New Medicine Assessment

HYDROCORTISONE SODIUM PHOSPHATE (SOFTACORT) EYE DROPS

for Treatment of mild non-infectious allergic or inflammatory conjunctival diseases.

Recommendation: BLACK:

NOT recommended for use by the NHS in Lancashire and South Cumbria.

This preparation did not demonstrate a significant difference in effectiveness compared to agents already used to treat mild non-infectious allergic or inflammatory conjunctival diseases.

Summary of supporting evidence:

- Evidence appears to be limited to one small, manufacturer sponsored trial, with no control group.
- No serious adverse events (AEs) were observed during the study. Most AEs were mild and none were severe.
- Duration of treatment in the trial did not exceed 14 days so safety data for longer treatment courses (off-license) is not available.
- If treatment duration was limited to a short course following specialist initiation, then there would be little need for primary care prescribing.
- NICE recommends that the prescribing of ocular steroids for dry eye disease should be by a specialist in secondary care.
- Prolonged use of corticosteroid treatment has shown to cause ocular hypertension/glaucoma especially for patients with previous IOP increase induced by steroids or with pre-existing high IOP or glaucoma, and also cataract formation, especially in children and elderly population.
- If corticosteroids are used in chronic or recurrent conjunctivitis, baseline and periodic measurement of IOP and pupillary dilation should be performed to evaluate for glaucoma and cataract.
- Systemic effects may arise from absorption of drugs into the general circulation either directly from the conjunctival sac or after the excess preparation has drained down through the tear ducts into the nasal cavity.
- Single use eye drops are more costly and produce more waste packaging than standard drops; their use should be limited to those requiring *preservative-free* eye treatment.
- Softacort single-use eye drops are mid-range in cost vs other single use steroid eye drops.
- Pan Mersey and Moorfields have hydrocortisone 0.335% preservative free eye drops on their formularies.
- Hydrocortisone is considered a weaker corticosteroid, therefore there is a theoretical risk that this could result in a more prolonged course being required or repeat steroid courses, to achieve the same clinical efficacy as more potent steroid.

Details of Review

Name of medicine (generic & brand name)**:**

Hydrocortisone sodium phosphate (Softacort)

Strength(s) and form(s):

3.35 mg/ml eye drops, 0.4ml solution in single-dose container

Dose and administration:[1]

The recommended dosage is 2 drops, 2 to 4 times daily, in the affected eye.

The duration of this dosing regimen will generally vary from a few days to a maximum of 14 days. Gradual tapering off up to one administration every other day may be recommended in order to avoid a relapse.

A single-dose container contains enough solution to treat both eyes. For single use only.

This medicinal product is a sterile solution that does not contain a preservative. The solution from one individual single-dose container is to be used immediately after opening for administration to the affected eye(s).

Patients should be instructed:

- to avoid contact between the dropper tip and the eye or eyelids,

- to use the eye drops, solution immediately after first opening of the single-dose container and to discard the single-dose container after use.

Nasolacrimal occlusion by compression of lacrimal ducts for one minute may reduce systemic absorption.

In case of concomitant treatment with other eye drops, solution, instillations should be spaced out by 5 minutes.

BNF therapeutic class / mode of action:[2]

Steroid > Hydrocortisone has equal glucocorticoid and mineralocorticoid activity

Licensed indication(s):

Treatment of mild non-infectious allergic or inflammatory conjunctival diseases.1

Proposed use (if different from, or in addition to, licensed indication above):

As per licensed indication.

Course and cost:

2 drops, 2 to 4 times daily, in the affected eye, for maximum 14 days.

30 single-dose units = £10.99

Maximum licensed use = 4 x 14 = 56

Assuming 60 will be issued, 2 x £10.99 = £21.98 maximum cost per 14 day course

Prices as per Drug Tariff Aug 2022

Current standard of care/comparator therapies:

- See 'Relevant NICE guidance' section of this document for a summary of the primary care recommended therapies for **inflammatory conjunctival diseases**.
- The TFOS DEWS II Report recommends topical corticosteroids for a limited duration at step 2 and topical corticosteroids for longer duration at step 4, in the staged management of **dry eye disease**.[3]

- Other available topical ocular steroids include:[4]
  - prednisolone acetate 1% (most potent)
  - dexamethasone 0.1%
  - betamethasone 0.1%
  - prednisolone sodium phosphate 0.5%
  - fluorometholone 0.1% (least potent)

NB. Not all ocular steroids are available as single use formulations.

Relevant NICE guidance:

NICE CKS

- **Conjunctivitis – allergic:**[5] Education, lifestyle measures, environmental modification, saline drops or artificial tears, topical antihistamine or dual action mast cell stabilizer/topical antihistamine, topical ocular diclofenac.
- **Dry eye syndrome:**[6] Education, lifestyle measures, environmental modification, optimise other medications, tear supplementation. The National Institute for Health and Care Excellence (NICE) recommend that people with dry eye disease which does not respond to several drops of artificial tears per day should be referred to secondary care for consideration of specialist treatment such as ciclosporin or corticosteroids.
- **Blepharitis:**[7] Do not prescribe topical steroids.

Technology Appraisals

- Ciclosporin for treating dry eye disease that has not improved despite treatment with artificial tears (2015)

Background and context

Conjunctivitis is inflammation of the conjunctiva due to allergic or immunological reactions, infection (viral, bacterial or parasitic), mechanical irritation, neoplasia, or contact with toxic substances. Ocular allergy is the commonest form of non-infectious conjunctivitis and can significantly impact productivity and quality of life. Some less common severe forms of ocular allergy can also be sight-threatening. The prevalence of ocular allergy (seasonal and perennial allergic conjunctivitis) has been increasing worldwide.[8] Allergic conjunctivitis is a common condition estimated to affect up to 40% of the population.[5]

Dry eye syndrome is a chronic condition characterised by inflammation of the ocular surface and reduction in quality and/or quantity of tears. Many factors including Meibomian gland dysfunction, blepharitis, age-related lacrimal gland deficiency, low blink rate, malposition of eyelids, contact lens wear, corneal refractive surgery, medication, and underlying conditions such as Sjogren's syndrome and diabetes mellitus can lead to dry eye symptoms. Dry eye syndrome is estimated to affect between 5% and 33% of the adult population worldwide.[6]

Steroids disrupt the inflammatory cascade by immobilizing arachidonic acid, downregulating multiple cytokine pathways including the vascular endothelial growth factor (VEGF) pathway, stabilizing cell membranes and mast cell granules, inhibiting leukocyte interaction, and slowing diapedesis. Ocular steroids are potent and relatively inexpensive, but their side effects are considerable.[9]

Summary of evidence

Summary of efficacy data in proposed use:

The College of Optometrists (2022)[10]

For dry eye, topical steroids (such as fluorometholone or loteprednol) may be considered for short-term use in some cases. The usual precautionary surveillance is required.

American Academy of Ophthalmology (2018)[11]

Seasonal/Perennial Allergic Conjunctivitis: Mild allergic conjunctivitis can be treated with an over-the-counter topical antihistamine/vasoconstrictor agent or with the more effective second-generation topical histamine H1-receptor antagonists. If the condition is frequently recurrent or persistent, mast-cell stabilizers can be used. If the symptoms are not adequately controlled, a brief course (1 to 2 weeks) of topical corticosteroids with a low side effect profile can be added to the regimen.

If corticosteroids are used in chronic or recurrent conjunctivitis, baseline and periodic measurement of IOP and pupillary dilation should be performed to evaluate for glaucoma and cataract.

TFOS DEWS II Report (2017)3

The management of dry eye disease (DED) is complicated, due to its multifactorial aetiology. critical to appropriate management. The ultimate aim of DED management is to restore the homeostasis of the ocular surface and tear film, through breaking the vicious cycle of the disease. In general, management approaches begin with conventional, low-risk and easily accessible patient-applied therapies such as over-the-counter lubricants for early stage disease, and progress to more advanced therapies for more severe forms of DED. However, it must be understood that there is significant heterogeneity in the DED patient population. The approach cannot be overly formulaic and these recommendations may be modified and overlapped as required by practitioners based on an individual patient profile.

Chan et al (2021)

A systematic review and critical appraisal of clinical practice guidelines (CPGs) and summary of the recommendations for non-infectious and infectious conjunctivitis. CPGs published on non-infectious and infectious conjunctivitis between 2010 and March 2020 were reviewed and evaluated, fifteen CPGs from five sources remained for data extraction.

For conditions that were acute, persistent, recurrent, or not resolved by non-pharmacological interventions, a topical dual-acting agent was recommended. Besides topical corticosteroid, immunosuppression was strongly recommended for severe non-infectious conjunctivitis.

Kallab et al (2019)[12]

Sixty patients with chronic DED were included in this study. Patients were randomized to receive hydrocortisone 0.335% eye drops (Softacort) in two different application schemes: Group 1 was treated for 12 days four times a day followed by 2 days two times a day (14 days in total, intense treatment group). Group 2 received treatment for 8 days three times a day and 3 days two times a day resulting in a total treatment period of 11 days (standard treatment group). Patients in both groups were asked to continue and document the use of their own topical lubricants in a diary. The primary outcome of the study was defined as change in conjunctival hyperemia at visit 3 (2 weeks after treatment start). A clinically relevant change in conjunctival hyperemia grading was considered 20% or more compared to baseline. IOP was measured at three time points after treatment start as a safety variable.

Conjunctival hyperemia as assessed using the Efron scale significantly decreased in the study eye by - 25.0 ± 24.2% in the intense treatment group and by - 18.6 ± 18.8% in the standard treatment group, at the end of the treatment period (visit 3). At visit 4, this effect was still present (- 23.9 ± 21.2% in the intense treatment group and - 27.5 ± 23.3% in the standard treatment group, p = 0.001 each vs. baseline). No statistically significant difference in the change in Efron scale was observed between the two treatment groups (p = 0.26, intense and standard treatments).

Frequency of artificial tear instillation was 3.0 ± 2.4 drops/day at baseline in the intense treatment group and significantly decreased to 1.2 ± 2.3 drops/day at visit 3 (p = 0.001 vs. baseline) and to 2.5 ± 2.2 drops/day at visit 4 (p = 0.04 vs. baseline). In the standard treatment group, frequency of artificial tear instillation decreased from 3.4 ± 3.1 drops/day at baseline to 0.9 ± 1.2 at visit 3 and 2.4 ± 3.1 drops/day at visit 4 (p \ 0.001 vs. baseline each). No difference was observed between the two groups (p = 0.42).

This study did not include a control group, had a small sample size and follow up was limited to 14 days after cessation of treatment. The study was funded by Laboratories Thea, France, who manufacture Softacort.

Elabjer et al (2020)[13]

Records of 15 consecutive patients with mild to moderate DED (13–32 points) according to the ocular surface disease questioning (OSDI scoring tool), treated twice daily with topical preservative-free hydrocortisone 0.335% were collected between February 2019 and March 2019. All patients used concomitantly preservative-free lubricants with sodium hyaluronate as an active ingredient.

Data was collected from 2 visits: one prior to treatment (Day 0) and one 15 days later (Day 15). On both occasions, a clinical eye examination and the following tests were performed: central precorneal tear film, fluorescein tear breakup time, Schirmer test, corneal grading staining carried out according to the Oxford schema, ocular surface disease index, spatial distribution of the precorneal tear film thickness on a pachymetry map and IOP.

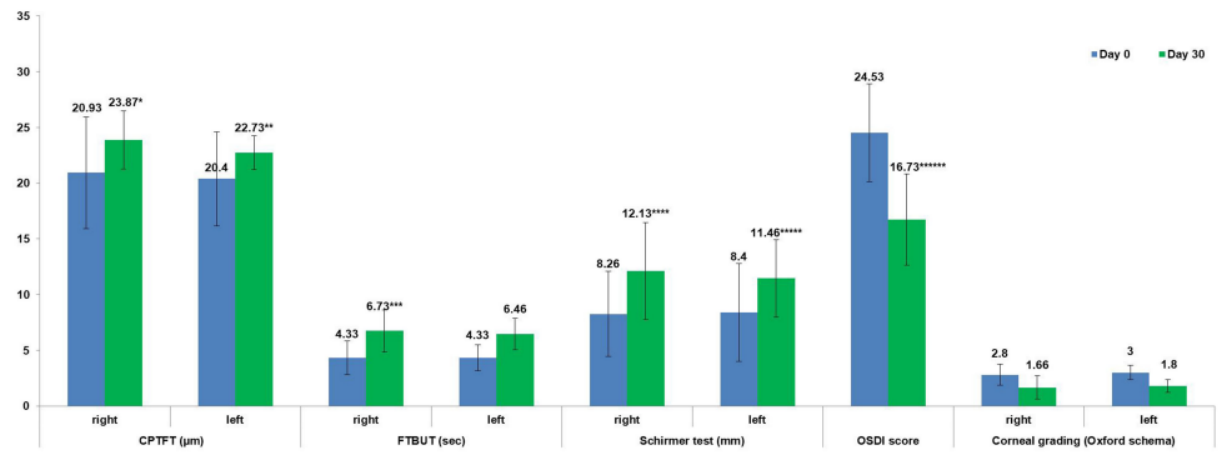

Figure 1 Mean results for central precorneal tear film thickness, fluorescein tear breakup time, Schirmer test, ocular surface disease index and corneal grading at Day 0 and Day 15. *p=0.000015, **p=0.0003, ***p=0.009, ****p=0.03, *****p=0.002, ******p=0.001.
Abbreviations: CPTFT, central precorneal tear film thickness; FTBUT, fluorescein tear breakup time; OSDI, ocular surface disease index; corneal grading staining done by Oxford schema; sec, second.

Limitations of this study consist of its retrospective setting with no reference group and its small sample size. Furthermore, as DED is a chronic condition, a longer follow-up time would have been needed to evaluate improvement stability.

Summary of safety data:

BNF (2022)[14]

Systemic effects may arise from absorption of drugs into the general circulation either directly from the conjunctival sac or after the excess preparation has drained down through the tear ducts into the nasal cavity. The extent of systemic absorption following ocular administration is highly variable due to a number of factors (e.g. drainage, blink rate, tear turnover). Nasal drainage of drugs is associated with eye drops much more often than with eye ointments.

The three main dangers associated with topical corticosteroid use are:

- a 'red eye', when the diagnosis is unconfirmed, may be due to herpes simplex virus, and a corticosteroid may aggravate the condition, leading to corneal ulceration, with possible damage to vision and even loss of the eye. Bacterial, fungal, and amoebic infections pose a similar hazard;
- 'steroid glaucoma' can follow the use of corticosteroid eye preparations in susceptible individuals;
- a 'steroid cataract' can follow prolonged use.

Kallab et al (2019)12

IOP did not change at the end of the treatment period in either the intense dose (baseline, 14.1 ± 1.8; day 14, 13.9 ± 2.0 mmHg) or in the standard dose group (baseline, 12.8 ± 1.9; day 14, 13.3 ± 2.1 mmHg). No difference between the two groups was observed (p = 0.45).

No serious adverse events (AEs) were observed during the study. Most AEs were mild and none was severe.

MHRA (2017)[15]

Corticosteroids: rare risk of central serous chorioretinopathy with local as well as systemic administration

Central serous chorioretinopathy is a retinal disorder that has been linked to the systemic use of

corticosteroids. Recently, it has also been reported after local administration of corticosteroids via inhaled and intranasal, epidural, intra-articular, topical dermal, and periocular routes.

Central serous chorioretinopathy (CSCR) is characterised by the accumulation of subretinal fluid at the posterior pole of the fundus, ultimately causing retinal detachment. CSCR typically affects one eye only and can cause vision to be blurry and distorted, with objects often appearing smaller and distorted in the affected eye. Patients may also have difficulty with bright lights and contrast sensitivity.

Summary of product characteristics1

Contraindications

- Hypersensitivity to the active substance or to any of the excipients;
- Known glucocorticosteroid-induced ocular hypertension and other forms of ocular hypertension;
- Acute herpes simplex virus infection and most of the other corneal viral infections at the acute stage of ulceration (except when combined with specific chemotherapeutic agents for herpes virus), conjunctivitis with ulcerative keratitis even at the initial stage (positive fluorescein test);
- Ocular tuberculosis;
- Ocular mycosis;
- Acute ocular purulent infection, purulent conjunctivitis and purulent blepharitis, stye and herpes infection that may be masked or aggravated by anti-inflammatory drugs.

Special warnings and precautions for use

Topical steroids should never be given for an undiagnosed red eye.

Thinning of the cornea and sclera (caused by diseases) may increase the risk of perforations with the use of topical steroids.

Patients should be monitored at frequent intervals during treatment with hydrocortisone eye drops. Prolonged use of corticosteroid treatment has shown to cause ocular hypertension/glaucoma especially for patients with previous IOP increase induced by steroids or with pre-existing high IOP or glaucoma, and also cataract formation, especially in children and elderly population.

The use of corticosteroids may also result in opportunistic ocular infections due to the suppression of host response or to the delay of their healing. In addition, topical ocular corticosteroids may promote, aggravate or mask signs and symptoms of opportunistic eye infections.

Wearing of contact lenses during treatment with corticosteroid eye drops should be avoided.

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Undesirable effects

Burning and stinging may occur immediately after instillation. These events are usually mild and transient and have no consequences.

Increase of intra-ocular pressure induced by corticosteroid topical treatment has been generally observed within 2 weeks of treatment.

Diabetics are also more prone to develop subcapsular cataracts following topical steroid administration.

The following adverse drug reactions have not been observed with hydrocortisone, but are known

with other topical corticosteroids: Allergic and hypersensitivity reactions, delayed wound healing, posterior capsular cataract, opportunistic infections (herpes simplex infection, fungal infection), glaucoma, mydriasis, ptosis, corticosteroid-induced uveitis, changes in corneal thickness, crystalline keratopathy, blurred vision.

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

Strengths and limitations of the evidence:

Strengths

- No serious adverse events (AEs) were observed during the study. Most AEs were mild and none were severe.
- Pan Mersey and Moorfields have hydrocortisone 0.335% preservative free eye drops on their formularies.
- The role of steroid eye drops is established.

Limitations

- Evidence appears to be limited to one small, manufacturer sponsored trial, with no control group.
- Duration of treatment in the trial did not exceed 14 days so safety data for longer treatment courses (off-license) is not available.
- Prolonged use of corticosteroid treatment has shown to cause ocular hypertension/glaucoma especially for patients with previous IOP increase induced by steroids or with pre-existing high IOP or glaucoma, and also cataract formation, especially in children and elderly population.

Summary of evidence on cost effectiveness:

Hydrocortisone 0.335% (Softacort)

2 drops, 2 to 4 times daily in the affected eye, for maximum 14 days.

30 single-dose containers = £10.99

Maximum use = 4 x 14 = 56

Assuming 60 will be issued, 2 x £10.99 = £21.98 maximum cost per course

Prices as per Drug Tariff Aug 2022

Comparator single-use therapies

Prednisolone 0.5% 0.5ml minims = £0.61/unit

Dexamethasone 0.1% 0.5ml minim = £0.57/unit

Hydrocortisone 0.335% 0.4ml unit dose = £0.36/unit

Dexamethasone 1mg/ml 0.4ml unit dose= £0.32/unit

Dexamethasone 0.1% 0.3ml unit dose = £0.28/unit

Prescribing and risk management issues:

Shelf life:

2 years in the outer packaging.

After first opening of the sachet: use the single-dose containers within 1 month.

After first opening of the single-dose container: use immediately and discard the single-dose container after use.

Commissioning considerations:

Innovation, need and equity implications of the intervention:
None identified
Financial implications of the intervention:
In the 12 month period from July 2021 to July 2022 Softacort was issued 217 times in primary care across L&SC. There was prescribing across all localities, with minimal prescribing in BwD and East Lancs.
Service Impact Issues Identified:
None identified
Equality and Inclusion Issues Identified:
None identified
Cross Border Issues Identified:
The **Pan Mersey APC** have hydrocortisone 0.335% preservative free eye drops on their formulary as 'Amber Initiated', meaning that the product requires specialist initiation of prescribing. Prescribing to be continued by the specialist until stabilisation of the dose is achieved and the patient has been reviewed. **Moorfields Eye Hospital** NHS Foundation Trust have hydrocortisone 0.335% eye drops on their formulary for the following indications: (i) Treatment of mild non-infectious allergic or inflammatory conjunctival diseases. (licensed) (ii) Treatment of mild non-infectious allergic or inflammatory ocular surface diseases. (off-label) (iii) Minimising of ocular surface scar tissue formation. (off-label use). The **Greater Manchester Medicines Management Group** (GMMMG) do not have hydrocortisone eye drops on their formulary.
Legal Issues Identified:
None identified
Media/ Public Interest:
None identified

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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