 |
| IGF (ng/ml) | 0.31 | 105 |
| PDGF (ng/ml)  | 1.33 | 15.4 |
| Albumin (mg/ml) | 0.023 | 53 |
| Substance P (pg/ml) | 157 | 70.9 |
| Vitamin A (mg/ml) | 0.02 | 46 |
| Lysozyme (mg/ml) | 1.4 | 6 |
| Surface IgA (μg/ml) | 1190 | 2 |
| Fibronectin (μg/ml) | 21 | 205 |
| Lactoferrin (ng/ml) | 1,650 | 266 |

Since the first reported use of auto-SED by Fox in 1984,4 SED have demonstrated to be effective for the treatment of complex dry eye disease secondary to a wide range of clinical conditions causing ocular surface disease (Stevens-Johnson syndrome, Sjögren's syndrome, persistent epithelial defects, graft-versus-host disease, post-LASIK dry eyes, neurotrophic keratopathy, diabetes mellitus, superior limbic keratoconjunctivitis, recurrent corneal erosions, aniridic keratopathy) and supportive therapy for ocular surface reconstruction and stem cell therapy. Demand for the service has been steadily increasing but access to care has been restricted to certain patients in the country. The treatment is reserved for patients who have severe disease that is refractory to standard interventions, or for those who require supportive therapy for specialised ocular surface surgical procedures, or for use in the acute management of ocular surface injury (chemical, mechanical, thermal, immunological).

### Serum Eye Drops Service UK

NHS Blood and Transplant (NHSBT) has been providing a SED service since 2003 and prepares SED from the patient's own blood (Auto-SED) or from male-volunteer blood donors (Allo-SED). SED is an unlicensed medicine that is currently being considered for exclusion from the National Tariff as a High Cost Drug. NHSBT follows strict standard operating procedures. Patients for Auto-SED are required to be of reasonably good health, with no significant cardiovascular or cerebrovascular disease, and free of bacterial infection. Anaemia (Hb <11 g/dl) is a relative contraindication. Allo-SED can be provided for patients who are medically unsuitable to provide an autologous donation. Donations are screened as for hepatitis B and C, HIV I & II, HTLV I & II and syphilis. One full blood donation produces ~up to 150 bottles of SED bottles diluted 50% with saline with a shelf life of 12 months from the date of donation. The majority of the early literature focusses on Auto-SED with recent emergence of interest in Allo-SED. Allo-SED has the advantage of providing treatment if the requirement is immediate or if the patient is unable to donate blood due to their complex medical history (immune-mediated disease, blood cancers, intensive care patients), poor cardiovascular status, anaemia and poor venous access.

### Eligibility Criteria

The patient population eligible for treatment are those with OSD refractory to conventional licensed therapy, those requiring acute management of ocular surface injury and supportive therapy for ocular surface reconstructive procedures.

### Outcome measures

Putative data collection tools for baseline and follow-up for both clinical ([**Appendix 1**](file:///C%3A%5CUsers%5Csaaeha.rauz%5CDocuments%5CMy%20Documents%5COther%20Documents%5CSenLect%5CASE%5CNHSBT%20meet%5CSED%20Guidance%5CSED_draft%5CAppendix%201%20-%20Baseline%20Audit_14052017.docx) **and** [**2**](file:///C%3A%5CUsers%5Csaaeha.rauz%5CDocuments%5CMy%20Documents%5COther%20Documents%5CSenLect%5CASE%5CNHSBT%20meet%5CSED%20Guidance%5CSED_draft%5CAppendix%202%20-%20Follow-up%20Audit_14052017.docx)) and patient-reported outcomes using the OSDI tool ([**Appendix 3**](file:///C%3A%5CUsers%5Csaaeha.rauz%5CDocuments%5CMy%20Documents%5COther%20Documents%5CSenLect%5CASE%5CNHSBT%20meet%5CSED%20Guidance%5CSED_draft%5CAppendix%203%20-%20OSDI_14052017.docx)) and visual analogue scale have been proposed by NHSBT. Interim data analyses (January 2016) of the ocular surface disease index (OSDI) score show a mean reduction in OSDI score of 36%, from 65 (severe) pre-commencement of treatment to 42 (moderate) after 4 months of treatment.

## Population to whom the Guideline applies e.g. the age range, gender, clinical description (ICD10) and co-morbidity (ICD10) and any exclusions

The provision of SED is applicable to any patient with ocular surface disease. Children <16 years of age are provided with non-CJD risk allogeneic serum imported from Europe. Auto-SED is contraindicated in patients who are anaemic, have insufficient venous access, unable to donate the full unit of blood, unable to give consent, and are unconscious or unable to travel to a donor centre. Allo-SED has the advantage of providing treatment if the requirement is immediate or if the patient is unable to donate blood due to their complex medical history (immune-mediated disease, blood cancers, and critical care patients), poor cardiovascular status, anaemia and poor venous access. A diagnostic breakdown of the population who could potentially benefit from SED is given in **Table 4**.

Table 4: Diagnostic categories of the patient population who may require SED

|  |  |  |
| --- | --- | --- |
| Main category | Subcategory | ICD10Barny - To be inserted |
| Sjögren’s-related dry eye | Primary and secondary Sjögren’s Syndrome |  |
| Other immune related dry eye | Ocular Mucous Membrane Pemphigoid |  |
| Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis |  |
| Graft-versus-Host Disease |  |
| Other immune-related dry eye |  |
| Non-immune dry eye | Other non-immune |  |
|  |  |
| Neurotrophic Disease | Diabetic cornea |  |
| Herpetic aetiology |  |
| Dry eye induced neuropathic pain |  |
| Other neuropathic disease including secondary to Surgery, LASIK etc |  |
| Injury and Trauma | Ocular Surface Toxicity |  |
| Chemical |  |
| Thermal |  |
| Mechanical |  |
| Radiation |  |
| Surgical |  |
| Other Trauma |  |
| Exposure Keratopathy | Critical care unit/ high dependency unit/ burns unit |  |
| Thyroid associated ophthalmopathy |  |
| Immune-mediated proptosis |  |
| Non-immune mediated proptosis |  |
| Other exposure keratopathy |  |
| Supportive | Ocular surface reconstruction |  |
| Corneal transplant |  |
| Other supportive |  |
| Inherited ocular surface disease | Aniridia |  |
| Ectodermal dysplasia |  |
| Epidermolysis Bullosa |  |
| Other inherited ocular disease |  |

## Scope for Change

SED is a highly specialised and high cost intervention for patients with ocular surface or corneal conditions including severe anterior segment inflammation refractory to conventional topical therapy5 and other licensed options. There are no nationally accredited criteria for entering the SED programme and there is an absence of robust systems for recording of outcomes or stopping strategies, leading to variation in practice and geographical inequity in access to treatment.

# Objectives

## Aims

This Guidance aims to set out defined criteria for the use of SED, monitoring of clinical and patient-reported outcomes, thereby improving patient morbidity and care.

## The clinical questions covered by the guidelines

1. Are SED more effective at treating patients with ocular surface disease, than conventional treatment?
2. Is there evidence of superiority in the cost and clinical effectiveness of autologous serum eye drops (Auto-SED) versus allogeneic serum eye drops (Allo-SED) at treating patients with ocular surface disease?
3. What effect does dose size have on the effect of treatment with SED for patients with ocular surface disease?
4. What effect does concentration of formulation have on the effect of treatment with SED for patients with ocular surface disease?
5. What effect does duration of treatment have on the effect of treatment with SED for patients with ocular surface disease?
6. What effect does frequency of treatment have on the effect of treatment with SED for patients with ocular surface disease?
7. Which clinical outcome measures best record the treatment effect for monitoring ocular surface disease?
8. Which patient reported outcome measures best record the treatment effect for monitoring impact on patient debility?

## Description of the key stakeholders and end users

### Target Audience:

* + Ophthalmologists (Consultants and SAS doctors) caring for adults and children with OSD in secondary and tertiary care

### **Other Beneficiaries**:

* + Multi-professional teams who have patients with ocular surface manifestations of systemic diseases including Haematologists, Rheumatologists, Neurologists, Dermatologists, General Physicians and General Practitioners who will review patients with ocular surface disease
	+ Healthcare professionals and practitioners such as those working in Intensive Care Medicine, specialist Nurses, Optometrists and Orthoptists.
	+ The guideline should also be of relevance to Specialist Registrars in training and Specialist Nurses.
* Commissioners and providers of services for adults and children with OSD.
* Adults and children with ocular surface diseases and their families and carers.

### Stakeholders:

* Royal College of Ophthalmologists
* Bowman Club
* NHS Blood and Transplant (NHSBT)
* Ocular Tissue Advisory Group (OTAG)
* Serum Eye Drop Patient Support Group
* British Society of Blood and Marrow Transplant (BSBMT)

# Methods

## Methodology

This guideline has been developed in accordance with the Guideline Development Manual of The Royal College of Ophthalmologists (found at RCOphth.ac.uk) following the pre-specified stages to ensure that the recommendations are aligned with the strength of evidence available from the review of the literature.

## Search strategy

Key questions for the guideline were developed using the PICO framework to provide a structured basis for the identifying the evidence. A systematic review of the literature was undertaken using the explicit search strategies devised in collaboration with the Cochrane Eyes and Vision Group. Databases searched include Medline, Embase, and the Cochrane Library for literature published between 1992 & 2017. Further searches were undertaken on various websites including the US National Guidelines Clearinghouse. All search strategies used are shown in [**Appendix 4**](file:///C%3A%5CUsers%5Csaaeha.rauz%5CDocuments%5CMy%20Documents%5COther%20Documents%5CSenLect%5CASE%5CNHSBT%20meet%5CSED%20Guidance%5CSED_draft%5CAppendix%204%20-%20Search%20Strategy_14052017.docx).

The evidence base for this guideline was identified and synthesised in accordance with the accepted methodology with each of the selected papers was evaluated by two members of the group using standard checklists before conclusions were considered as acceptable evidence. The literature search focused on the best available evidence to address the key review questions by including the following types of evidence

* Published guidelines
* Systematic reviews
* Randomised controlled trials
* Cohort and case control studies
* Case series

Papers not published in the English language, conference abstracts and letters were excluded.

## Levels of evidence and Grades of Recommendations

Evidence was graded by the Guideline Development Group according to its strength using the Scottish Intercollegiate Guidelines Network framework (SIGN 50 – **Table 5**). The strength of each recommendation took into account the quality of the evidence.

Table 5: Scottish Intercollegiate Guidelines Network framework (SIGN 50)

|  |  |
| --- | --- |
| **Type of Evidence** | **Description** |
| 1++ | High-quality meta-analyses, systematic reviews of RCTs, or RCTswith a very low risk of bias |
| 1+ | Well-conducted meta-analyses, systematic reviews of RCTs, or RCTswith a low risk of bias |
| 1- | Meta-analyses, systematic reviews of RCTs, or RCTs with a high riskof bias\* |
| 2++ | High-quality systematic reviews of case–control or cohort studiesHigh-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal |
| 2+ | Well-conducted case–control or cohort studies with a low risk ofconfounding, bias or chance and a moderate probability that the relationship is causal |
| 2- | Case–control or cohort studies with a high risk of confounding, bias,or chance and a significant risk that the relationship is not causal |
| 3 | Non-analytic studies (for example, case reports, case series) |
| 4 | Expert opinion, formal consensus |

# Results

## Are SED more effective at treating patients with ocular surface disease, than conventional treatment?

### Scope:

There is wide consensus amongst specialists in ocular surface disease that SED have a role in the treatment of disorders such as severe immune-mediated dry eye disease, persistent and recurrent corneal epithelial defect, neurotrophic keratopathy and patients who require supportive therapy post ocular surface reconstruction. The treatment is reserved for those who are unresponsive or partially responsive to all available licensed conventional therapeutic options. The evidence underpinning the benefit of treating patients with ocular surface disease and whether SEDs are more effective than those on conventional treatment has been reviewed.

### Evidence

A Cochrane review on the use of SED in adults with dry eye was published in 20176 and summarised the results of 5 RCTs (Celebi 2014;7 Kojima 2005;8 Noda-Tsuruya 2006;9 Tananuvat 2001;10 Urzua 201211). They concluded that SED 20% may provide some benefit in improving patient-reported symptoms in the short term (2 weeks), but that there appears to be no evidence of improvement over a longer period. Of note, there was unclear evidence to suggest improvement for objective measures of the ocular surface disease. The authors recommended that further large, high-quality RCTs using standardised questionnaires, objective clinical tests and objective biomarkers are warranted to assess the benefit of SED in the longer term. (Evidence 1++, Positive/Equivocal).

Another systematic review12 evaluated the use of blood derived topical therapy (including SED) in ocular surface disease, concluding that the use of SED in dry eye disease improved OSDI scores, fluorescein staining score and TBUT, as well as reducing concurrent use of topical lubricants. SED also appeared to be effective in the treatment of PED, but study numbers were small. (Evidence 1++, Positive/Equivocal).

Whilst there is paucity of strong supporting evidence, several reviews have reported a trend for superiority of SED in alleviating some of the clinical signs and symptoms in Sjögren’s13 and non- Sjögren’s dry eye disease, limbal epithelial stem cell deficiency, graft-versus-host-disease, persistent epithelial defects, recurrent corneal erosions, post-refractive surgery14 and Stevens-Johnsons syndrome/toxic epidermal necrolysis.15 A double masked RCT in 40 eyes16 demonstrated improved tear film stability and patient comfort with SED, supported by three other case series in 123 eyes of 63 dry eye patients17, 56 eyes of 28 patients18 and in 17 patients with Graft Versus Host Disease19. Improved recovery time from corneal abrasions induced during vitrectomy surgery has also been shown.20

A publication by a panel of North American experts on the management of dry eye in Sjögren’s syndrome21 corroborated the recommendation for the use of serum drops by the 2007 International Management and Therapy Subcommittee of the International Dry Eye Workshop.3 Both publications acknowledged the limited evidence, but recommended their use for severe dry eye unresponsive to conventional measures.

[**Table 6**](#_Tables) shows a summary of all the studies included in the evidence review.

In the United Kingdom, the NHSBT is conducting an evaluation of new patients who are enrolled onto the SED programme. These data, capture baseline and follow up findings that include patient perceptions of their disease using a validated tool for ocular surface disease (OSDI) and clinical findings using a corneal function score (Oxford Ocular Surface Grading System), Tear film break-up time and Schirmer’s test. The results are pending but should provide useful information on the effectiveness of SED amongst patients with ocular surface disease and will form the largest published case series using Auto-SED and Allo-SED.

### Recommendation:

SEDs will benefit patients who:

1. Have refractory or partially responsive ocular surface disease to all licensed indications implemented in a stepwise approach ([see Section 5: Good Practice Points](#_Good_Practice_Points_1)).
2. Have specific clinical indications (recurrent corneal erosions, persistent epithelial defects, limbal epithelial stem cell failure) where additional licensed interventions are available and should be implemented ahead of prescribing serum eye drops.
3. Need early urgent intervention (chemical, mechanical, immunological injury) or scheduled intervention (supportive therapy for surgical intervention) with serum eye drops ([see Section 5: Good Practice Points](#_Good_Practice_Points_1)).

## Is there evidence of superiority in the cost and clinical effectiveness of autologous serum eye drops (Auto-SED) versus allogeneic serum eye drops (Allo-SED) at treating patients with ocular surface disease?

### Scope:

Patients with inflammatory ocular surface disease frequently have systemic manifestations which preclude the ability to donate blood for the production of autologous serum, require Allo-SED. This may be due to general health issues such as patients who have poor venous access and patients who are unable to attend an apheresis/donor centre. Such patients include those patients with poor mobility e.g. multiple sclerosis, rheumatic disease and those in critical care situations.

Patients with underlying immune-mediated disease may have circulating antibodies, growth factors and pro-inflammatory cytokines within their serum that may exacerbate disease if administered topically to the surface of the eye. These patients may benefit from Allo-SED rather than Auto-SED. Patients in this grouping include those with graft-versus-host disease, acute toxic epidermal necrolysis or mucous membrane pemphigoid. The evidence interrogating the superiority and cost-benefit of Allo-SED versus Auto-SED in these situations is evaluated.

### Evidence

There are no studies that have performed a direct comparison of effectiveness of Auto-SED versus Allo-SED in the treatment of ocular surface disease. Lekahnont et al. 22 performed a prospective study of 181 eyes, where 178 were received Auto-SED, and 3 Allo-SED. However, given the large discrepancy in group sizes, this was not felt to be a valid comparison study.

There are also no published studies comparing the direct and indirect cost effectiveness of Auto-SED versus Allo-SED, or studies that determine the impact of the economic benefit or burden of the treatment. In the United Kingdom, the NHSBT provides Auto-SED and Allo-SED at a cost of approximately £1,100 for 3-5 months’ supply (including delivery to the patient’s home address with same day courier).

### Recommendation:

1. Allo-SED is recommended to patients who are unable to donate one unit of blood for the production of SED.
2. Allo-SED is also recommended for patients 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.

## What effect does dose size have on the effect of treatment with SED for patients with ocular surface disease?

### Scope:

SED provide a physiological tear substitute for patients with ocular surface disease with nutritional properties in addition to reduction of biomechanical trauma or friction provided by commercially available substitutes. Published comparisons of serum, plasma and tear components highlight similarities between these biofluids but do not provide ranges to gauge the bio-variability of each constituent within Auto-SED versus the natural tear film. The composition of the Auto-SEDs made from donations from patients with diabetes, immune-mediated diseases, those on cytotoxic drugs or with sepsis will have potentially damaging serum constituents that could lead to severe ocular surface toxicity. The evidence regarding the biological variability of the composition of Auto-/Allo-SED and the dose of each blood constituent that is optimal for a therapeutic effect versus the dose that could lead to ocular surface toxicity, was considered to be important.

### Evidence:

There are no published studies that specifically compare the effects of individual constituents in SED for the treatment of ocular surface disease, including physiological constituents or serum levels of putative toxins.

### Recommendation:

1. Auto-SED should be avoided in patients with uncontrolled diabetes, refractory immune-mediated diseases, those on cytotoxic agents or their bi-products are known to damage proliferating cells (e.g. cyclophosphamide) and patients with sepsis.

## What effect does concentration of formulation have on the effect of treatment with SED for patients with ocular surface disease?

###  Scope:

Published data shows the similarities between tear and serum constituents. Manufacturing process (clotting time, centrifuging, temperature etc) varies from country to country and there appears to be no internationally agreed standard operating procedures for the production of SED. This includes whether it is clinically more effective to treat patients with SED manufactured without dilution and delivered as 100% serum, or if diluted, what is the optimal diluent and concentration to achieve the desired clinical effect.

### Evidence:

Published studies have used varying concentrations of SED: most commonly 20%, followed by 50% and 100%. SEDs are usually diluted with Sodium Chloride 0.9% to achieve the desired final product concentration.

There is only one published study (Cho et al 2013)23 which compared the efficacy of SED with different diluents in patients with dry eyes (Sjögren’s syndrome and non-Sjögren’s syndrome) and persistent epithelial defects. In this study, SED were administered as: 100% serum, 50% serum with 0.9% NaCl, 50% serum with sodium hyaluronate 0.3% or 50% serum with ceftazidime 5%. The authors concluded that 100% SED helped to improve subjective symptoms and objective findings in both Sjögren’s and non-Sjögren’s dry eye, and increases healing speed in eyes with persistent epithelial defects. However, in the non-Sjögren’s dry eye group, 50% SED (diluted with 0.9% NaCl) showed similar improvements as 100% SED. The authors also reported that SED diluted in 0.9% NaCl showed the best effects, and despite their expectations, there was no synergistic effect of hyaluronic acid when used at a diluent for SED. SED diluted with ceftazidime was found to be least effective due to the antibiotics own epithelial toxicity. The results of this study are summarised in [**Table 7.**](#_Tables)

### Recommendation:

1. The use of Auto-SED and Allo-SED as a 50% dilution in 0.9% Sodium chloride is recommended (as provided by NHSBT, the only accredited SED production facility in the UK).

## What effect does duration of treatment have on the effect of treatment with SED for patients with ocular surface disease?

The Scope for this Question is combined with Question 4.6. Please see section 4.6.

## What effect does frequency of treatment have on the effect of treatment with SED for patients with ocular surface disease?

### Scope:

Clinical guidance given to patients on how frequently they should administer SED and for what duration varies from patient to patient, and their underlying clinical condition. Some patients commence treatment for a short duration (1-2 donations providing 4-6 months treatment) on a 2 hourly basis to determine whether a high pulse of topical treatment may induce remission whilst others are on life-long treatment. The evidence for optimal duration and frequency, and indication for when to stop treatment is considered to be important.

### Evidence:

No studies have examined optimal frequency and/or duration of SED therapy for a specific clinical indication. There are no studies evaluating when it might be safe to stop SED therapy.

There is considerable variations in treatment frequency in published studies (4x/day to hourly usage). There is no clear evidence to suggest that more frequent instillation results in improved symptoms and clinical findings. Similarly, the optimal duration of treatment with SED is unclear due to heterogeneity in the published studies. The duration of treatment in studies ranges from 2 weeks to 6 months – this however often coincides with the study duration, and it is unclear how many patients continue on SED after conclusion of the study.

### Recommendation:

Providers of SED should consider clear stopping strategies after initiation of SED treatment. This may depend upon the underlying clinical indication for the therapy:

1. Patients with persistent epithelial defects and those who have supportive SED to aid surgical success, should be treated with SED for a defined treatment period e.g. until six weeks after the epithelial defect heals or 3 months post-surgery.
2. Patients with chronic ocular surface disease (e.g. ocular mucous membrane pemphigoid, Primary Sjögren’s syndrome, graft-versus-host-disease) would benefit from longer term therapy. It is recommended that a trial *without* SED should be considered after 1 year of therapy to ascertain whether symptom and sign outcome remission has been achieved, and whether that remission is long-lived.

## Which clinical outcome measures best record the treatment effect for monitoring ocular surface disease?

The scopes for Questions 1.7 and 1.8 are combined. Please see section 4.8.

## Which patient reported outcome measures best record the treatment effect for monitoring impact on patient debility?

### Scope:

Consistent recording of clinical and patient reported outcomes enables a unified approach to objective assessment of treatment response to novel or highly specialised interventions such as SEDs. The generation of cohort registries and datasets (as recommended by the Quality, Innovation, Productivity and Prevention programme) facilitates the quantification of efficacy in a clinical setting, serious adverse events, and ultimately the impact of SED on the health economic burden. Nevertheless, it is recognised that patient perceptions of disease influencing severity scoring outweigh observed clinical signs in some patients with ocular neuropathic pain. The presence and validity of published clinical and patient reported outcome instruments for use in monitoring the clinical effect of SED for standardisation of outcome reporting and patient benefits, was determined.

### Evidence:

There is a heterogeneity in outcome reporting in the monitoring of the effects of SED. There are no studies that have specifically validated objective scores for clinical examination findings (ocular surface staining score, Schirmer’s test, tear film break-up time), laboratory investigations (impression cytology, surface expression markers, blood or urine tests) nor patient reported outcome measures (visual analogue scales, ocular surface disease index (OSDI), visual function questionnaires) for recording the treatment effect of SED. Given the absence of specific information, recommendations are extrapolated from generic tools used for patients with ocular surface disease.24

### Recommendation:

1. Patients treated with Auto-SED and Allo-SED should be enrolled into a national programme of outcome reporting that includes patient reported outcomes (e.g. OSDI) and a corneal function score (e.g. Oxford Surface Staining Score) (**See Appendix 1, 2 and 3**).
2. Frequency and duration of treatment together with serious adverse events should be advised in the reporting procedure.
3. Attempt to withdraw treatment and duration of remission should be recorded.

# Good Practice Points and Recommendations

This guideline recommends that Serum Eye Drops are beneficial for patients with severe ocular surface disease including patients with severe dry eye, persistent and recurrent corneal epithelial defects, neurotrophic keratitis and for patients requiring supportive therapy in acute injury or surgery. Severity should be defined with subjective and objective parameters and all licensed treatments must be exhausted before Serum Eye Drops are considered. Treatment effect should be monitored with both patient and clinical reported outcomes with consideration given for implementing stopping strategies. Good practice includes clinical audit to document efficacy, adverse reactions, and collection of data through a centralised patient registry to monitor longer term outcomes. Registry development and integration of direct and indirect costs to define effectiveness of treatment is essential. Further research is required to determine bio-substance variability in serum donations, potential toxicity of autologous drops in some patients, identification of biomarkers for monitoring effectiveness, and determining optimal frequency, dosing and duration of SED treatment for each indication.

## Clinical Indications for Treatment

* ***Severe dry eye:*** most common in Sjögren’s syndrome (both primary and secondary to rheumatic diseases typically rheumatoid arthritis and systemic lupus erythematosis), immunobullous disorders usually mucous membrane pemphigoid, Stevens-Johnson syndrome, 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 diseased, following corneal infections, limbal epithelial stem cell failure, neurotrophic keratitis.
* ***Neurotrophic keratitis:*** this may be congenital, secondary to diabetic autonomic neuropathy, herpes zoster ophthalmicus, Vth cranial nerve tumours, and surgery leading to corneal anaesthesia.
* ***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 or radiation injury

## Patients Not Suitable for Serum Eye Drops

* Patients who have mild to moderate disease.
* Patients who have not tried all available licensed therapeutic strategies.

## Eligibility Criteria

All patients must meet clinically defined severity criteria according to the primary disease process and have exhausted readily available treatment options. The criteria are as follows (NHSE Specialised Service Circular SSC1728 March 2017):

### Severity Scoring:

* Severe, persistent dry eye symptoms for > 1 year
* No evidence of any reversible cause
* Patient severity score
	+ Visual Analogue Sore (0-10): >8
	+ Ocular surface disease index (OSDI, Max 100): >33
* Tear film Break Up Time: <3
* Staining domains:
	+ Van Bjisterveld score (Max 9) = 8 to 9
	+ Ocular Surface Staining Score (Max 12) = 9 to 12
	+ Oxford Staining Score (Max 15) = 21 to 25
* Frank epithelial defect persistent >2 weeks

### Therapeutic Categories:

#### Patients with refractory or partially responsive ocular surface disease:

Treatment for patients with ocular surface disease should begin by implementing conservative self-help options and supplementary tears with non-preserved artificial substitutes, tear modification with acetylcysteine, where possible tear stimulation with pilocarpine, disease modification with anti-inflammatories and surface modification strategies. If there is absence of significant relief for the patient as measured by clinical and patient reported outcomes, SED may be considered as a therapeutic option. A stepped approach is recommended:

1. ***Conservative:***
	* Humidifiers.
	* Warm compresses with proprietary lid warming devices accompanied by effective lid massage and hygiene with use of homemade solution or commercially available lid wipes.
	* Omega 3 and omega 7 supplementation.
	* Moist-chamber goggles for reduction of evaporation (effective by 30%).
	* All associated eye disease (lid malposition, trichiasis, blepharospasm) treatment is optimised.
2. ***Lubricants and Tear Substitution:***
	* Basic lubricant preparations including hypromellose, carmellose and carbomer gels.
	* Regular, frequent (at least 2 hourly) high grade non-preserved ocular lubricants (Hydroxypropylguar, hyaluronates (HA), HA combinations (carboxymethylcellulose, polysaccharide, disaccharide or xanthan gum, soybean with phospholipids (7% soybean oil and 3% natural phospholipids)) and liposomal sprays.
3. ***Tear modification:***
	* Acetylcysteine available commercially as 5% with benzalkonium chloride preserved preparation or unpreserved from 5-10% prescribed as a hospital special.
4. ***Tear Stimulation:***
	* Use of secretagogues either with oral pilocarpine max 5 mg four times per day (start with 2.5 mg once daily and build up) or pilocarpine 4% (3 drops = 6mg build up max 3x daily)25 for those who are unable to swallow.
5. ***Disease Modification:***
	* Topical anti-antinflammatories such as non-preserved topical glucocorticoids, topical calcineurin inhibitors including Ikervis (NICE TA369 December 2015).
	* Systemic disease modifiers such as metallomatrix proteinase inhibitors e.g. doxycycline 50-100mg for a minimum of 3 months (or sub-anitmicrobial dose of doxycycline (SDD, 20mg26 periostat®) may be prescribed long-term for those intolerant to 50mg). Low dose of macrolides if SDD is unsuccessful.
6. ***Punctal Occlusion:***
	* Punctal plugs and cautery (lower lid and then upper lid). Avoid early occlusion due to retention of pro-inflammatory tear constituents that may exacerbate ocular surface disease. Ideally use plugs that are visible at the punctal orifice.
7. ***Surface Modification:***
	* Where possible silicone hydrogel therapeutic contact lenses or rigid gas permeable scleral contact lenses provide a protective barrier to the ocular surface.
	* Rigid gas permeable scleral contact lenses are vaulted away from the ocular surface supported by the anterior sclera, enable a pre-corneal therapeutic reservoir to be created.

#### Recurrent corneal erosions

* + As 5.3.2.1 above PLUS:
		- Therapeutic contact lenses
		- Corneal epithelial debridement
		- Amniotic membrane graft to the cornea (including ProKera®, OmniLenz®)

#### Persistent epithelial defects

* + As 5.3.2.1 above PLUS:
		- Exclude infection
		- Therapeutic contact lenses
		- Amniotic Membrane Graft to the cornea (including ProKera®, OmniLenz®)
		- Medical or Surgical tarsorrhaphy

#### Limbal epithelial stem cell failure

* + As 5.3.2.1 above PLUS:
		- Therapeutic contact lenses
		- Amniotic membrane graft to the cornea
		- Medical or Surgical tarsorrhaphy

#### Surgical interventions

* + Ocular surface reconstruction or surgical intervention in at risk eyes outlined in section 1.4 Table 4:
	+ SED treatment is required as supportive pre-conditioning and post-operative therapy to optimise the ocular surface to aid surgical success

#### Acute ocular surface trauma

* + In acute thermal, mechanical, chemical or immunological injury where there is limbal ischaemia or substantial ocular surface epithelial loss, or in cases of exposure keratopathy in critical care environments, SED is recommended as an early intervention to aid rapid rehabilitation of acute injury and prevent long-term damage sequelae.

## Autologous versus Allogeneic Treatment

1. Auto-SED should be avoided in patients with conditions that could have circulating mediators in the blood stream that could have a damaging effect on the surface of the eye. These include uncontrolled diabetes, refractory immune-mediated diseases, those on cytotoxic agents whose bi-products are known to damage proliferating cells (e.g. cyclophosphamide) and patients with sepsis.
2. Allo-SED is recommended for patients who are unable to donate blood for the production of SED due to poor general health, mobility and patients who have poor venous access.
3. Allo-SED is also recommended for patients 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.

## Monitoring

Treatment effect should be monitored with both patient and clinical reported outcome instruments both locally and in a centralised registry. This is essential for determining long term clinical and post effectiveness of treatment.

Health related quality of life (HRQoL) burden increases with the severity of disease although disproportionate symptoms to signs (ocular neuropathic pain) is recognised. Objective grading of patient perceptions of disease using patient-reported outcome utility instruments specific for ocular surface disease, is recommended e.g. the Ocular Surface Disease Index tool (**Appendix 2**). This is a 12 item questionnaire sub-divided into three domains: visual function (6); ocular symptoms (3); environmental triggers (3) where 0=no disability and 100= complete disability.

Objective baseline clinical outcome tools to capture patient data such as ethnicity and residential post code, centre details, confidentiality statement, date of treatment, clinical indication, type of serum eye drop treatment (autologous, allogeneic), clinical outcome measures and scores (visual acuity, meniscus height, presence of filaments, tear film osmolarity, tear film break-up time, ocular surface staining score, epithelial defect measurements (if present), Schirmer’s test together with a guide to standardising clinical outcome measurements, is recommended (**Appendix 3**).

Follow-up outcome tool undertaken at 6 months post initiation of treatment, additionally captures whether the patient is still on treatment, has been transferred to another hospital, whether the treatment has been discontinued and whether there have been adverse local reactions or events (**Appendix 4**). Ideally, longer term outcome data to determine duration of treatment, or what proportion of patients are on indefinite duration treatment is required.

## Stopping Strategies

Attempt to withdraw treatment to ascertain whether symptom and sign outcome remission has been achieved, and whether there is prolonged remission is essential. Different clinical groups will require different stopping strategies:

1. Chronic ocular surface disease such as those with ocular mucous membrane pemphigoid, SJS/TEN, primary Sjögren’s Syndrome, graft-versus-host-disease, a treatment withdrawal trial should be considered after 1 year of therapy, before reinstating treatment if symptoms relapse.
2. Persistent epithelial defects should be treated with SED for a defined treatment period e.g. until six weeks after the epithelial defect heals
3. Those who require supportive SED to aid surgical success or those with acute injury, treatment withdrawal should be considered 6 months post-surgery or post-injury.

# Executive Summary

To be completed when final version of full guidance confirmed

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# Quick Guideline Reference

 To be completed when final full guidance is agreed

# Appendices

## Resources

### Appendix 1: Baseline clinical data

### Appendix 2: Follow-up clinical data

### Appendix 3: Ocular Surface Disease Index Score

### Appendix 4: Search Strategies

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## Details of the source of any funding

## Details of the external peer-reviewers

## Membership of the Guideline Development Group

* Chair: Saaeha Rauz
* OTG: Su-Yin Koay
* Specialty Experts: Stephen Kaye

Francisco Figueiredo

* RCOphth: Barny Foot

Michael Burdon (non-specialty ophthalmologist)

* NHSBT: Akila Chandrasekar

Richard Lomas

* Patient Representative: Elizabeth Dancey

## Contribution of authors

The Multidisciplinary team involved in producing these guidelines was led by Miss Saaeha Rauz, Clinical Senior Lecturer and Clinical Ophthalmologist, who chaired the team, proposed and led the development of the guidelines. Mr Barny Foot represented the Royal College of Ophthalmologists Quality Team supported guidance development. Professor Stephen Kaye and Professor Francisco Figueiredo who provided Ocular Surface Specialist clinical input. Dr Akila Chandrasekar and Mr Richard Lomas were the NHSBT representatives and provided source data of SED service. Mrs Elizabeth Dancey contributed as a Patient and Carer representation and Dr Su-Yin Koay provided Ophthalmology Trainee Group participation

# Tables

Table 6: Characteristics and outcomes of clinical trials using blood products for ocular surface disease (Q1)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Reference | Patient characteristics | Type | Data Source | Number of eyes/ patients | Intervention | Dilution (of intervention) | Frequency | Duration of treatment | Placebo | Concurrent therapy | PROM | Objective score | Level of evidence | Benefit |
| Pan et al 2017 | DED (SS, nSS, post LASIK) | Cochrane systematic review | 5 RCTs |  | Auto-SED |  |  |  |  |  | Improved symptoms in short term (2 weeks), but not sustained | Equivocal | 1++ | Positive/Equivocal |
| Soni et al 2016 | DED, PED | Systematic review | 6 RCTs, 4 clinical reports |  | Auto-SED, Allo-SED, UCS, PRP |  |  |  |  |  | Improved OSDI | Improved TBUT, F and RB staining.  | 1++ | Positive |
| Akpek et al 2011 | SS | Review | 3 clinical studies |  | Auto-SED |  |  |  |  |  | Equivocal | Equivocal | 4 | Equivocal |
| Azari et al 2015 | PED, GVHD, DED, SS, RCE, aniridia | Review | 46 clinical studies |  | Auto-SED |  |  |  |  |  | Suggested improvement | Improved | 4 | Positive |
| Ciralsky et al 2013 | SJS, TEN | Review | 2 clinical studies |  | Auto-SED |  |  |  |  |  | Not mentioned | improved | 4  | Positive |
| Celebi et al 2014 | DED | Cross-over RCT |  | 40 / 20 | Auto-SED | 20% | 4x | 1 month | Preservative free lubricants |  | Improved OSDI | Improved TBUT, Equivocal Schirmers | 1+  | Positive |
| Kojima et al 2005 | DED (3), pSS (17) | Parallel RCT |  | 37/ 20 | Auto-SED | 20% AutoSED | 6x | 2 weeks |  |  | Improved pain scores | Improved TBUT, F/RB score. Equivocal Schirmers. | 2++  | Positive |
| Noda Tsuruya et al 2006 | LASIK  | Parallel RCT |  | 27/54 | Auto-SED | 20% AutoSED  | 5x | 6 months (started 1 week post op) | Softsantear (sodium chloride 0.1%) | 0.3% hyaluronate 5x, 0.1% FML, Taravind antibiotics. All discontinued 1 week post op. | Equivocal subjective dryness scores  | Improved TBUT and F staining. Equivocal Schirmers.  | 1+ | Positive/Equivocal |
| Urzua et al 2012 | DED | Parallel RCT |  | 12/12 | Auto-SED | 20% AutoSED | 4x | 2 weeks | Systane eye drops (Polyethylene Glycol 0.4% andPropylene Glycol 0.3%) |  | Improved OSDI | Improved TBUT and OXFORD staining (p>0.05)  | 1+ | Positive/ Equivocal |
| Schulze et al 2006 | Diabetics with corneal ED (post PPV) | Parallel RCT |  | 13/13 | Auto-SED | 100% AutoSED | Hourly | Varied (until ED healed), max 14 days | 0.18% sodium hyaluronate - Vislube | Isoptomax 4x, atropine 4x, neosynephrine 4x | Not assessed | SED quicker epithelisation  | 1+ | Positive |
| Tanuvat et al 2001 | DED (pSS,sSS, NHL, GVHD, SJS, RhA, idiopathic) | Parallel RCT |  | 24/12 | Auto-SED | 20% AutoSED | 6x | 2 months | Unpreserved saline and dilute fluorescein | Lubricant eye drops |  | Improved F/RB staining. IC improved (p>0.05). Equivocal Schirmer/TBUT.  | 2- | Positive/Equivocal |

DED: dry eye disease, SS: Sjögren’s syndrome, pSS: primary Sjögren’s syndrome, sSS: secondary Sjögren’s syndrome, nSS: non-Sjögren’s syndrome, PED: persistent epithelial defect, GVHD: graft versus host disease, RCE: recurrent corneal erosions, RhA: rheumatoid arthritis, NHL: non-Hodgkin’s lymphoma

SED: serum eye drops, UCS: umbilical cord serum, PRP: platelet rich plasma

OSDI: ocular surface disease index, TBUT: tear break up time, F: fluorescein, RB: Rose Bengal

Table 7 Concentration of serum eye drops for the treatment of ocular surface disease (Q4)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Reference | Patient characteristics | Type | Interven-tion | Number of eyes / patients | Background Treatment | Concentration  | Duration of treatment  | Frequency  | Comments | PROM | Objective score | Level of evidence | Benefit |
| Cho et al 2013 | pSS, nSS, PED | Prospective | Auto SED | 42/22 | Sodium hyaluronate 0.1% 4x | 100%50% (in Na0.9)50% (in HA0.3)50% (in Cef0.5) | 12 weeks | 6x | No difference re: what used for dilution | pSS: SED 100% improvement in OSDI nSS: No difference between SED 100% and 50%  | pSS: SED 100% improved fluorescein staining vs all SED 50%nSS: SED 100% similar to SED 50% (Na0.9), SED 50% (Ha0.3) and 50% (Cef0.5) less effective.PED: SED 100% quickest epithelial closure | 1+ | Positive |

pSS: primary Sjögren’s syndrome, nSS: non Sjögren’s syndrome, PED: persistent epithelial defect, SED: serum eye drops, Na0.9: sodium chloride 0.9%, HA 0.3: hyaluronic acid 0.3%, Cef0.5: ceftazidime