The ROYAL COLLEGE of OPHTHALMOLOGISTS

Clinical Guidelines

Serum Eye Drops for the Treatment of Severe Ocular Surface Disease

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Executive Summary

Serum eye drops (SED) are a useful adjunctive treatment for patients with severe ocular surface disease (OSD), especially those with a compromised tear film. Serum contains a large number of epitheliotrophic factors that are present in tears. These factors are likely to be responsible for the therapeutic benefits observed with SED therapy compared to conventional commercially available ocular lubricants. Prescribed and over-the-counter tear substitutes primarily alleviate symptoms through reduction of friction and shear-forces caused by blink-induced biomechanical trauma. This mechanism of action appears largely to be independent of structural chemistry and viscosity of the lubricant product. By contrast, SED provide a variety of nutritional molecules such as vitamins, glucose, growth factors and immunoglobulins. These help to restore an environment that promotes reepithelialisation and supports ocular surface health.

SED are currently classified by the Medicines and Healthcare products Regulatory Agency (MHRA) as an unlicensed medicinal product (i.e. hospital 'special'). The MHRA advises that anyone prescribing an unlicensed product must be satisfied that there is a special need for the unlicensed medicinal product, and that the unlicensed medicine should not be supplied where an equivalent licensed medicinal product can meet the special needs of the patient. This College guideline sets out recommendations and good practice points for the safe use of SED for the treatment of severe OSD. It aims to improve not only compliance with MHRA advice, but also standardise practice and improve patient morbidity. The following areas have been addressed:

- Patient groups that may benefit from the use of SED
- Clinical situations for the use of autologous SED (Auto-SED) and allogeneic SED (Allo-SED)
- SED formulation, frequency of therapy and withdrawal
- Monitoring of treatment efficacy

Full guidance can be found at EYE on line Full report: **www.nature.com/articles/eye2017209**
Executive Summary: **www.nature.com/articles/eye2017208**

Key Recommendations and Good Practice Points for Implementation

The criteria used for the summary of grades of recommendations are found in Table 1 below.

Table 1: Recommendations

Grade	Explanation
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
B	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
C	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
GPP	Good practice points based upon consensual expert opinion where the evidence base does not support A-C grading
MHRA	Medicines and Healthcare products Regulatory Agency Guidance Note 14*
R	Further research is required in this area

** MHRA. 2014. The supply of unlicensed medicinal products ("specials") MHRA Guidance Note 14.*

Recommendation 1: MHRA Guidance Note 14 (2014), supply of unlicensed medicinal products ("specials")	Grade
Serum eye drops are an unlicensed medicine. The MHRA guidance note on the supply of unlicensed medicinal products ("specials") applies to delivery of this service.	MHRA
Note 2.2: Anyone supplying an unlicensed medicinal product, where an equivalent licensed medicinal product is available must be satisfied as to the existence of a special need for the unlicensed medicinal product. MHRA expects that documentary evidence of this special need should be obtained by manufacturers, importers or distributors and that this evidence should be made available on request of the Licensing Authority.	MHRA
Note 2.3: An unlicensed medicine should not be supplied where an equivalent licensed medicinal product can meet the special needs of the patient. Responsibility for deciding whether an individual patient has "special needs" which a licensed product cannot meet should be a matter for the doctor responsible for the patient's care. Examples of "special needs" include an intolerance or allergy to a particular ingredient.	MHRA

Recommendation 2: Serum eye drops should be considered in the following groups of patients	Grade
Patients who have refractory or partially responsive acute or chronic severe ocular surface disease where licensed interventions have been considered.	A
Patients with other ocular surface conditions such as recurrent corneal erosions, persistent epithelial defects and limbal epithelial stem cell failure may benefit if licensed interventions have been unsuccessful.	B
Supportive therapy such as for patients undergoing ocular surface reconstruction.	B

Recommendation 3: Clinical Situations where Autologous versus Allogeneic Serum Eye Drops should be considered	Grade
Autologous Serum Eye Drops (Auto-SED) should be considered for patients who are fit to donate one unit of blood, are able to travel to a blood donor centre, or the patient prefers serum eye drops to be made from their own blood.	GPP
Allogeneic serum eye drops (Allo-SED) should be considered in patients who are unable to donate one unit of blood such as those who are in poor general health, unable to attend a blood donor centre, less than age 16 years, or there is a clinical requirement for urgent treatment.	GPP
Clinical trials comparing the clinical efficacy and cost effectiveness of Auto-SED versus Allo- SED are required.	R

Recommendation 4: Impact of the variability of individual nutritional constituents within the supplied serum eye drops batches on clinical and patient outcomes	Grade
Allo-SED should be considered as an option in patients with uncontrolled diabetes, refractory immune-mediated diseases, those on cytotoxic agents or where their bi- products are known to damage proliferating cells (e.g. cyclophosphamide) and patients with sepsis.	GPP
Detailed serum constituent analyses of sequential donations from patient and healthy donors is required to interrogate bio-variability of each donation and the impact this could have on ocular surface health.	R
Further work on the development of protocols that reduce variability of biological constituents is required e.g. pooling of serum samples from multiple donors with measured ranges of main constituents.	R

Recommendation 5: Concentration of formulation, duration and frequency of SED treatment for patients with ocular surface disease	Grade
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).	GPP
Frequency and duration of treatment depends upon individual circumstances. The doctor responsible for patient care should consider withdrawal and stopping strategies in all patients commenced on SED treatment before committing patients to indefinite treatment. Such strategies may include (i) withdrawal of treatment after one year of therapy in patients with ocular surface disease, to define induction of remission before reinstating indefinite treatment if symptoms relapse, or (ii) in patients with persistent corneal epithelial defects, withdrawal of treatment after surface of the eye has healed and restoring treatment if the surface shows signs of breakdown.	GPP
Further research is required on the optimal formulation and diluent. This includes considering whether a 100% formulation is as effective as one that is diluted. A search for vehicles or carriers that improve the retention time and patient satisfaction is recommended.	R
Further work is required on the frequency and duration of serum eye drops treatment used for each clinical indication. Clinical trials should specifically consider when it might be safe to implement treatment withdrawal in patients who have achieved measured success or remission according to pre-set defined criteria.	R

Recommendation 6: Monitoring of treatment response and progression of disease	Grade
Instruments for assessment of the impact of treatment on health-related quality of life and objective grading of patient perceptions of disease using utility instruments specific for ocular surface disease, should be considered for use regularly in the clinical setting. These include the OSDI or the shorter DEQ-5.	GPP

Consistent recording of clinical outcome measures and scoring of disease should be considered. This includes visual acuity, meniscus height, presence of filaments, tear film break-up time, ocular surface staining score e.g. Ocular Staining Score, epithelial defect measurements (if present) and Schirmer's test without anaesthetic.	GPP
It is advised that patients treated with Auto-SED and Allo-SED should be enrolled into a national programme. Frequency and duration of treatment together with serious adverse events should be recorded using a standard reporting procedure. A minimum follow-up of 6 months and then annually should be considered.	GPP
Development and validation of SED-specific patient reported outcome tools and minimal clinical datasets for efficient outcome reporting is required.	R