Medicines Management Programme

Prescribing and cost guidance for the treatment of dry eye syndrome

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List of Abbreviations

ADDE	Aqueous deficient dry eye
BAK	Benzalkonium chloride
BD	Twice daily
BE	Both eyes
CHMP	Committee for Medicinal Products for Human Use
CMC	Carboxymethyl cellulose
D1	Instil one drop
DDU	Daily dose unit
DES	Dry eye syndrome
DP	Drugs Payment
EDE	Evaporative dry eye
GMS	General Medical Services
HPMC	Hydroxypropyl methylcellulose
HSE	Health Service Executive
MDPF	Multidose preservative-free
MDU	Multidose unit
MGD	Meibomian gland dysfunction
MMP	Medicines Management Programme
NMIC	National Medicines Information Centre
OSDI	Ocular Surface Disease Index
OTC	Over the counter
PCRS	Primary Care Reimbursement Service
PEG	Polyethylene glycol
PRN	As required
PVA	Polyvinyl alcohol
PVP	Polyvinylpyrrolidone
QDS	Four times daily
SDU	Single dose unit

SmPC	Summary of Product Characteristics
SPEED	Standard Patient Evaluation of Eye Dryness
TBUT	Tear breakup time
TFOS	Tear Film and Ocular Surface Society
TSP	Tamarind seed polysaccharide

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1. Background

Dry eye syndrome (DES) is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability with potential damage to the ocular surface.[1] It is more common with increasing age and affects more women than men.[2] Symptoms suggestive of dry eye include ocular irritation, redness, mucus discharge, fluctuating vision and decreased tear meniscus or plugged meibomian glands.[3]

Artificial tears and ocular lubricants are considered the mainstay of treatment for DES. There are over 30 preparations reimbursed by the Primary Care Reimbursement Service (PCRS). The choice of preparation depends on a number of factors including composition, viscosity, strength, pack size, in-use expiry, presentation, presence or absence of preservative and suitability for contact lens wearers. Reimbursement costs per product range from €2.15 to €10.50.[4] In Ireland in 2020, just over 840,600 prescription items for ocular lubricants and artificial tears were dispensed on the Community Drug Schemes at a cost to the Health Service Executive (HSE) of €11.25 million. This expenditure represents utilisation by over 112,000 people in Ireland.[5]

2. Purpose

The purpose of this document is to outline, in general terms, the pharmacological treatments that are reimbursed by the PCRS on the Drugs Payment (DP) and General Medical Services (GMS) schemes for the treatment of DES. It provides practice tips and pricing information on reimbursed treatments for DES. It is aimed primarily at supporting cost-effective prescribing.

This report should be used in conjunction with clinical judgement and decision-making appropriate to the individual patient. Prescribers should refer to resources such as the Summary of Product Characteristics (SmPC) and package leaflets of the individual medicinal products and devices.

3. Scope

There are a wide range of products reimbursed under Community Drug Schemes for the treatment of DES. Only preparations which are available over the counter (OTC) in community pharmacies are outlined in this document. Prescription-only preparations for dry eye, including ciclosporin, and the use of eye lubricants following ocular surgery, are outside the scope of this document.

During the review process, the PCRS was notified by Alcon Laboratories Ireland Limited, of their intention to withdraw Tears Naturale® eye drops from the Irish market. The proposed date for

discontinuation of the product was 10th August 2021. As such, Tears Naturale® was not considered as part of this MMP review process.

4. Definitions

For the purpose of this report the associated cost refers to the reimbursed cost of the eye preparation as listed on the HSE PCRS website (www.pcrs.ie). Only reimbursable eye preparations available for the treatment of DES, and accessible OTC, are included in this review. The prices listed do not include mark-up or dispensing fees that private/DP scheme patients may be charged. Costs are correct as of 1st November 2021. OTC prices may differ significantly from the reimbursed price.

The terms "artificial tears" and "ocular lubricants" are used interchangeably throughout this document.

The term "suitable with contact lenses" refers to the use of an eye preparation when the contact lens is in the eye.

5. Consultation

As part of the evaluation of the treatment of DES, a period of consultation was undertaken in which submissions from all relevant stakeholders were invited. This consultation was open for six weeks and ran from 26th March 2021 until the 6th May 2021.

6. Dry eye syndrome

DES, also referred to as keratoconjunctivitis sicca, is a common condition with a prevalence ranging from 8% to 34% depending on the criteria used.[2] It is characterised by inflammation of the ocular surface and reduction in quality and/or quantity of tears. The tear film is composed of three layers: an inner mucin layer secreted by goblet cells, a middle aqueous layer secreted by lacrimal and accessory glands on the upper eyelid, and an outer lipid layer secreted by meibomian glands in the upper and lower eyelids. The function of the tear film is to keep the cornea and conjunctiva healthy by supplying nutrients, flushing away waste products, and acting as a protective barrier.[6]

DES is divided into two general types: evaporative and aqueous-deficient.[2] Evaporative dry eye (EDE) is thought to be more common than aqueous-deficient dry eye (ADDE), and in many cases both forms occur concurrently.[7,8] Estimates of the degree of overlap of the two categories have been proposed by clinicians based on clinical judgement and range from 30% - 70%.[8]

EDE is most commonly a result of a deficient lipid layer in the tear film caused by meibomian gland dysfunction (MGD).[6,9] MGD is commonly characterised by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. It can cause alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.[9] External causes include allergy, topical medication use (including preservative content), and contact lens use.[2] Features of EDE include excessive watering of the eye on a windy day and blepharitis or ocular rosacea.[10]

ADDE refers chiefly to a failure of lacrimal tear secretion and is divided into two main groups: Sjögren's syndrome-related dry eye and non-Sjögren's syndrome-related dry eye. Dry eye in Sjögren's syndrome (an autoimmune disease) is often severe and requires more aggressive treatment.[2] Features of ADDE include inability to produce tears when crying, sore eyes on waking without a history of recent eye surgery, and pain.[10]

DES may be classified further by severity. Patients with mild DES may have symptoms of irritation, itching, soreness, ocular discomfort, burning or intermittent blurred vision. Patients with moderate dry eye disease have increased discomfort and frequency of symptoms, and the negative effect on visual function may become more consistent. Patients with severe dry eye disease have an increasing frequency of visual symptoms that may become constant as well as potentially disabling.[3]

Clinicians should consider the need to treat patients with DES in a comprehensive way, taking into account their symptoms, meibomian gland physiology, tear film lipid quality and quantity, tear production, loss and runoff. If only one form of DES (ADDE or EDE) is addressed therapeutically, patients may continue to suffer symptoms and report dissatisfaction with the prescribed treatment.

6.1 Assessment of dry eye syndrome

There is no gold standard protocol for diagnosis of DES and no one test is sufficient for diagnosis due to poor reliability of many common tests, multiple causative components of the disease and a lack of well-defined cut-off values to distinguish disease from normal. Furthermore, there are a number of factors which influence the diagnosis including the invasive nature of some tests, external influences such as diurnal or seasonal fluctuations, similarities with other conditions such as ocular allergy and the lack of correlation, at times, between the signs and symptoms of disease.[11] There are a number of tests and evaluations used to diagnose DES including:

- symptom questionnaires which allow for diagnostic screening, assessment of treatment efficacy and grading of disease severity. They are one of the most repeatable of the dry eye diagnostic evaluations. Examples include:

  - the Ocular Surface Disease Index (OSDI) which is a commonly used, validated questionnaire with 12 questions related to experience during the previous week regarding ocular symptoms, the severity, how these affect visual function and the ocular response to environmental triggers;
  - the Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire which helps to identify symptoms and focuses on their severity and frequency;
  - the dry eye questionnaire which has 21 questions that relate to the frequency and intensity of symptoms.
- measurement of tear breakup time (TBUT) to determine tear film stability, specifically local evaporation from the tear film surface. The time (in seconds) between a blink and the appearance of a dark spot in the fluorescein is the TBUT where 10 seconds or greater is considered normal
- evaluation of tear quantity with Schirmer's test (using a strip of filter paper placed under the lower eyelid). The strip is removed after 5 minutes and the length of the tear-wetting is measured in millimetres (mm). A reading of 10 mm or greater is generally considered the cut-off for a normal value
- assessment of corneal and conjunctival epithelium integrity using stains and dyes
- evaluation of meibomian glands and
- assessment of osmolarity where the concentration of solutes in the tear film are measured. Higher levels indicate a reduced aqueous component, either by increased evaporation or reduced aqueous secretion.[2,7,11]

7. Management of dry eye syndrome

7.1 Patient self-management

There are a number of precautions which can be undertaken to lessen the symptoms of DES, which, in mild cases, may be sufficient to avoid the need for pharmacological treatment. They include:

- maintaining good eye hygiene
- limiting contact lens use to shorter periods
- stopping smoking
- using a humidifier to moisten ambient air
- limiting screen time and taking frequent breaks

- reviewing any systemic medication that can induce or aggravate eye symptoms (e.g. antihistamines, diuretics, ß blockers, oestrogen therapy, tricyclic antidepressants, selective serotonin reuptake inhibitors, isotretinoin)
- dietary modifications.[2,8,9]

7.1.1 Good eyelid hygiene

Maintaining good eyelid hygiene is important to control posterior blepharitis or MGD. A gentle eyelid massage following the use of a warm compress can help improve expression of meibomian gland secretions. Patients should be advised to clean their eyelids twice daily initially, then once daily as symptoms improve.[9,12]

Recommendations for good eyelid hygiene include:[9,12]

- a warm compress (a clean cloth warmed with hot water) should be applied to closed eyelids for 5–10 minutes once or twice daily — the compress should not be too hot as it may burn the skin
- the eyelid can be cleansed by wetting a cloth or cotton bud with cleanser (for example baby shampoo diluted 1:10 with warm water) and gently wiping along the lid margins to clear any lid debris
- eyelid hygiene should be continued even when symptoms are well controlled to minimise number and severity of relapses
- patients should avoid eye make-up, especially eyeliner. If this is not possible, make-up which washes off easily is preferable. Make-up products should be replaced regularly and
- contact lenses should not be worn while cleaning the eyelids.[9,12]

7.2 Pharmacological treatments

Pharmacological interventions, including artificial tear substitutes, may be necessary for the management of DES. These products enhance tear stability and thus reduce loss by evaporation which, in turn, helps to maintain moisture in the eye and relieves chronic ocular inflammation associated with dry eyes.[13] The role of lubricants in the reduction of tear film osmolarity has been investigated but further studies linking their ability to reduce tear film osmolarity and thus impact upon the symptoms of DES, are warranted.[8]

Artificial tears have been traditionally used for the treatment of DES to improve symptoms. However, it is important to note that tear substitutes are not specifically designed to improve symptoms, but to prevent their build-up. Consequently, they should be instilled regularly throughout the day to avoid symptom aggravation and not used on an as-required basis.[14]

Ideally, artificial tears should be able to repair the damaged tear film with minimal frequency of instillation and limited side effects.[13] A treatment for DES should be trialled for 6-8 weeks before assessing benefit.[9,15]

7.2.1. Factors affecting choice of eye preparation

Although there are wide ranges of products available, there is limited evidence to demonstrate a substantial difference in effectiveness.[16,17] The choice of eye preparation may be influenced by a number of factors including product viscosity, addition of preservatives or phosphates, manual dexterity considerations, frequency of use, severity of condition, cost of different treatment options and contact lens use.

Viscosity

Viscosity-enhancing agents increase lubrication and prolong the retention time of the preparation on the ocular surface. The types of viscosity-enhancing agents used in eye preparations include carbomer 940 (polyacrylic acid), carmellose/carboxymethyl cellulose (CMC), dextran, hyaluronic acid (sodium hyaluronate), hydroxypropyl-guar, hypromellose/hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP) and polyethylene glycol. Differences in viscosity can influence utilisation. Eye drops with high viscosity can increase retention time on the ocular surface, but may cause visual disturbances and result in unwanted debris on the eyelids and lashes, leading to decreased tolerability and compliance. Very high viscosity eye drops are typically recommended for overnight use, while low-viscosity drops are more commonly used in the daytime.[8] Eye ointments containing paraffin may be uncomfortable and blur vision; they should only be used at night and never with contact lenses.[18]

Preservatives

Preservatives are used in eye preparations to prevent microbial growth and bacterial contamination which could lead to severe eye infections. They are also used to extend the shelf-life, particularly of multidose ophthalmic preparations.[19] Chronic exposure to preservatives is known to induce toxicity and adverse changes to the ocular surface; however, preparations with preservatives may be sufficient for patients with mild dry eye and an otherwise healthy ocular surface.[3,8] The European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) considers that preservative-free drops are a valuable alternative for some, but not all patients.[20] However, when tear substitutes are used frequently and chronically, preservative-free tear substitutes are generally recommended.[9]

Benzalkonium chloride (BAK) is the most frequently used preservative in eye drop preparations, however a report issued by the Tear Film and Ocular Surface Society (TFOS) in 2017 stated that ocular

lubricants preserved with BAK should be avoided in patients with severe DES who require frequent administration of eye drops, or those who use ocular lubricants in conjunction with other chronic topical therapies, such as glaucoma medications.[8] In order to address this issue, newer preservatives have been designed to have a lower impact on the ocular surface (e.g. sodium chlorite degrades to chloride ions and water upon exposure to UV light after instillation), however some reports suggest that these newer agents may also show negative effects on the ocular surface.[8]

The development of technologies that provide multidose preservative-free (MDPF) eye drops has been a significant advancement in ophthalmology in recent years. The use of mechanical pump systems, specialised membranes/filters and unidirectional flow values have allowed the production of preservative-free eye drops, whilst maintaining product sterility and extended (up to six months) shelf-life on opening.[21-23] These medical devices have several advantages over traditional eye drop bottles or single dose unit vials (SDUs). The potential toxicity of preservatives can be avoided and patients may prefer the convenience of a bottle over several boxes of SDUs. MDPF eye drop preparations have calibrated drop volumes, minimal product waste and have a lower environmental impact compared with SDUs.[24]

Phosphates

Phosphate-containing eye drops may need to be avoided in patients with significantly damaged corneas. In 2012, the CHMP reviewed the use of phosphate buffers in medicinal products given as eye drops to determine whether they might cause corneal calcification.[25] This review was initiated based on 117 possible or confirmed case reports of corneal calcification. The review group found that there was some evidence to suggest this side effect could occur in patients who already had severe damage to their cornea and used phosphate-containing eye drops. This could contribute to additional visual loss. However, they noted some patients with severe corneal damage developed calcification despite not using phosphate-containing eye drops. Given the large volume of usage of these products, the Committee considered the benefits of phosphate-containing eye drops to outweigh their risks. They recommended that the SmPC and patient leaflets for these products should have corneal calcification mentioned as a possible side effect in patients who already have significantly damaged corneas.[25]

Manual dexterity

Manual dexterity of the patient is a consideration when prescribing eye preparations. Some preparations are supplied in soft bottles that patients with reduced manual dexterity (e.g. rheumatoid arthritis) may find easier to squeeze.[18]

Frequency of use

Consideration should be given to:

- preservative-free preparations when tear substitutes are used more than six times a day over a prolonged period of time[9]
- expiry dates - some preparations with long expiry dates (up to six months in-use) may be more cost-effective if tear substitues are required infrequently. Prescriptions should not be repeated for these items without assessing need.

Severity of condition

For patients with moderate-to-severe DES, the absence of preservatives is of more critical importance than the particular polymeric agent used in ocular lubricants. In patients with mild-to-moderate DES, preserved drops are typically well tolerated when used 4-6 times per day or less.[26]

Cost

The cost of different treatment options should be a consideration for both prescription and OTC use of eye preparations.

Contact lens use

Some eye preparations are incompatible with contact lenses.

7.2.2 Regulation of eye preparations

Eye preparations may be regulated as either medicinal products or medical devices. Eye drops with a pharmacological, immunological or metabolic principal mode of action fall under the definition of a medicinal product if they may be used in or administered to humans either with a view to restoring, correcting or modifying physiological functions. Eye drops with a physical mode of action that are clearly indicated for a medical purpose are acceptable as medical devices. Artificial tears may be regulated as either medical devices or as medicinal products, depending upon their mode of action.[27]

7.2.3 Artificial tears and ocular lubricants reimbursed under Community Drug Schemes in Ireland

Table 1 (page 10) lists the preparations used in the treatment of DES, which are reimbursed under the Community Drug Schemes in Ireland as of September 2021 (all are also available OTC in community pharmacies). Six of these preparations are available to the Irish market via parallel-importation. The Health Products Regulatory Authority defines parallel-importation as:

> The importation, from an EU Member State or an EEA country, of a medicinal product which is equivalent to one already authorised on the Irish market, by an importer who is someone

other than the importer appointed by the marketing authorisation holder of the product on the Irish market.[28]

In this review, products imported via parallel importation have been excluded from the reimbursed cost-comparison of preparations for DES.

Table 1: Preparations for the treatment of dry eye syndrome reimbursed under Community Drug Schemes, and their characteristics[29-55]

Eye Preparation	Active Ingredient(s)^	Strength (%)	Pack size	Preservative	Phosphate	Presentation	Cost (€)	In-use expiry	Suitable with contact lenses
GelTears®	Carbomer	0.20	10 g	BAK	None	MDU	2.89	28 days	No
Liposic®	Carbomer	0.20	10 g	Cetrimide	None	MDU	2.91	28 days	No
Liquivisc®	Carbomer	0.25	10 g	BAK	None	MDU	2.96	28 days	No
Vidisic®	Carbomer	0.20	10 g	Cetrimide	None	MDU	3.16	28 days	No
Vidisic®	Carbomer	0.20	0.6 ml x 30	None	Yes	SDU	8.31	None	No
Xailin® Gel	Carbomer	0.20	10 g	Not in eye¥	None	MDU	2.89	28 days	No
Carmellose Sodium (Alissa)	Carmellose	0.50	0.4 ml x 30	None	None	SDU	3.50	None	Yes
Celluvisc	Carmellose	0.50	0.4 ml x 30	None	None	SDU	3.89	None	Yes
Celluvisc	Carmellose	1.00	0.4 ml x 60	None	None	SDU	10.50	None	No
Celluvisc (Imbat)*	Carmellose	1.00	0.4 ml x 60	None	None	SDU	6.54	None	No
Celluvisc (Lexon)*	Carmellose	1.00	0.4 ml x 30	None	None	SDU	6.54	None	No
Celluvisc (PCO)*	Carmellose	1.00	0.4 ml x 30	None	None	SDU	6.54	None	No
Xailin® Fresh	Carmellose	0.50	0.4 ml x 30	None	None	SDU	3.50	None	Yes
Artelac®	Hypromellose	0.32	10 ml	Cetrimide	Yes	MDU	2.30	28 days	No
Artelac®	Hypromellose	0.32	0.5 ml x 30	None	Yes	SDU	5.59	None	No
Artelac®	Hypromellose	0.32	0.5 ml x 60	None	Yes	SDU	9.59	None	No
Artelac® (Imed)*	Hypromellose	0.32	0.5 ml x 60	None	Yes	SDU	9.31	None	No
Artelac® (Lexon)*	Hypromellose	0.32	0.5 ml x 60	None	Yes	SDU	9.30	None	No
Artelac® (PCO)*	Hypromellose	0.32	0.5 ml x 60	None	Yes	SDU	9.30	None	No
Hydromoor®	Hypromellose	0.30	0.4 ml x 30	None	None	SDU	4.32	None	Yes
Tears Naturale®	Hypromellose Dextran 70	0.30 0.10	15 ml	BAK	None	MDU	2.20	28 days	No
Minims® Artificial Tears	Hytellose NaCl	0.44 0.35	0.5 ml x 20	None	None	SDU	7.07	None	No info
Liquifilm Tears®	Polyvinyl alcohol	1.40	15 ml	BAK	Yes	MDU	2.15	28 days	No
Artelac® Every Day	Sodium hyaluronate	0.24	10 ml	None	Yes	MDU	5.96	6 months	Yes

Eye Preparation	Active Ingredient(s)^	Strength (%)	Pack size	Preservative	Phosphate	Presentation	Cost (€)	In-use expiry	Suitable with contact lenses
Artelac® Night	Sodium hyaluronate Carbomer	0.24 0.20[56]	10 ml	None	None	MDU	6.46	6 months	No
Blink® Intensive	Sodium hyaluronate PEG 400	0.20 0.25	10 ml	Not in eye¥	None	MDU	6.35	45 days	Yes
HydraMed®	Sodium hyaluronate TSP	0.20 0.20	0.5 ml x 30	None	None	DDU	5.67	12 hours	Yes
HydraMed®	Sodium hyaluronate TSP	0.20 0.20	10 ml	None	None	MDU	5.67	3 months	Yes
Hylo-Care®	Sodium hyaluronate Dexpanthenol	0.10 2.00	7.5 ml	None	None	MDU	6.54	6 months	Yes
Hylo-Forte®	Sodium hyaluronate	0.20	7.5 ml	None	None	MDU	6.72	6 months	Yes
Hy-Opti	Sodium hyaluronate	0.10	10 ml	None	Yes	MDU	6.16	8 weeks	No
Hy-Opti	Sodium hyaluronate	0.20	10 ml	None	Yes	MDU	6.72	8 weeks	No
Hylo-Tear®	Sodium hyaluronate	0.10	7.5 ml	None	None	MDU	6.16	6 months	Yes
Thealoz Duo®	Sodium hyaluronate Trehalose	0.15 3.00	10 ml	None	None	MDU	6.75	3 months	Yes
Hylo Night®	Retinol palmitate	250 I.U./g	5 g	None	None	MDU	2.91	6 months	No
Lacri-Lube®	There are no specific active ingredients in these eye ointments. All ingredients of eye ointments are listed in Appendix 1.		3.5 g	None	None	MDU	2.43	28 days	No
Lacri-Lube®			5 g	None	None	MDU	3.07	28 days	No
Xailin® Night			5 g	None	None	MDU	2.76	60 days	No

BAK: benzalkonium chloride; DDU: daily dose unit; MDU: multidose unit; NaCl: sodium chloride; PEG: polyethylene glycol; SDU: single dose unit; TSP: tamarind seed polysaccharide

*** Parallel import ¥disappears upon contact with the eye ^ excipients are detailed in the appendix**

NOTE: Eye preparations in the table are listed alphabetically by active ingredient, and then alphabetically by brand name in ascending order of strength.

7.2.4 First- and second-line pharmacological treatment options

There are many preparations available for the treatment of DES but there is a lack of high-quality comparative evidence on safety or efficacy of individual products.[2,6,16,17] The Drug and Therapeutics Bulletin publication on the management of dry eye (2016) recommends that, in the absence of comparative evidence, it is reasonable to start with the lowest cost preparation.[2]

✓ **First-line treatments**

There are three first-line options available for the treatment of mild-to-moderate DES in patients with an otherwise healthy ocular surface: hypromellose, carbomer and polyvinyl alcohol (PVA). Hypromellose provides temporary relief from symptoms and may require more frequent administration than carbomer or PVA. However, the higher viscosity of the latter products may mean that they are less well-tolerated.[2] Consideration should be given to longer retention times versus impact on vision.[9] There are a number of hypromellose and carbomer formulations available as SDUs, however **those listed in this section as first-line treatment options refer to the multidose formulations only.**

Hypromellose 0.3% acts as a lubricant and a tear substitute. It is the traditional treatment of choice when a lubricating drop is required. Hypromellose may need to be administered frequently (e.g. hourly) initially in order for the patient to achieve adequate relief, and then a reduced frequency may be sufficient.[15] An example of a hypromellose-containing product is Artelac® 0.32%.

Carbomer clings to the surface of the eye due to its hydrophilic properties and high molecular weight. This can reduce the required frequency of administration to four times daily in patients who otherwise require high frequency administration of hypromellose.[21] Carbomer-containing products include GelTears® 0.2% gel, Liposic® 0.2% gel, Vidisic® 0.2% gel, Xailin® Gel 0.2% and Liquivisc® 0.25% gel.

Polyvinyl Alcohol (PVA) products increase the persistence of the tear film and can be useful when ocular surface mucin is reduced.[15] An example of a PVA-containing product is Liquifilm Tears® 1.4%.

These treatments should be trialled initially before second-line treatment options are considered.

Carbomer, hypromellose and PVA eye drops are recommended by the MMP as first-line agents for the treatment of DES.

✓ **Preservative-free alternatives**

All eye preparations listed above contain preservatives which may not be suitable for some patients. Xailin® Gel may be an alternative first-line option for these patients. Xailin® Gel is a carbomer-based eye lubricant. It contains sodium perborate which is a disappearing preservative that turns into water and oxygen upon contact with the eye, thereby minimising the irritation that may be caused by traditional preservatives. Contact lenses must be removed prior to the use of Xailin® Gel.[32]

Xailin® Gel may be an appropriate first-line agent for patients requiring a preservative-free treatment.

First-line treatment options are listed in table 2 below. The treatments highlighted in green have the lowest acquisition cost.

Table 2: First-line treatment options

First Line: PVA, Hypromellose or Carbomer PVA and carbomer may require less frequent administration but may be less well tolerated							
Main Ingredient	**Eye Preparation**	**Strength (%)**	**Preservative**	**Pack Size**	**Directions for use**	**In-use expiry**	**Cost (€)**
Carbomer	GelTears®	0.20	BAK	10 g	D1 3-4 times daily	28 days	2.89
Carbomer	Liposic®	0.20	Cetrimide	10 g	D1 3-5 times daily and at night	28 days	2.91
Carbomer	Liquivisc®	0.25	BAK	10 g	D1 up to four times daily	28 days	2.96
Carbomer	Vidisic®	0.20	Cetrimide	10 g	D1 3-5 times daily	One month	3.16
Carbomer	Xailin® Gel¥	0.20	Sodium perborate*	10 g	D1 2-4 times daily PRN	28 days	2.89
Hypromellose	Artelac®	0.32	Cetrimide	10 ml	D1 3-5 times daily or PRN	28 days	**2.30**
PVA	Liquifilm Tears®	1.40	BAK	15 ml	D1-2 PRN	28 days	**2.15**

D1: instil one drop D1-2: instil one to two drops PRN: as required BAK: benzalkonium chloride PVA: polyvinyl alcohol
¥ first-line option for patients who require a preservative-free preparation *preservative-free in the eye

Practice Point

- **First-line treatment options should be considered initially when prescribing for patients with DES. Consider prescribing products with the lowest acquisition cost. If there is insufficient improvement after 6-8 weeks, consider an alternative first-line agent or a second-line option.**

✓ **Second-line treatments**

Lubricants containing sodium hyaluronate can be used following an unsuccessful trial (6–8 weeks) of first-line treatment options.[15]

Sodium hyaluronate (also known as hyaluronic acid) is found naturally in the human body in connective tissue but also in the vitreous body, synovial fluid and in the tear fluid of the eye. In ophthalmology it is used for its hygroscopic, viscoelastic and wound-healing properties.[8,57,58,59] There is some evidence that high-molecular weight hyaluronic acid offers more benefits for the ocular surface than low-molecular weight hyaluronic acid. The viscosity of hyaluronic acid preparations depends on the molecular weight and the concentration of hyaluronic acid contained within the product. The greater the molecular weight and concentration, the greater the viscosity.[59]

There are 11 preparations containing sodium hyaluronate reimbursed in Ireland for the treatment of DES. Preparations vary by strength, viscosity, in-use expiry, number of drops per bottle and presence of additional agents including dexpanthenol, trehalose, tamarind seed polysaccharide (TSP) and polyethylene glycol (PEG) 400.

- **Dexpanthenol** is a derivative of the B complex vitamins. It has hygroscopic properties which prevent epithelial dryness and maintain the ocular surface integrity.[60] It is an additional agent in Hylo-Care®.
- **Trehalose** is contained in Thealoz Duo®. Combining trehalose with sodium hyaluronate in eye drops has been shown to elicit corneal re-epithelialization in response to corneal cross-linking compared with sodium hyaluronate alone.[61]
- **TSP** possesses mucomimetic, mucoadhesive and pseudoplastic properties. The 'mucin-like' molecular structure of TSP is similar to corneal and conjunctival mucin, which is thought to play an essential role in protecting and wetting the corneal surface and may explain its increased retention on the eye surface.[62] TSP is an additional active ingredient in the Hydramed® preparations.
- **PEG 400** is contained in Blink® Intensive. It is a demulcent that forms a protective layer over a mucous membrane to relieve inflammation or irritation and to preserve the ocular surface microenvironment. It lubricates, protects and provides viscosity to the eye drop.[63]

There is little clinical evidence available to confirm superiority amongst the various strengths of sodium hyaluronate-containing products. Manufacturers generally indicate the percentage of sodium hyaluronate included in their formulation, however it has been suggested that such partial information could be of limited value when trying to determine the best preparation for a patient with dry eye.[64] The molecular weight and polydispersion index (which reflects the uniformity of the

molecular weight distribution) of sodium hyaluronate, together with other physicochemical properties, can also contribute notably to the overall viscosity and clinical indications of a formulation.[64] Some recent studies suggest that maximal sodium hyaluronate performance is achieved by a wide range of sodium hyaluronate concentrations, with higher molecular weight products showing superior efficacy.[65,66] Higher viscosity is not always the desired feature of a hyaluronate dry eye treatment. Solutions that are more viscous may be useful to aid epithelial recovery, whilst less viscous preparations are used when an increase in tear clearance is required.[14]

Preparations containing sodium hyaluronate which are available as multidose units (MDU) are listed in table 3 below. The product with the lowest acquisition cost that provides relief of symptoms should be used. The treatment highlighted in green has the lowest acquisition cost.

Table 3: Second-line treatment options containing sodium hyaluronate

(All are preservative-free)

Eye Preparation	Strength (%) of sodium hyaluro-nate	Pack Size (ml)	Directions for use	In-use expiry	Cost (€)	Number of drops	Annual utilisation and expenditure at D1 both eyes once daily^		Annual utilisation and expenditure at D1 both eyes three times daily^	
							Number of bottles	Annual ingredient cost (€)	Number of bottles	Annual ingredient cost (€)
Artelac® Every Day	0.24	10	D1 PRN	6 months	5.96	235¥	4	23.84	10	59.60
Blink® Intensive	0.20	10	D1-2 PRN	45 days	6.35	200*	9	57.15	11	69.85
HydraMed®	0.20	10	D1 one or more times daily	3 months	5.67	250	4	**22.68**	9	**51.03**
Hylo-Care®	0.10	7.5	D1 3 times daily	6 months	6.54	225	4	26.16	10	65.40
Hylo-Forte®	0.20	7.5	D1 2-3 times daily	6 months	6.72	225	4	26.88	10	67.20
Hy-Opti	0.10	10	D1 2-3 times daily	8 weeks	6.16	250	7	43.12	9	55.44
Hy-Opti	0.20	10	D1 2-3 times daily	8 weeks	6.72	250	7	47.04	9	60.48
Hylo-Tear®	0.10	7.5	D1 3 times daily	6 months	6.16	225	4	24.64	10	61.60
Thealoz® Duo	0.15	10	D1 4-6 times daily	3 months	6.75	300	4	27.00	8	54.00

D1: Instil one drop; D1-2: instil one to two drops; PRN: as required; ^ Costs calculated over 365 days taking number of drops per bottle and in-use expiry into consideration, rounded up to the nearest whole bottle; * Data not available, average number of drops of 10 ml preparations used (Reference 67) ¥Company communication (Reference 68)

When sodium hyaluronate is indicated, the MMP recommends the product with the lowest acquisition cost that provides relief of symptoms.

Practice Point

- **Many sodium hyaluronate preparations have long in-use expiry dates (up to six months) after opening. This may need to be highlighted to patients to avoid wastage.**
- **Do not prescribe sodium hyaluronate preparations on a monthly-basis without checking the patient's requirement.**

7.2.5 Alternative pharmacological treatment options

Single dose units/Daily dose units:

SDUs have the advantage of being preservative-free and are suitable for patients who may not have the dexterity to use a MDU. They are often used in the in-patient hospital setting to avoid contamination and to reduce waste. SDUs are more expensive than MDUs and most must be discarded immediately after a single use. HydraMed® is available as daily dose units (DDUs) which are resealable vials and may be used multiple times up to 12 hours after first opening.

SDUs containing hypromellose, carbomer, hyetellose, sodium hyaluronate and carmellose are reimbursed by the PCRS. The physicochemical characteristics of carbomers and hypromellose were previously discussed under first-line treatments.

Carmellose: ocular lubricants containing carmellose sodium can be used as an alternative second-line treatment for mild-to-moderate DES if first-line options have failed.

Carmellose is a high-molecular-weight polysaccharide derived from natural cellulose obtained through chemical modification. Carmellose is one of the viscous polymers used in artificial tears to prolong their permanence on the ocular surface. Carmellose binds directly to corneal epithelial cells for several hours. In addition, its binding to matrix proteins stimulates the migration of epithelial cells, which contributes to the healing of corneal wounds.[59]

The presentations of carmellose on the Irish market are limited. They are available only in SDUs. Therefore, unlike in other jurisdictions where carmellose-containing MDUs are recommended second-line in the treatment of DES, the associated cost of carmellose SDUs is prohibitive in Ireland.

SDUs and DDUs used in the treatment of DES reimbursed in Ireland are listed in table 4. Products in green have the lowest annual cost taking the following into consideration: pack size, in-use expiry and frequency of administration.

Table 4: Single dose units/Daily dose units

Single Dose Units/Daily Dose Units										
Main Ingredient	Eye Preparation	Strength (%)	Pack Size	Directions for use	In-use expiry	Cost (€)	Annual utilisation and expenditure at D1 both eyes twice daily^		Annual utilisation and expenditure at D1 both eyes four times daily^	
							Number of packs	Annual ingredient cost (€)	Number of packs	Annual ingredient cost (€)
Carbomer	Vidisic®	0.20	0.6 ml SDU x 30	D1 3-5 times daily	Single use	8.31	25	207.75	49	407.19
Carmellose	Carmellose sodium (Alissa)	0.50	0.4 ml SDU x 30	No info	Single use	3.50	25	**87.50**	49	**171.50**
Carmellose	Celluvisc	0.50	0.4 ml SDU x 30	D1-2 2-4 times daily	Single use	3.89	25	**97.25**	49	**190.61**
Carmellose	Celluvisc	1.00	0.4 ml SDU x 60	D1-2 PRN	Single use	10.50	13	136.50	25	262.50
Carmellose	Xailin® Fresh	0.50	0.4 ml SDU x 30	D1 2-4 times daily	Single use	3.50	25	**87.50**	49	**171.50**
Hypromellose	Artelac®	0.32	0.5 ml SDU x 30	D1 3-5 times daily PRN	Single use	5.59	25	139.75	49	273.91
Hypromellose	Artelac®	0.32	0.5 ml SDU x 60	D1 3-5 times daily PRN	Single use	9.59	13	124.67	25	239.75
Hypromellose	Hydromoor®	0.30	0.4 ml SDU x 30	D1 PRN	Single use	4.32	25	108.00	49	211.68
Hytellose	Minims® Artificial Tears	0.44	0.5 ml SDU x 20	D1-2, 3-4 times daily or PRN	Single use	7.08	37	261.96	73	516.84
Sodium hyaluronate	HydraMed®	0.20	0.5 ml DDU x 30	D1 one or more times daily	12 hours	5.67	13	**73.71**	25	**141.75¥**

D1: Instil one drop; D1-2: instil one to two drops; DDU: daily dose unit; PRN: as required; SDU: single dose unit; ^ Costs calculated over 365 days; ¥Costs calculated assuming six-hourly usage

Prescribing of SDUs/DDUs

Costs associated with SDUs are dependent on frequency of use. Annual costs associated with all SDUs available in Ireland for the treatment of DES are demonstrated in table 4 above. Costs have been calculated based on twice-daily and four-times daily usage. The HydraMed® vial is resealable and allows for use for up to 12 hours. Costs were calculated assuming six-hourly use of HydraMed® vials (which requires two vials per 24 hours).

The prescribing of all SDUs/DDUs warrants consideration due to the high cost associated with their use compared with MDUs. Given the availability of other preservative-free options, the use of SDUs/DDUs should be restricted to specific circumstances when a patient:

- is intolerant of, or has failed all alternative treatments
- has dexterity issues e.g. arthritis in hands or tremor
- is an inpatient in a hospital setting.

Practice Point

Due to the high acquisition cost of SDUs, prescribing should be reserved for circumstances where:

- **there are no alternative preparations available**
- **the patient has dexterity issues**
- **the patient is an inpatient in hospital.**

7.2.6 Additional first- and second-line pharmacological treatment for night-time use

Eye ointments containing a paraffin (e.g. liquid paraffin with white soft paraffin and wool alcohols) can be used in addition to other options to lubricate the eye surface, especially in cases of recurrent corneal epithelial erosion.[15] These products can be particularly beneficial for patients with ADDE.[57] Paraffin-based eye ointments may cause temporary visual disturbance and are best suited for application before sleep. Ointments should not be used while wearing contact lenses.[15,69]

Examples of liquid paraffin containing products include Lacri-Lube®, Xailin® Night and Hylo Night®. Hylo Night® also contains retinol palmitate and has an expiry of six months from date of opening.

Prescribers should note that ointments with long expiry dates, which are to be used over a number of months at night time only, should not be written on repeat prescriptions without determining patient requirement. Ocular ointments which may be used alone, or as additional lubrication at night, are listed in table 5 below. Products highlighted in green have the lowest cost taking pack size and in-use expiry into consideration.

Table 5: Ocular ointments for additional lubrication at night

Additional Lubrication: Eye ointments (if required)				
Brand	**Pack Size (g)**	**Directions for use**	**In-use expiry**	**Cost (€)**
Hylo Night®	5	Apply at night	6 months	**2.91**
Lacri-Lube®	5	Apply PRN	28 days	3.07
Lacri-Lube®	3.5	Apply PRN	28 days	2.43
Xailin® Night	5	Apply PRN	60 days	**2.76**

PRN: as required

Artelac Night® contains sodium hyaluronate, carbomer and glycerol. It is a highly viscous eye drop and is designed to remain on the surface of the eye. It can be used when required but is marketed for use before bed for long-lasting relief from symptoms of dry eyes. See table 6 below.

Table 6: Ocular drops for additional lubrication at night

Additional Lubrication: Eye drops (if required)				
Brand	**Pack Size (ml)**	**Directions for use**	**In-use expiry**	**Cost (€)**
Artelac® Night	10	D1 PRN	6 months	6.46

D1: instil one drop PRN: as required

8. Considerations before prescribing

- Consider precipitating factors of DES before prescribing ocular lubricants e.g. medication use (anticholinergics, ß blockers, diuretics), environmental factors, allergy, infection, blepharitis, screen time.
- Ocular lubricants should be prescribed, if needed, in conjunction with advice on modifiable risk factors.
- Prescribe by BRAND name to ensure that the preparation with the lowest acquisition cost is used (refer to MMP prescribing algorithm for preferred prescribing choices).
- Consider expected duration of treatment and frequency of use; some ocular lubricants with longer expiration dates may represent better value if less frequent dosing required.
- Consider preservative-free preparations where the patient:
    - has a true preservative allergy
    - has evidence of epithelial toxicity to preservatives contained in the preparation
    - needs to use more than six applications of eye drops daily over a prolonged period of time[9]
    - wears contact lenses
    - uses multiple eye products.

9. When to refer

Patients should be referred for specialist assessment if:

- a serious eye condition e.g. acute glaucoma, keratitis, iritis or corneal ulcer is suspected
- an underlying condition e.g. Sjögren's syndrome is suspected
- symptoms cannot be adequately controlled in primary care
- the patient has abnormal lid anatomy or function
- there is diagnostic uncertainty
- vision deteriorates.[6,9]

10. Discussion

The management of DES is highly complicated because of its multifactorial aetiology and lack of a single clinical assessment. In addition, patient-reported symptoms frequently do not correspond to observed changes in clinical signs.[14,70] The ultimate goal of DES treatment is to restore homeostasis of the ocular surface and tear film by breaking the cycle of the disease. When diagnosing dry eye, clinicians should clearly determine the underlying aetiology, such as EDE or ADDE, and/or other ocular

surface diseases, and should administer relevant treatments accordingly in order to properly manage the condition.[70]

Management algorithms recommend a series of treatments according to disease stage and treatment cost but the issue is complicated in DES because the disease often differs from patient to patient in both severity and nature. The coexistence of many factors in DES can limit the ability of prescribers to adhere to one particular algorithm.[70]

DES treatments should be offered in conjunction with self-management advice as discussed in section 7.1. Clinicians should prescribe the product with the lowest acquisition cost, taking into consideration the expected duration of treatment, frequency of use, requirement for a preservative-free alternative, patient dexterity, contact lens use and expiry date of the eye preparation. All preparations should be trialled for 6-8 weeks prior to assessing benefit. Patients should be advised if they have been prescribed an eye preparation with a long expiry. Prescriptions for these longer-expiry preparations should not be repeated without assessing patient need.

11. Conclusion

DES is an often-chronic disease that tends to need prolonged treatment. It is a highly prevalent condition which may have a very significant effect on patient quality of life. Artificial tear substitutes are a therapeutic option that can be used in combination with multidisciplinary recommendations including hygienic, nutritional, environmental and lifestyle measures. Suitability of preparation, regular review to assess patient response and need, and cost-awareness are important factors that will contribute to appropriate and cost-effective prescribing in this area in the future.

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Appendix 1

Eye Preparation [29-55, 70, 71]	Presentation	Excipient(s)
GelTears®	MDU	Benzalkonium chloride, water for injections, sorbitol, sodium hydroxide
Liposic®	MDU	Cetrimide, sorbitol, medium-chain triglycerides, sodium hydroxide, water for injections
Vidisic®	MDU	Cetrimide, sorbitol, water for injections, sodium hydroxide
Xailin® Gel	MDU	Sodium perborate and excipients^
Vidisic®	SDU	Sorbitol, disodium phosphate dodecahydrate, sodium hydroxide, water for injections
Liquivisc®	MDU	Benzalkonium chloride, sorbitol, lysine monohydrate, sodium acetate trihydrate, polyvinyl alcohol, water for injections
Celluvisc 0.5%	SDU	Sodium chloride, sodium lactate, potassium chloride, calcium chloride dehydrate, magnesium chloride hexahydrate, sodium hydroxide or hydrochloric acid, purified water
Carmellose Sodium (Alissa) 0.5%	SDU	Water for injections
Xailin® Fresh	SDU	Sodium lactate solution, sodium hydroxide, sodium chloride, potassium chloride, magnesium chloride hexahydrate, calcium chloride dihydrate, hydrochloric acid and water for injection
Celluvisc 1% & Celluvisc 1% Parallel Imports (pack sizes 30 & 60)	SDU	Sodium chloride, sodium lactate, potassium chloride, calcium chloride, purified water
Hydromoor®	SDU	Sodium chloride, potassium chloride, borax, boric acid and water for injections
Tears Naturale®	MDU	Benzalkonium chloride solution, disodium edetate, sodium chloride, potassium chloride, sodium hydroxide and/or hydrochloric acid, concentrated, purified water
Artelac®	MDU	Cetrimide, disodium phosphate dodecahydra, sodium dihydrogen phosphate dehydrate disodium edetate, sorbitol, water for injections
Artelac® & Artelac® Parallel Imports (pack sizes 30 & 60)	SDU	Disodium phosphate dodecahydrate, sodium dihydrogen phosphate dehydrate, sorbitol, water for injections
Minims® Artificial Tears	SDU	Purified water, borax, boric acid
Liquifilm Tears®	MDU	Sodium chloride, sodium phosphate dibasic, sodium phosphate monobasic, benzalkonium chloride, disodium edetate, hydrochloric acid or sodium hydroxide, purified water
Hylo-Care®	MDU	Citric acid anhydrous, sodium citrate, water for injections
Hy-Opti 0.1% & 0.2%	MDU	Sodium phosphate dibasic dodecahydrate, sodium phosphate monobasic monohydrate, sodium chloride, water.
Hylo-Tear®	MDU	Citric acid anhydrous, sodium citrate, sorbitol, water for injections
Thealoz Duo®	MDU	Sodium chloride, trometamol, hydrochloric acid, water for injections
Blink® Intensive	MDU	OcuPure® preservative (sodium chlorite), boric acid, sodium borate, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, purified water
HydraMed®	DDU	Mannitol, sodium citrate, citric acid monohydrate, water for injections
HydraMed®	MDU	Mannitol, sodium citrate, citric acid monohydrate, water for injections
Hylo-Forte®	MDU	Citric acid anhydrous, sodium citrate, sorbitol, water for injections
Artelac® Every Day	MDU	Sodium chloride, potassium chloride, disodium phosphate dodecahydrate, sodium dihydrogen phosphate-dihydrate and water for injection
Artelac® Night	MDU	Glycerol, medium chain triglycerides, sodium hydroxide and water for injections
Lacri-Lube® (pack sizes 3.5 g & 5 g)	MDU	White soft paraffin, liquid paraffin, wool alcohols
Xailin® Night	MDU	White soft paraffin, white mineral oil, lanolin alcohols
Hylo Night®	MDU	Liquid paraffin, light liquid paraffin, wool fat, white soft vaseline

DDU: daily dose unit; MDU: multidose unit; SDU: single dose unit; * Parallel import; ^No further detail provided on company website