Corby Clinical Commissioning Group
Kettering General Hospital NHS Trust
Nene Clinical Commissioning Group
Northampton General Hospital NHS Trust
Northamptonshire Healthcare Foundation Trust

Northamptonshire Prescribing Advisory Group NPAG

REVIEW OF ARTIFICIAL TEARS AND OCULAR LUBRICANTS FOR THE TREATMENT OF DRY EYE

Preferred artificial tears and ocular lubricants for the treatment of dry eye products are identified and the products which are designated "green" by the Northamptonshire Prescribing Advisory Group are listed below.

All other products are "double red" (not recommended for prescribing) for new initiations. Treatment may be continued for existing patients, although switching to "green" products is advised where possible and the patient agrees to the change.

Treatment algorithms have also been developed to aid treatment selection and support decision making.

FIRST LINE
Hypromellose generic 0.3% eye drops
Isopto Plain (hypromellose 0.5% eye drops)
Isopto Alkaline (hypromellose 1% eye drops)
Clinitas gel (Carbomer 0.2% ophthalmic gel)
Viscotears (Carbomer 0.2% ophthalmic gel)
Sno Tears (Polyvinyl alcohol 1.4% eye drops)
FIRST LINE – IF PRESERVATIVE FREE REQUIRED
Hydromoor SDU (Hypromellose 0.3% eye drops)
Lumecare preservative free drops (Hypromellose 0.3% eye drops)
Viscotears SDU (Carbomer *0.2%* liquid gel)
Liquifilm tears SDU (Polyvinyl alcohol 1.4% eye drops)
SECOND LINE
Lacri-Lube eye ointment (white soft paraffin, liquid paraffin, non-ionic hydrous wool fat)
VitA-POS eye ointment (retinol palmitate 250IU/g, liquid paraffin, wool fat) (sterile for 6 months)
Systane eye drops (hydroxypropyl guar, polyethylene glycol 400 0.4%, propylene glycol 0.3%)
Systane Balance eye drops (propylene glycol 0.6%) (lipid layer replacement therapy for meibomian gland dysfunction {MGD} related dry eye and reflex tearing secondary to MGD)
Optive (Carmellose sodium 0.5%, glycerin 1%)
Optive Plus (Carmellose sodium 0.5%, glycerin 1%, castor oil 0.25%)
SECOND LINE – IF PRESERVATIVE FREE REQUIRED
Celluvisc (Carmellose 0.5% and 1% SDU eye drops)
Systane SDU eye drops (hydroxypropyl guar, polyethylene glycol 400 0.4%, propylene glycol 0.3%)
THIRD LINE
Lumecare eye drops (sodium hyaluronate 0.15%)
Artelac rebalance eye drops (sodium hyaluronate 0.15%)
THIRD LINE – IF PRESERVATIVE FREE REQUIRED
Hylo-Tear (Sodium hyaluronate 0.1% eye drops) (sterile for 6 months)
Hylo-Forte (Sodium hyaluronate 0.2% eye drops) (sterile for 6 months)

Patients referred to secondary care should advise the ophthalmologist which preparations they have used previously. It may be necessary for a consultant ophthalmologist to move to a 3rd line agent for cases of severe dry eye.

REVIEW OF ARTIFICIAL TEARS AND OCULAR LUBRICANTS FOR THE TREATMENT OF DRY EYE

Dry eye disease affects up to 8% of the general population. Menopausal and post-menopausal women have a greater tendency towards the condition; 78% of all sufferers from dry eye disease are women. Other contributing factors include long-term contact lens use, concomitant use of medication such as antidepressants or antihistamines, exposure to extremes of hot or cold weather, effects of air conditioning, smoking and excessive exposure to some visual activities such as computer use, television viewing or prolonged reading. There is also an increased prevalence of dry eye disease among those with autoimmune diseases.

There are no national clinical guidelines covering the management of dry eye disease. The accepted main reference source is a report published in 2007 by the International Dry Eye Workshop commonly referred to as the DEWS report.

A key principle for the management of dry eye disease is augmentation of the tear film through the topical administration of artificial tear substitutes. These products enhance tear stability thus reducing loss by evaporation; this, in turn, helps to retain moisture in the eye and relieve the chronic ocular inflammation associated with dry eyes. Artificial tear substitutes help to reduce patient discomfort, improve quality of life and reduce the risk of damage to the corneal epithelium.

Ocular lubricants eye formulations are characterised by being either hypotonic or isotonic buffered solutions containing electrolytes, surfactants and various types of viscosity agents. The DEWS report concluded that although many topical lubricants with various viscosities improve symptoms there is no evidence to suggest that any one agent is superior to another. However, ocular surface inflammation can be exacerbated by the presence of preservatives. Benzalkonium chloride is a preservative frequently used in ophthalmic preparations; evidence suggests that it can destabilise the tear film and also damage the epithelial cells. In patients with mild dry eye, benzalkonium chloride containing products may be well tolerated when used four to six times a day or less. In patients with moderate to severe dry eye, the potential for benzalkonium chloride toxicity is much higher due to decreased tear secretion. The risk of toxicity to preservatives also increases in those people who are using other preservative containing topical eye preparations such as glaucoma treatments. Hence, preservative free products have an increasing role in patients with more severe dry eye conditions and those on concurrent topical therapy for other eye conditions. Preservative free formulations are also indicated for those with a known history of allergy to preservatives and those who wear contact lenses. Preservatives and other excipients such as cetrimide can accumulate on the surface of the contact lens and may cause irritation and possible damage to the surface of the eye.

It should be noted that irritation can still occur with preservative-free drops due to other excipients (for example buffers or electrolytes) in the preparation.

Preservative-free formulations are available in a variety of delivery systems. Many are supplied as single-dose units. These are often small tubes or plastic ampoules designed to administer one drop and to be discarded. <u>These can usually be used to administer a drop into both eyes before discarding</u>, although some medical devices can be used for up to 12 hours after opening.

Some preservative-free formulations are available in 10ml bottles. These are usually patented designs containing either a filter or valve to prevent the entry of micro-organisms. As these preparations are registered as medical devices, they are not subject to medicinal product licensing requirements. Thus the requirement for eye drops to have a 4 week shelf-life after opening does not apply and these multi-dose products can be used for 2-6 months after opening.

Other formulations contain what have been described as 'vanishing' preservatives, for example sodium chlorite or sodium perborate (for example PURITE® used in Optive drops). Sodium chlorite degrades to sodium and chloride free radicals and water upon exposure to UV light after instillation. Sodium perborate is converted to sodium borate, hydrogen peroxide, water and oxygen on contact with the tear film. In higher concentrations, sodium perborate has been reported to be an eye irritant. For patients with severe dry eye, even vanishing preservatives may not totally degrade, due to a decrease in tear volume, and may be irritating.

Presentations

Multi-dose bottle preparations of ocular lubricants are convenient to store and transport. Those licensed as medicinal products must have a 28 day expiry after opening but many ocular lubricants registered as medical devices have extended shelf lives of up to six months after first opening.

Single dose units are bulky to store, particularly if several different eye drops are used. They are less convenient for the patient to carry, especially if they are being used many times a day. They have a greater unopened shelf-life than multidose vials but generate more waste.

Eye ointments may be uncomfortable and blur vision. They should only be used at night, and never with contact lenses.

Recommendations

Under the NORTHAMPTONSHIRE PRESCRIBING ADVISORY GROUP (NPAG) traffic light system, Green status refers to medicines which are appropriate for initiation in both primary and secondary care. Prescribing is appropriate within licensed or local recommendations

First-line treatments

Hypromellose

- **Generic multi-dose hypromellose eye drops 0.3% should be used first line when a lubricating eye product is clinically indicated and are designated GREEN (in bold below).** Hypromellose may need to be administered very frequently (e.g. hourly) in order for the patient to get adequate relief. As illustrated in the cost comparison and excipient table below, many multi-dose hypromellose eye drop formulations contain benzalkonium chloride (BAC). **Preservative free products should only be used when preservatives are not tolerated or contraindicated** (e.g. for allergic patients).
- **Isopto Plain and Isopto Alkaline are also inexpensive brands of hypromellose and are designated GREEN.**

Product	Excipients	Drug Tariff/MIMs Price
Hypromellose generic 0.3% eye drops	**May include benzalkonium**	**£1.21 10ml**

	chloride (BAC)	
Isopto Alkaline eye drops (hypromellose 1%)	**BAC**	**£0.94 10ml**
Isopto Plain eye drops (hypromellose 0.5%)	**BAC**	**£0.81 10ml**
Artelac eye drops (hypromellose 0.32%)	Cetrimide, disodium edetate	£2.99 10ml
Lumecare drops (hypromellose 0.3%)	BAC	£1.67 10ml
Tears Naturale eye drops (hypromellose 0.3% + dextran)	BAC, disodium edetate	£1.89 15ml
Single use only preservative free		
Hydromoor SDU (hypromellose 0.3%)		**£5.75 (30)**
Lumecare preservative free drops (hypromellose 0.3%)		**£5.72 (30)**
Tears Naturale single dose (hypromellose 0.3% + dextran)		£13.26 (28)
Artelac SDU (hypromellose 0.32%)		£13.60 (30) £26.20 (60)

Carbomers and Polyvinyl Alcohol

- Products containing carbomers or polyvinyl alcohol are longer acting than hypromellose and may present suitable alternatives if hypromellose does not provide adequate symptom relief. The tables below summarize the products available, excipients and comparative costs:

Carbomers

- Carbomer formulations cling to the surface of the eye and can reduce the frequency of application to four times daily.

- **In the absence of evidence of superiority of one product over another, the lower cost products are preferred – Carbomer 980 eye drops 0.2% liquid gel (Clinitas or Viscotears) are designated GREEN.** Preservative free products (e.g. single dose Viscotears) should only be used when preservatives are not tolerated or contraindicated.

Product	**Excipients**	**Drug Tariff/MIMs Price**
Clinitas Carbomer gel	**Cetrimide**	**£1.49 10g**
Viscotears liquid gel	**Cetrimide**	**£1.59 10g**
Artelac nighttime gel	Cetrimide,	£2.96 10g
GelTears	BAC	£2.80 10g
Liquivisc gel (carbomer 974P, polyacrylic 0.25%)	BAC	£4.50 10g
Lumecare long lasting tear gel	cetrimide	£2.10 10g
Viscotears liquid gel (single dose)		£5.42 (30)

Polyvinyl Alcohol (PVA)

- PVA containing products increase the persistence of the tear film and can be useful when ocular surface mucin is reduced.

- **In the absence of evidence of superiority of one product over another, the lowest cost product is preferred – *Sno Tears* eye drops are designated GREEN.** Preservative free products (e.g. single dose Liquifilm) should only be used when preservatives are not tolerated or contraindicated.

Product	Excipients	Drug Tariff/MIMs Price
Sno Tears eye drops	**BAC, disodium edetate**	**£1.06 10ml**
Liquifilm tears	BAC, disodium edetate	£1.93 15ml
Single use only preservative free		
Liquifilm tears single dose		**£5.35 (30)**

Second-line treatments

Paraffins

- Paraffin based eye ointments physically lubricate the eye and protect the eye surface from epithelial erosion. They should be used second line for those who have failed to respond adequately to first line treatments.
- Paraffin ointments may feel uncomfortable and normally blur vision; they are best used at night and should never be used with contact lenses.
- There are differences between the constituents of the individual products which might affect tolerability.
- **All three products are similarly priced (see below) with no compelling evidence of superiority of one product over another; Lacri-Lube eye ointment 3.5g or VitA–POS are currently the lower cost options and are both designated GREEN.**

Product	Consitiuents	Drug Tariff/MIMs Price
Lacri-Lube eye ointment	**White soft paraffin,liquid paraffin, non-ionic hydrous wool fat**	**£2.51 (3.5g) £3.32 (5g)**
VitA-POS eye ointment (sterile for 6 months)	**Retinol palmitate 250IU/g, liquid paraffin, wool fat.**	**£2.75 (5g)**
Simple eye ointment	Liquid paraffin 10%,wool fat 10% in yellow soft paraffin	£3.20 (4g)

Carmellose

- Carmellose 0.5% and 1% eye drops preservative-free, single dose products offer an alternative second-line option.
- If 2 or more packs of Celluvisc would be needed per month and a preservative-free drop is not required, it is less expensive to use Optive or Optive Plus as only 1 x 10ml will be needed.
- **Optive eye drops can be used for up to 6 months after opening.**
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Product	Excipients	Drug Tariff/MIMs Price
Optive (Carmellose sodium 0.5%, glycerin 1%)	**PURITE®**	**10ml=£7.49**
Optive Plus (Carmellose sodium 0.5%, glycerin 1%, castor oil 0.25%)	**PURITE®**	**10ml=£7.49**
Single use only preservative free		
Celluvisc single dose		**0.5%: 30 x 0.4ml=£4.80. 1%: 30 x 0.4ml=£3.00.**
Carmize		0.5% 10ml=£7.49. 0.5% 30 x 0.4ml=£5.75. 1% 30 x 0.4ml =£3.00.
Melophthal single dose)		0.5%: 30 x 0.4ml=£5.75 1%: 30 x 0.4ml=£3.00.

Hydroxypropyl guar

- Hydroxypropyl guar preparations (Systane, Systane Ultra) work by stabilising the tear film and increasing tear break-up time. Hydroxypropyl guar is a pH sensitive compound which adapts its viscosity to the ocular surface pH. The surface pH is higher in dry eyes; this results in these preparations becoming more viscous the drier the eye, thus preventing surface desiccation and reducing friction. Hydroxypropyl guar also acts as a mucomimetic
- Systane Ultra formulations contain the same ocular lubricants as Systane but with two additional ingredients: AMP (a pH adjuster) and sorbitol (a sugar). AMP maintains the pH level of Systane Ultra at 7.9 compared to a pH of 7.0 for Systane. This higher pH ensures that the sorbitol and the borate ions in the product do not form a gel matrix within the bottle.
- The claimed advantage of Systane Ultra over Systane is that it is a liquid product at the time of administration and is not associated with the momentary loss of vision experienced following the application of gel-type formulations like Systane.
- While there are theoretical advantages to using Systane Ultra preferentially over Systane, there does not appear to be any comparative evidence to support this claim. The cost comparison below confirms Systane Ultra as significantly more expensive than Systane with no clinically proven advantages.
- **Systane eye drops are recommended as a second line option for those who have not responded sufficiently to hypromellose and alternative first line treatments; they are designated GREEN.** The single dose preservative free products are comparably priced to the multi-dose bottles.
- Systane Balance may be considered for layer replacement therapy for meibomian gland dysfunction (MGD) related dry eye and reflex tearing secondary to MGD
- **Systane eye drops can be used for up to 6 months after opening.**

Product	Contents	Drug Tariff/MIMs Price
Systane eye drops	**Hydroxypropyl guar, polyethylene glycol 400 0.4%, propylene glycol 0.3%**	**£4.66(10ml)**
Systane Balance	**Propylene glycol 0.6%**	**£7.49**
Systane Ultra eye drops	Hydroxypropyl guar, sorbitol, polyethylene glycol 400 0.4%, propylene glycol 0.3%	£6.69 (10ml)

Single use only preservative free		
Systane eye drops single dose	**Hydroxypropyl guar, polyethylene glycol 400 0.4%, propylene glycol 0.3%**	**£4.66 (28)**
Systane Ultra eye drops single dose	Hydroxypropyl guar, sorbitol, polyethylene glycol 400 0.4%, propylene glycol 0.3%	£6.69 (30)

Third-line treatments

Sodium hyaluronate

- There are a wide range of different sodium hyaluronate eye preparations available (see below):

Product	Sodium hyaluronate content	Drug Tariff/MIMs Price
Artelac Rebalance eye drops	**0.15%**	**£4.00 10ml**
Lumecare Sodium Hyaluronate eye drops	**0.15%**	**£3.97 10ml**
Oxyal eye drops	0.15%	£4.15 10ml
Rohto Dry Eye Relief eye drops	0.2% + tamarind seed polysaccharide	£4.10 10ml £4.75 (20*0.5ml)
Single use only and / or preservative free		
Hylo - Tear eye drops (P/F, 6month expiry)	**0.1%**	**£9.80 10ml**
Hylo – Forte eye drops (P/F, 6month expiry)	**0.2%**	**£10.80 10ml**
Clinitas eye drops SDU	0.4%	£5.70 (30)
Hyabak eye drops	0.15%	£7.99 10ml
Hylo – Care eye drops	+ dexpanthenol 2%	£10.30 10 ml
Lubristil eye drops	0.15%	£4.99 (20*0.3ml)
Ocusan eye drops	0.2%	£5.25 (20*0.5ml)
Vismed Gel ophthalmic gel	0.3%	£7.95 10ml £5.98 (20*0.45ml)
Vismed eye drops	0.18%	£6.81 10ml £5.10 (20*0.5ml)

- Hyaluronic acid is found naturally in the human body, mainly in connective tissue, but also in vitreous body and synovial fluid and in the tear fluid of the eye.
- Sodium hyaluronate has water retaining properties and provides a low resistance to blinking. It is highly effective at entrapping water and preventing evaporation; this prolongs any beneficial effects.
- There is very limited clinical evidence to support the use of sodium hyaluronate eye preparations in the treatment of dry eye. The evidence that is available confirms a longer duration of action and a superior affect in terms of relief of symptoms and prevention of

further corneal damage. There is no clinical evidence to inform the debate over optimum strength. As a result of this, **NPAG recommend that, where a sodium hyaluronate preparation is indicated, a product of low acquisition cost should be used.**

- Hylo products have the advantage of longer expiry dates after opening which enables the administration of the full 300 doses from each container and may reduce wastage. They are also the sodium hyaluronate products of choice at recognised centres of excellence in ophthalmology such as Moorfields , Birmingham and Midland Eye Centre and Manchester Royal Eye Hospital.
- **The lower strength Hylo-Tear eye drop formulation (sodium hyaluronate 0.1%) is preferred with Hylo-Forte eye drops (sodium hyaluronate 0.2%) reserved for those who have failed to respond to the 0.1% strength. Both products are therefore also designated GREEN.**
- **Hylo eye drops can be used for up to 6 months after opening.**

References

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Contributors -

Consultant Ophthalmologists, Northampton General Hospital
Miss Menon, Consultant Ophthalmologist, Kettering General Hospital
Chris Moore, Pharmacist, Kettering General Hospital
Rachel Westwood, Lead Surgical Pharmacist, Northampton General Hospital
Shamsul Hoque, Pharmacist, Northampton General Hospital
Sue Smith. Head of Prescribing and Medicines Management, NHS Nene and NHS Corby CCGs

All prices quoted correct as of October 2013.

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Prescribing Guidelines for Lubricating Eye Drops

Does the patient have: Known sensitivity to preservatives Wears Soft contact lenses

NO → Standard 1st Line Treatment (if at any time you suspect a reaction to preservative refer to relevant step of Preservative Free Treatment algorithm)

YES → **See separate algorithm for Preservative Free Treatment**

1st Line Treatment

Hypromellose 0.3%
If this doesn't provide sufficient relief consider either a carbomer or polyvinyl alcohol products which are longer acting.
Either Carbomers
e.g. Viscotears
or
Polyvinyl alcohol
e.g Sno Tears

2nd Line Treatment

Hydroxypropyl Guar
e.g. Systane

Liquid Paraffin
e.g. OC Lacri-Lube or VitA-POS – should be applied at night

Carmellose 0.5% and 1%

3rd Line Treatment

Sodium Hyaluronate
There is no evidence to suggest there are any differences in efficacy between the different strengths of sodium hyaluronate
Advice is to select a product with a low acquisition cost.

Failure to respond to 3rd Line Treatment – Refer to an opthalmologist

Symptoms of mild to moderate dry eyes:	Dryness, scratchy, gritty, foreign body sensation, burning, redness
Suspect severe dry eyes if:	Constant redness, photophobia, impaired vision, history of dry mouth, history of autoimmune disease/vasculitides or Sjogren's syndrome, Trouble keeping their eyes open/blepharospasm, Filaments on the surface of the eye

Prescribing Guidelines for Preservative Free Lubricating Eye Drops

Does the patient have: Known sensitivity to preservatives Wears Soft contact lenses

YES

1st Line Treatment

Hypromellose 0.3% single dose
If this doesn't provide sufficient relief consider either a carbomer or polyvinyl alcohol products which are longer acting.
Either Carbomers
e.g. Viscotears single dose
or
Polyvinyl alcohol
e.g liquifilm tears single use drops
Apply qds for a period of 8 weeks. Emphasize compliance. If first course fails, try another drop from the above category for another 8 weeks

2nd Line Treatment

Hydroxypropyl Guar
e.g. Systane preservative free single dose drops

Liquid Paraffin
e.g. Lacri-Lube (preservative free) or VitA-POS (preservative free)– should be applied at nights

If failure to respond to 2nd Line Treatment proceed to 3rd Line Treatment

3rd Line Treatment

Sodium Hyaluronate
- **Hylo initially**
- **Hylo Forte if Hylo inadequate**

Failure to respond to 3rd Line Treatment – Refer to an opthalmologist

Symptoms of mild to moderate dry eyes:	Dryness, scratchy, gritty, foreign body sensation, burning, redness
Suspect severe dry eyes if:	Constant redness, photophobia, impaired vision, history of dry mouth, history of autoimmune disease/vasculitides or Sjogren's syndrome, Trouble keeping their eyes open/blepharospasm, Filaments on the surface of the eye