

Prescribing and Clinical Effectiveness Bulletin

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

In this special edition of the *PACE Bulletin* we review the use of artificial tears and ocular lubricants for the treatment of dry eye. Preferred products are identified and a summary of formulary approvals is provided below. Treatment algorithms have also been developed to aid treatment selection and support decision making.

SUMMARY OF PACEF DECISIONS: FEBRUARY 2013 UPDATE

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Hypromellose generic 0.3% eye drops	For the treatment of dry eyes	GREEN Approved for Joint Formulary First Line
Carbomer 980 ophthalmic gel (<i>Clinitas Carbomer Gel</i>)	For the treatment of dry eyes	GREEN Approved for Joint Formulary Alternative First Line (carbomer preparation)
Carbomer 0.2% ophthalmic gel (<i>Viscotears</i>)	For the treatment of dry eyes	GREEN Approved for Joint Formulary Alternative First Line (carbomer preparation)
Polyvinyl alcohol 1.4% eye drops (<i>Sno Tears</i>)	For the treatment of dry eyes	GREEN Approved for Joint Formulary Alternative First Line (PVA preparation)
<i>Systane</i> eye drops (hydroxypropyl guar, polyethylene glycol 400 0.4%, propylene glycol 0.3%)	For the treatment of dry eyes	GREEN Approved for Joint Formulary Second line (hydroxypropyl guar preparation)
<i>Lacri-Lube</i> eye ointment (white soft paraffin, liquid paraffin, non-ionic hydrous wool fat)	For the treatment of dry eyes	GREEN Approved for Joint Formulary Second Line (preservative free paraffin preparation)
Sodium hyaluronate 0.1% eye drops (<i>Hylo-Tear</i>)	For the treatment of dry eyes	GREEN Approved for Joint Formulary Third Line (hyaluronate preparation)
Sodium hyaluronate 0.2% eye drops (<i>Hylo-Forte</i>)	For the treatment of dry eyes	GREEN Approved for Joint Formulary Third Line (hyaluronate preparation)

This bulletin has been created specifically to convey details of decisions taken at the Prescribing and Clinical Effectiveness Forum (PACEF) to all stakeholders across the Lincolnshire Healthcare Community in both primary and secondary care. Back issues of the *PACE Bulletin* and other PACEF publications are available through the Lincolnshire NHS website (www.lincolnshire.nhs.uk). Click on 'Commissioning' and follow the links to PACEF.

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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.

PACEF 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.** 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).

Product	Excipients	Price
Hypromellose generic 0.3% eye drops	May include benzalkonium chloride (BAC)	£1.21 10ml
<i>Artelac</i> eye drops (hypromellose 0.32%)	Cetrimide, disodium edetate	£2.99 10ml
<i>Isopto Alkaline</i> eye drops (hypromellose 1%)	BAC	£0.94 10ml
<i>Isopto Plain</i> eye drops (hypromellose 0.5%)	BAC	£0.81 10ml
<i>Lumecare</i> drops (hypromellose 0.3%)		£1.67 10ml
<i>Tears Naturale</i> eye drops (hypromellose 0.5% + dextran)	BAC, disodium edetate	£1.89 15ml
Single use only preservative free		
<i>Artelac</i> SDU (hypromellose 0.32%)		£13.60 (30) £26.20 (60)
<i>Hydromoor</i> SDU (hypromellose 0.3%)		£5.75 (30)
<i>Lumecare</i> preservative free drops (hypromellose 0.3%)		£5.72 (30)
<i>Tears Naturale</i> single dose (hypromellose 0.3% + dextran)		£13.26 (28)

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.

Product	Excipients	Price
<i>Artelac</i> nighttime gel	Cetrimide,	£2.96 10g
<i>Clinitas</i> Carbomer gel		£1.49 10g
<i>GelTears</i>	BAC,	£2.80 10g
<i>Liposic</i> gel	cetrimide	£2.96 10g £7.92 3 x 10g
<i>Liquivisc</i> gel (carbomer 974P,	BAC	£4.50 10g

polyacrylic 0.25%)		
Lumecare long lasting tear gel	cetrimide	£2.10 10g
Viscotears liquid gel	cetrimide	£1.59 10g
Viscotears liquid gel (single dose)		£5.42 (30)

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

Polyvinyl Alcohol (PVA)

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

Product	Excipients	Price
<i>Liquifilm</i> tears	BAC, disodium edetate	£1.93 15ml
<i>Liquifilm</i> tears single dose		£5.35 (30)
<i>PVA 1.4% Tubilux</i> eye drops		£1.63 15ml
<i>Sno Tears</i> eye drops	BAC, disodium edetate	£1.06 10ml

- **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.

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	constituents	Price
<i>Lacri-Lube</i> eye ointment	White soft paraffin, liquid paraffin, non-ionic hydrous wool fat	£2.51 (3.5g) £3.32 (5g)
Simple eye ointment	Liquid paraffin 10%, wool fat 10% in yellow soft paraffin	£3.21 (4g)
<i>VitA-POS</i> eye ointment	Retinol palmitate 250IU/g, liquid paraffin, wool fat.	£2.75 (5g)

Carmellose

- Carmellose 0.5% and 1% eye drops (*Celluvisc*) are preservative-free, single dose products that offer an alternative preservative free option.

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*, PACEF were unable to find 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.

Product	Contents	Price
<i>Systane</i> eye drops	Hydroxypropyl guar, polyethylene glycol 400 0.4%, propylene glycol 0.3%	£4.66(10ml)
<i>Systane</i> eye drops single dose	Hydroxypropyl guar, polyethylene glycol 400 0.4%, propylene glycol 0.3%	£4.66 (28)
<i>Systane Ultra</i> eye drops	Hydroxypropyl guar, sorbitol, polyethylene glycol 400 0.4%, propylene glycol 0.3%	£6.69 (10ml)
<i>Systane Ultra</i> eye drops single dose	Hydroxypropyl guar, sorbitol, polyethylene glycol 400 0.4%, propylene glycol 0.3%	£6.69 (30)

- ***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. *Systane Ultra* eye drops should only be used for those who have not responded sufficiently to the standard *Systane* product.** The single dose preservative free products are comparably priced to the multi-dose bottles.

Third-line treatments

Sodium hyaluronate

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

Product	Preservative free (as listed MIMS)	Sodium hyaluronate content	Price
Artelac Rebalance eye drops		0.15%	£4.00 10ml
<i>Artelac Splash</i> eye drops SDU	√	0.2%	£7.00(30) £11.20 60
<i>Clinitas</i> eye drops SDU	√	0.4%	£5.70 (30)
<i>Hyabak</i> eye drops	√	0.15%	£7.99 10ml
<i>Hylo - Tear</i> eye drops	√	0.1%	£9.80 10ml
<i>Hylo – Forte</i> eye drops	√	0.2%	£10.80 10ml
<i>Hylo – Care</i> eye drops	√	+ dexpanthenol 2%	£10.30 10 ml
<i>Lubristil</i> eye drops	√	0.15%	£4.99 (20)
<i>Lumecare Sodium Hyaluronate</i> eye drops		0.15%	£3.97 10ml
<i>Ocusan</i> eye drops	√	0.2%	£5.25 (20)
<i>Oxyl</i> eye drops		0.15%	£4.15 10ml
<i>Rohto Dry Eye Relief</i> eye drops		0.2% + tamarind seed polysaccharide	£4.10 10ml £4.75 (20)
<i>Vismed Gel</i> ophthalmic gel	√	0.3%	£7.95 10ml £5.98 (20)
<i>Vismed</i> eye drops	√	0.18%	£6.81 10ml £5.10 (20)

- 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, **PACEF recommend that, where a sodium hyaluronate preparation is indicated, a product of low acquisition cost should be used, such as *Artelac Rebalance* eye drops (0.15% sodium hyaluronate), *Lumecare Sodium Hyaluronate* eye drops (0.15% sodium hyaluronate) or *Oxyl* eye drops (0.15% sodium hyaluronate).**
- **Following a review of the evidence available, PACEF supported a request from local ophthalmologists to have the *Hylo* range of products available for use. *Hylo* products have the advantage of longer expiry dates after opening which enables the administration of the full 300 doses from each container and reduces 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 designated GREEN.****

- Hyaluronate is generally well tolerated, but there are differences in the excipients used in different formulations. As a result of this, *Artelac Rebalance* eye drops (0.15% sodium hyaluronate) and the single dose formulation *Artelac Splash* (0.2% sodium hyaluronate) are approved as alternatives in patients unable to tolerate products from the *Hylo* range.

References

1. www.dryeyesmedical.com
2. <http://www.dryeyesmedical.com/research.aspx>
3. *The Ocular Surface*, 2007, pp.77. 2007 Report of the International Dry Eye Workshop (DEWS). [Online] Tear Film and Ocular Surface Society. Available at: www.tearfilm.org/dewsreport
4. *MIMS* May 2013

Acknowledgements

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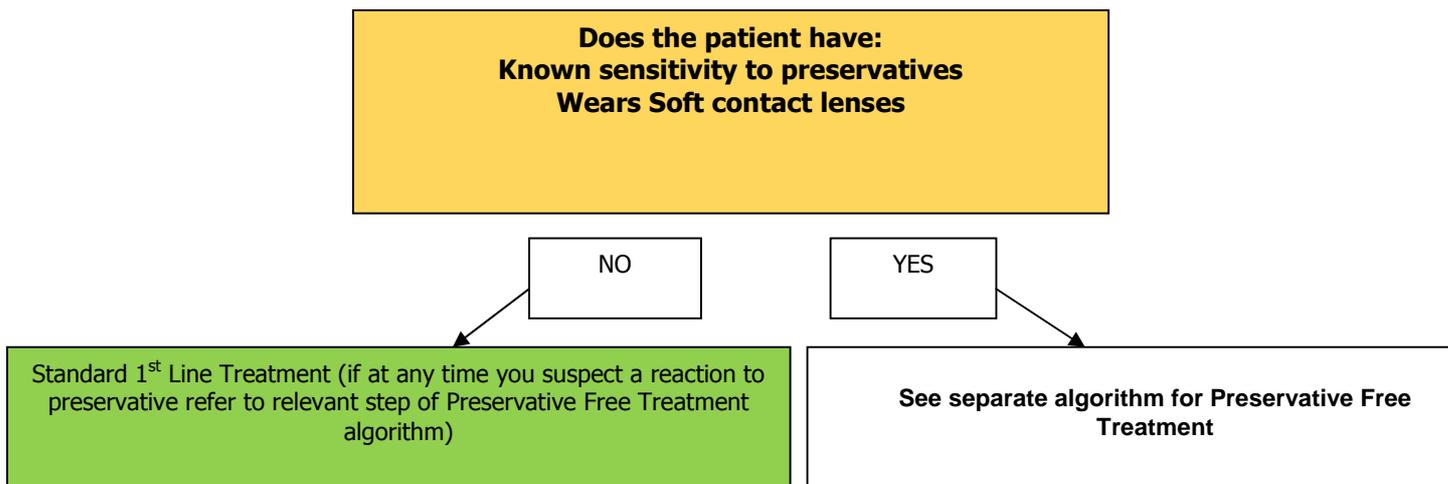
Cathy Johnson
Interface Lead Pharmacist
Greater East Midlands Commissioning Support Unit

Stephen Gibson
Head of Prescribing and Medicines Optimisation
Greater East Midlands Commissioning Support Unit

All prices quoted correct as of May 2013.

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Prescribing Guidelines for Lubricating Eye Drops



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. Clinitas Gel or Viscotears
or
Polyvinyl alcohol
e.g. Sno Tears
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

If failure to respond to at least two 1st Line treatments proceed to 2nd Line Treatment

2nd Line Treatment

Hydroxypropyl Guar
e.g. Systane
e.g. Systane Ultra – should only be reserved for those who have not responded sufficiently to standard Systane
Liquid Paraffin
e.g. OC Lacri-Lube or VitA-POS – should be applied at night

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

3rd Line Treatment

Sodium Hyaluronate
There is no evidence to suggest there are any differences in efficacy between the different strengths of sodium hyaluronate
PACEF advice is to select a product with a low acquisition cost.
e.g. Artelac Rebalance, or Oxyal, or Vismed

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

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

**United Lincolnshire Hospitals and
Prescribing and Clinical Effectiveness Forum**

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 e.g. Hydromoor
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

If failure to respond to at least two 1st Line treatments proceed to 2nd Line Treatment

2nd Line Treatment

Hydroxypropyl Guar
e.g. Systane preservative free single dose drops
e.g. Systane Ultra preservative free single dose drops – should only be reserved for those who have not responded sufficiently to standard Systane
Liquid Paraffin
e.g. OC 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
There is no evidence to suggest there are any differences in efficacy between the different strengths of sodium hyaluronate
PACEF advice is to select a product with a low acquisition cost.
e.g. Clinitas single use drops (sodium hyaluronate 0.4%)
Vismed single use drops (sodium hyaluronate 0.18%)
Hylo-Tear (sodium hyaluronate 0.1%) preservative free drops or Hylo- Forte (sodium hyaluronate 0.2%) preservative free drops

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

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

