Treatment of Sjögren's Syndrome – Topical Treatment of Dry Eyes and Mouth

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INTRODUCTION —

Sjögren's syndrome (SS) is a multi-system disorder that may present to many different specialists including general internal medicine and its subspecialties (especially rheumatology, chest medicine, neurology, hematology, nephrology, psychiatry), surgery and its subspecialties (especially ophthalmology, otolaryngology), and related specialties such as oral medicine.

Although it is important that one physician, usually the rheumatologist, assumes overall responsibility for the care of the patient, SS is a paradigm for a condition requiring a multi-disciplinary team approach to management. Since patients see multiple specialists, treatments often are not coordinated and the therapy for one manifestation may lead to exacerbation of another aspect.

Therapy can be grouped into at least three separate aspects:

1) ***topical therapy of dry eyes and dry mouth***; similarly, treatment of other dry mucosal surfaces (nasal membranes, vaginal, upper airways) or skin require particular attention.

2) ***treatment of systemic manifestations*** of SS and recognition of therapies for other conditions (such as blood pressure or depression) that can exacerbate dryness complaints (see section on Systemic Therapy);

3) ***treatment of fatigue, vague cognitive, and pain syndromes*** that resemble the poorly defined syndrome termed "fibromyalgia" that do not correlate closely with measures of inflammation (see section on Systemic Therapy).

This section will focus on topical therapy of eyes, mouth and other mucosal surfaces.

Topical therapy depends upon the severity of symptoms, which may vary from simple artificial tears or artificial saliva to use of moisturizing agents for skin and vaginal dryness. It also depends on **recognition of local infections** such as ocular or oral infections (including viral, bacterial and candida)[1-3] that the patient may think are simply manifestations of dry eye and require a different topical therapy, as well as **recognition of vasculitis or thrombotic manifestations** affecting the mucosal membranes where more aggressive systemic immune modulatory or chemotherapeutic agents may be required (see

"Clinical Systemic Manifestations of Sjögren's Syndrome: Treatment of Glandular and Extraglandular Manifestations).

I. GENERAL PRINCIPLES OF TOPICAL THERAPY OF THE EYE

The rheumatologist does not replace the ophthalmologist, but must be familiar with the overall guidelines of topical eye care, as the SS patient may have problems related to the eyes. It is important for the rheumatologist to assess whether patients' presented objective signs are commensurate with their voiced symptoms. Also, the rheumatologist must determine how urgently patients must seek care of their ophthalmologist when acute ocular symptoms arise; e.g., if a patient's ocular symptoms need immediate evaluation "today" or whether they can wait until the ophthalmologist's "next available" appointment. General guidelines are provided in Table 1.

A. Topical treatment of KERATOCONJUNCTIVITIS SICCA — Aqueous Tear Deficiency

The primary focus of treatment of the dry eye is replacing or supplementing the deficient tears; most artificial tears are available over-the-counter (OTC) but they differ in their preservatives, type of vehicle to provide viscosity, and ease of application. Although a great deal of the process is "trial and error" based on patient preference, certain guidelines will help the patient and physician navigate through the large array of products. Several simple principles should be remembered:

a) *preserved tears should not be used more than four times per day*, to prevent the build up of preservatives on the corneal surface;

b) *tears differ in their viscosity* with the more viscous tears more likely to last longer, but also causing more blurring;

c) *ocular lubricants can be used at night*, but overuse is common, and is associated with blepharitis (discussed below) due to blockage of the meiobian gland;

d) *the use of artificial tears may vary with weather conditions and local environment*; for example, use of computers leads to decreased blink rate and airplanes are "famous" for low humidity environments, as well as the more easily recognized situations of dry winds that occur in drier parts of the country;

e) *it takes about 2-3 days to rebuild an adequate tear film but only about half an hour to destroy an adequate tear film in a windy, dry environment; thus,* patients should plan ahead with their use of tears.

f) *operating rooms and post-operative recovery rooms (where dry oxygen is generally blown across the face of the patient) also tend to be very low-humidity environments*--discussed below.

Additional **measures at preserving the tear film** may utilize minimizing tear loss through:

a) *decreasing drainage from the ocular surface by occluding the the puncta of the eyelid*, (a process called **punctual occlusion**), which may be done with "temporary collagen plugs that dissolve spontaneously, plastic plugs that are inserted by the opthalmologists, or permanent occlusion by electrocautery methods by theopthalmologist.

b) *Additional medicated eye drops* (such as topical cyclosporine or topical steroids)

c) *Solid pellets of carboxylmethylcellulose (lacriserts*) that dissolve more slowly in the eye

Although the term Keratoconjunctivitis Sicca (KCS) generally refers to an "acqueous tear deficiency," the changes and instability of the tear film are far more complex than simple a deficiency of water. The content of proteins is altered (including increased inflammatory cytokines and metalloproteinases), as well as alteration in the mucins that stabilize the tear film to the ocular surface, provide and provide viscosity, and alterations in the lipid layer that retards the evaporative rate. Thus, KCS symptoms really reflect the patient's sense of increased viscosity as the upper lid traverses the orbital globe and is inadequately lubricated by an unstable tear film.

Indeed, recent studies have demonstrated that the symptoms of dry eyes are better correlated with alterations in mucin content than in rate acqueous tear flow as measured by the familiar ***Schirmer's test***. Also, the lipid layer is and tear break up time are poorly correlated with the aqueous tear flow rate.

Artificial tears

For most patients with dry eyes, the regular use of artificial tears is the mainstay of treatment. Artificial tears differ in their presence/absence of preservatives, their osmolality, and their viscosity. The choice of tears is very much a matter of trial and error. A brief outline of several types of artificial tears is listed in Table 1. They differ in whether they form the gel in the bottle (carboxylmethylcellulose) or only at the higher pH of the ocular surface in other preparations.

For each preparation, higher viscosities are listed as either (a) mild, (b) moderate, (c) severe or (d) night-time. Thus, choice of a tear can be rather bewildering. Thus, it is a common misconception among patients,

rheumatologists, and many other specialists that over-the-counter artificial tears are simply interchangeable.

Examples of commonly used artificial tears that contain preservatives *include Liquifilm Tears®, Liquifilm Forte®, Tears Plus®, IsoptoTears®, Tears Naturale Polyquad®* and *Tears Naturale Forte®, Polytears®, Viscotears®, AkwaTears®,* and many others (Table 2). These tears differ in viscosity (i.e., how long they last) but the more viscous tear may cause blurring or blockage of the Meibomian glands (i.e., blepharitis, discussed below).

One artificial tear that differs in osmolality is *Hypotears®*, that has a decreased osmolality in order to compensate for higher salt concentrations in the dry eye. In another difference among artificial tears is the inclusion of a lipid-stabilizing agent in *Systane®* drops. Although these latter drops may have theoretical advantage, the choice of drops remains very much a balance of patient choice and the cost of drops.

Virtually all of the manufacturers of preserved tears also make a preservative-free tear version such as *Refresh®, Tears Naturale Free®, Moisture Eyes Free®, TheraTears Free®,* and many others. Given that these preservative-free tears are generally dispensed as single-use vials that are generally discarded after opening, and that a large quantity is required by the patient, they can be quite expensive to purchase at the drug stores or even supermarkets.

Thus, we urge patients to consider buying larger quantities of their chosen product over the Internet at sites such as: http://www.dryeyezone.com

General Guidelines to the Patient for Selecting an Artificial Tear

When deciding upon a choice of replacement fluid, a number of questions need to be asked (Table 2A-2B):

1. *How much replacement is needed?* Drops may need to be applied frequently, every two to four hours. If artificial tears are used more than four times a day, then a preservative-free tear should be used to avoid adverse effect of the preservative. Patients should be aware that their requirements may change depending upon the atmosphere in which they find themselves. As an example, the frequency of replacement should increase when entering a dry or low humidity environment.

2. *How long do the drops last?* Higher viscosity drops and ointments last longer but more frequently cause blurring. The duration of the benefit also depends on the evaporative rate, which is increased in SS patients. The lipid layer plays an important role in retarding evaporation. The main source of the lipid layer is the meiobian glands in the lower lid, so attention to blepharitis (lid

scrubs) and intake of 3 or 6 omega acids that contribute to the lipid layer is important[4, 5]

3. Do the drops cause burning or itching? These symptoms may indicate topical irritation (see below). In some patients, the patient may prefer a "hypotonic eye drop," as the dryness has led to a relatively high osmotic level in their residual tear film[6].

4. Does the patient have the manual dexterity to manipulate droppers and dispensers? In these patients, the use of punctual plugs (or punctual occlusion) may be considered[7].

5. Are all the symptoms due to SS or is there another diagnosis, such as blepharitis[8]?

Potential problems —
There are a number of problems that can be associated with the use of artificial tears; the physician should be familiar with these problems and the available solutions. As an example, most standard preparations contain preservatives, stabilizers, or solubilizers. Although they extend the lifetime of products, they may be associated with a degree of sensitivity (producing itching or irritation of the eye), especially if used, as many patients require, every two to four hours. If this occurs, an alternative preparation, using a different preservative can be tried.

Other types of drops include *Mucolytic agents* (e.g., acetylcysteine) which may useful when there is an overproduction of mucus which accumulates as filaments in the eye. However, the objectionable smell of this therapy limits compliance.

Time-Release Artificial Tears
A solid hydroxymethylcellulose pellet (*Lacrisert*®, Merck and Co, West Point PA) contain hydroxypropyl cellulose but no preservative) may be useful in some patients. The patient must have enough tears to dissolve the pellet and enough dexterity to place the Lacrisert® into the eye without damage to the corneal surface.

Ocular lubricants —
A more viscous preparation such as an ocular lubricant (examples: *Refresh PM®, Lacrilube®, Duratears®, Viscotears®)* may be used at night, during airline flights, or during time in a dry environment (such as in the operating room) when visual blurring is not a problem. At night, a longer-acting and more viscous lubricant ointment (e.g., *Refresh PM®, Genteal Gel*® or *Puralube®)* is useful because it reduces the rate of tear evaporation. It is not recommended for daytime use since it may also cause blurred vision.

When lubricants are used, only a small amount (such as 1/8" [2-3 mm]) may be used since larger amounts are likely to lead to blockage of the Meiobian glands

and subsequent blepharitis. Patients using lubricants at night should perform lid-scrubs (using warm water and diluted baby shampoo [about 1 part in 300]) in the morning to prevent blepharitis. A popular lubricant (*Genteal® Gel* [Novartis]) recently was withdrawn from the market after certain job lots were found to have bacterial contamination, but may return to the market when this problem is corrected.

Recognition of certain environments that exacerbate dry eyes

Patients should employ methods to prevent ocular complications. It may take two or three days to build (heal) the tear film, but only two to three hours in a dry environment for it to be disturbed. Among considerations to counsel patients:

a) Travel to areas with low humidity and dry winds are obvious red flags.

b) Automobile travel not only involves dry heating and air conditioning, but also presents additional problems of pollution from the road.

c) Many large offices that use central heating/air conditioning are extremely dry.

d) There has been recent recognition that the blink rate goes down dramatically among patients who sit at computer terminals for prolonged periods.

The increased frequency of use of artificial tears by patients in these environments may help to prevent complications and increase comfort.

We advise our SS patients to anticipate:

► *dry outdoor environments,*
► *dry indoor environments,*
► *increased pollution (including presence of smokers),*
► *strong winds,*
► *increased time of computer use that decreases blink rate*

…as an individual "weather forecast" for their ocular surface health, and prepare to "dress" their eyes accordingly.

As referenced above, another important environment to expect -- and prevent -- SS dry eye complications including corneal abrasions is *the Operating Room* where the humidity is very low, and particularly in the post-operative recovery room where the patient frequently has non-humidified oxygen administered by a facemask. To that end:

a) We recommend that patients use an *ocular lubricant prior to surgery* to help prevent complications.

b) As many operating rooms do not have certain specialized medicines used to treat the eyes of the SS patient available, we urge patients to *take their eye/mouth medications with them to the hospital* (despite the hospital's instructions to leave medications at home), as these "specialty" items are not on most hospital formularies.
   - We remind patients to ensure that their attending surgeon/hospitalist writes an order in the hospital chart permitting the patient to bring their own SS medicines from home and self-administer PRN and/or have them administered in the hospital.

c) We advise the use of artificial tears be started prophylactically in most patients before they go into dry environments.

B. Conservation of tears —

Various measures are employed to conserve the tear film for as long as possible.
- **Side shields** (e.g., *Moist Eye® Moisture Panels,* Eagle Vision Inc., Memphis TN) can be fitted onto glasses, reducing the evaporation rate of normal or artificial tears.
- **Ski or swim goggles** are very effective at reducing evaporation, but social considerations limit their use.
- **Wrap-around sunglasses** are more acceptable socially.
- Other general measures to minimize the loss of tears include use of **air humidifiers**, particularly in rooms in which a good deal of time is spent such as a bedroom and home office, as well as the occasional use of a **moist washcloth** over the eyes.

Punctal occlusion —
If frequent installation of artificial tears is inadequate or impractical, punctal occlusion is the treatment of choice. It is a highly effective method for maximizing the preservation of tears.

This technique involves sealing of the lacrimal puncta, through which the tears normally drain away to the nose; 90 percent of drainage occurs through the inferior punctum.

Several different types of punctual plugs are available and plugs (called “intra-cannicular plugs”) that do not protrude onto the corneal surface seem to be preferred [16].

However, it should be noted that local infections and even pyoderma-like reactions have been reported around the plugs [17,18]. A recent study by **Mansour** et al[9] compared the same SS patient when a punctal plug was placed in only one eye, and found significant improvement with the punctal occlusion.

Some ophthalmologists begin with *preliminary temporary plugs* (show picture 1) to ensure that punctal occlusion does not result in excess tear accumulation. However, temporary plugs often do not adequately block the puncta. Thus, failure to improve comfort with these temporary devices does not preclude the use of permanent punctal occlusion. Also, temporary plugs might be used to avoid a permanent change in patients who might regain near-normal lacrimal function with appropriate therapy.

The availability of intra-cannicular plugs (that do not protrude into the ocular surface) has the added advantage that they can be removed non-surgically.

When indicated, *laser or hand-held thermal cautery* can be used for a permanent closure.

It is important to realize that punctal occlusion is a tear preservation strategy; as a result, it is of little benefit, unless supplemented with artificial lubricants, in those with minimal to no tear production.

Ophthalmologists may also use *"bandage" contact lenses* to help retard tear evaporation [32]. Although evaporation may be retarded, the risk of corneal abrasion from irritants that get underneath the lens must be considered.

C. Corticosteroid and Cyclosporin containing artificial tears

Hong et al[10] recently reported fifty-three Sjögren's syndrome patients whose KCS was refractory to routine artificial tears and who were given preservative free steroid drops. All patients were treated with topical non-preserved 1% methylprednisolone solution. Initial therapy consisted of eye drops 4 times a day for 2 weeks, and then patients were reevaluated and tapered off the medication every 2 weeks until discontinuation. Tear film breakup time (TBUT), Schirmer test, corneal fluorescein staining, and subjective symptom scores were measured. Additionally, impression cytology of the bulbar conjunctiva was performed. Results:

a) A reduction in subjective symptoms and fluorescein staining, and an improvement in TBUT and Schirmer test results, was observed after treatment.
b) Impression cytology specimens revealed a significantly increased number of periodic acid-Schiff-positive cells after treatment.
c) After the first pulse therapy, mean time of benefit was 56.6 weeks and 11 patients recurred and were retreated.
d) After the second pulse therapy, mean time of improvement was 72.4 weeks and only 1 patient recurred.
e) No serious complications, including intraocular pressure elevation and cataract formation, were encountered during the entire follow-up period.

Topical cyclosporine —
The United States Food and Drug Administration approved the use of a cyclosporine ophthalmic emulsion (0.05 percent) based upon four studies that compared this agent to a castor oil-based vehicle in 1200 patients [19].

The following studies are illustrative of the effectiveness and adverse effects of topical cyclosporine use:

a) Of 293 subjects receiving ***cyclosporine***, a decrease of 38 percent in infiltrating CD3 positive T-cells in the conjunctival biopsies was seen versus a 15 percent increase in those receiving the vehicle alone [20].

b) Among 877 patients randomly assigned to receive twice-daily instillation of cyclosporine (0.05 percent, 0.1 percent) or vehicle alone, there was increased wetting on Schirmer testing in 15 percent of patients receiving the active drug [21].
   - *The most common adverse effect* was a burning sensation in the eyes after administration;
   - *Less frequent side effects* were red eye, epiphoria (watering eyes), foreign body sensation, itching, and blurred vision.

Into the Future for topical agents for dry eyes …

Current available therapies focus on alleviating symptoms and reducing objective signs in order to restore the health of the ocular surface. Depending on the etiology of the pathology, it is possible to use lubricants, secretagogues, biological tear substitutes or anti-inflammatory drugs, either independently or combined[11].

In the past several years, the therapies under clinical trial are devoted to stimulating tear components (e.g., diquafosol, a P2Y receptor agonist)[12], or mucin secretion (e.g., an amino acid analogue of quinolinone[13]). Others include *gefarnate*[14], a water-insoluble terpene fatty acid that contributes to restoring mucins on the ocular surface, or *cevimeline*, an oral cholinergic agonist that reduces the symptoms associated with dry eye.

Other potential compounds described in patents are in a lower phase of drug development. These compounds come from different families of therapies, and among others, can be found in the form of steroidal and nonsteroidal anti-inflammatory agents, vitamins A and D, neurotransmitters and neuropeptides.

Diquafosol —
An alternative method to deliver increased water to the ocular surface is the stimulation of fluid transit through the conjunctiva. Diquafosol tetrasodium is a purinogenic stimulator (P2Y2 receptor agonist) that stimulates fluid transit across the conjunctiva and increases mucin secretion on the ocular surface. A

submission to the FDA (originally in 2003) was amended in 2005 and is currently pending approval.

Tacrolimus —
Another study reported the use of 0.02 percent tacrolimus in aqueous suspension on tear production in dogs with keratoconjunctivitis sicca (KCS) [24]. They suggest that this agent (which is water soluble, in contrast to relatively insoluble cyclosporin), may be a promising alternative to topical CsA for treatment of KCS, and may be beneficial in patients with less than optimal response to topical CsA.

Topical NSAIDs —
Topical nonsteroidal eye drops (such as indomethacin) have been found to provide symptomatic relief, but they should be used with caution and under close monitoring, and the treatment should be promptly discontinued if corneal epithelial defects develop or worsen during treatment [25].

Other topical treatments for dry eyes — Corticosteroids, Testosterone
Other topical approaches that may be of benefit to SS patients are preservative-free corticosteroids[15] and calcium-containing compounds. Artificial tears containing androgen are currently in clinical trial, based on their promising study in murine models [26].

D. Other causes of painful eye symptoms in the SS patient

Blepharitis —
The evaporation of the tear film is limited by a thin lipid coating over the tear film [27]. The source of these lipids is the ***Meiobian glands*** that are predominately located in the margin of the eyelids near the eyelashes. The blepharitis can be *anterior* (generally staphylococcal or sebhorreic) or *posterior* (Meibomian gland dysfunction).

- ***Blepharitis is probably the most common disease entity seen in the general ophthalmologist's office*** [28].

In SS patients, *inflammation of the lower glands is common* and may be caused by "plugging" by viscous secretions (including the overuse of ocular lubricants and ointments) leading to a low-grade staphylococcal infection that alters glandular histopathology, and also gland dysfunction. Glandular dysfunction is also increased in patients with rosacea, and sebhorreic dermatitis.

Treatment consists of two phases (**acute** phase and **maintenance** phase).

Acute phase treatment involves intensive therapy to rapidly bring the disease under control.

In the maintenance phase, the goal is to indefinitely continue the minimum amount of therapy that is necessary to keep the disease quiet. A regimen of warm compresses followed by eyelid scrubs is the most critical element of effective blepharitis control. This therapy:

1. *removes the eyelid debris* (which can be colonized by bacteria),
2. *reduces the bacterial load* (mechanically as well as by lysis of bacteria due to detergent action of the soap in lid scrubbing), and
3. *stabilizes the tear film* by releasing oily secretions from the meibomian glands, thus reducing tear evaporation (so the dry eye symptoms are also reduced).

Warm compresses may be combined with **eyelid massage**. This is especially important in patients who have Meibomian gland dysfunction (MGD).

► *Therefore, after every one minute of warm compresses, massaging the eyelid gently will be useful.*

There are several ways of performing **lid scrubbing**. The scrubbing should be directed at the base of the eyelashes on the eyelid margin. Soaps (cleansing agent used) should not have excessive perfume or lotion content.

- *Neutrogena® bar soap:* This bar soap is used to form lather on the clean fingertips. Lather is then applied with fingertips on the eyelid margin and eyelash bases for up to 1 minute (with eyelids gently closed so that soap does not enter the eye). This is followed by a facial rinse.

- *Johnson's® Baby Shampoo:* The baby shampoo is first diluted 1:1 with water in a 'cup' formed by the palm of the hand. This is then mixed by rubbing with the clean fingertips and then applied in a gentle oval scrubbing motion to the margin and eyelash bases of the closed eyelid for 1 minute, followed by a fresh water facial rinse.

The soap solution (bar soap or baby shampoo) can alternatively be diluted in a container (e.g., plastic cup) and scrubbing performed using a washcloth wrapped around a finger (after dipping it in the diluted soap solution). A cotton-tip applicator may be used alternatively.

There are several commercially available cleansing pads that are presoaked in a cleansing solution (*OCuSOFT® Lid Scrubs* or *Novartis® Eye-Scrub)*. These cleansing pads are an equally effective, albeit more expensive method of lid scrubbing, and are claimed to be less irritating to the eyelids. One study showed them to be the preferred choice by patients as compared to other methods of lid scrubbing.

E. Additional issues in the SS patient such as safety of LASIK surgery

Patients with SS and refractive errors often ask whether they are candidates for keratoplasty by photoreactive methods such as LASIK® (laser keratoplasty for vision improvement).

▶ ***At present, the diagnosis of SS is considered a clinical contraindication to laser keratoplasty***, as it may exacerbate pre-existing dryness and even lead to corneal abrasions [29].

▶ **What are the risks of blepharoplasty and LASIK? —**
Another common question is the relative risk of increasing ocular damage after cosmetic surgery such as blepharoplasty. In some patients, the "tightening" of the eyelids may lead to poor apposition of the lids particularly at night and lead to "exposure" keratitis. This problem is also common in patients with co-existent thyroid exophathalmy, where examination with *Rose Bengal* reveals a thin crescent of increased staining in the area of exposure. Therapy for exposure keratopathy consists not only of moisturizers (discussed above) but also the use of paper strips to gently elevate the lower lid at night.

Patients with dry eyes may have exacerbation of their symptoms after LASIK (laser *in situ* keratomileusis) [30].

In SS patients, complications after LASIK correlate with:

- *delayed tear clearance*,
- *undercorrected aqueous tear deficiency*, and
- *nonrecognized lipid tear deficiency* [30]

▶ ***Heightened risk with Refractive surgery in Asian eyes:***
Asian patients had greater ocular surface staining, poorer tear film stability and lower tear volume before LASIK and at all times after LASIK.

- ***Chronic dry eye*** persisting six months or more after LASIK was diagnosed in 28 per cent of Asian eyes and 5 per cent of Caucasian eyes ($p < 0.001$).
- Asian patients with chronic dry eye were predominantly female, reported dry eye symptoms, had greater ocular surface staining and lower tear secretion, stability and volume before surgery [31].

Is contact lens use permitted? —
Some SS patients may tolerate contact lenses. The use of "rigid" lenses, (that do not maintain their integrity by imbibing fluid from the tear film), are preferred. Lenses should not be worn overnight.

III. XEROSTOMIA- TOPICAL TREATMENT AND ORAL AGENTS TO STIMULATE SECRETION

A. Treatment of dry mouth —

Treatment of dry mouth claims to alleviate symptoms and prevent complications such as dental caries, gum disease, halitosis, salivary gland calculi, and dysphagia. Two major components of this regimen are stimulation of existing salivary flow and replacement of salivary secretions.

B. Treatment of oral complication consequences of oral dryness is the loss of teeth —

Saliva has multiple functions within the oral cavity that include:

1) *Lubrication of the mucosa* so that the tongue can help with cleaning out residual food that leads to dental plaque and bacteria;

2) *Buffering of acids* that reabsorb calcium from teeth;

3) *The ability to modulate viral, bacterial, and fungal populations* in the mouth.

C. Replacement of oral secretions —

Replacement of oral secretions is most simply accomplished by frequent sips of water. The water does not have to be swallowed, but can be rinsed around the mouth and expectorated. Although water provides temporary moisture, it does provide the lubricating properties that are characterized by the mucin/water mixtures that constitute normal saliva.

A number of artificial saliva preparations that provide more viscosity/lubrication than water are available. These preparations contain hypro-mellose or methylcellulose, sometimes with animal mucins to reduce viscosity.

An illustrative selection (not all-inclusive) of products available in the United States and the United Kingdom are listed (show table 2A-2B). The efficacy of most of these preparations has not been subjected to critical analysis and they should only be tried after a proper trial of simple water.

There seems to be wide variation in individual preferences and, given the large number of products available, it is logical to encourage patients to try several different formulations. One explanation for the variable response may be differences in viscosity [13].

Artificial salivas provide longer lasting lubrication than water and are therefore useful at night or in patients with dentures. Most are dispensed as sprays, but lozenges or pastilles are available to subjects for whom sprays would be difficult to use, due to arthritis.

If simple measures such as sips of water or sugar-free chewing gum are insufficient, it is reasonable to try a spray such as *Oasis®, Salivart®, Mouth Kote®* and several other brands have recently appeared. In other patients, a gel such as *Oral Balance®* can be helpful particularly at night.

D. **Stimulation of existing salivary flow —**

- *Simply sucking on sugarless candies* or dried fruit slices such as peaches or nectarines can stimulate flow in many patients.
- *Citrus flavored sugarless tablets* (e.g., *Salivasure®*, Scandinavian Health and Beauty Products, Perkasie, PA) are available. These tablets may also contain malic acid, normally found in fruits such as apples or pears, which stimulates salivary flow.
- *Use of maltose lozenges* may reduce symptoms of oral dryness as suggested by an observational study in 100 subjects [2].
- *Sugar-free chewing gums*, containing various sweeteners such as aspartame, saccharin, and sorbitol can also be helpful.

Care must always be taken not to increase the risk of dental caries.

E. **Oral agents that stimulate saliva**

Secretagogues —
Two muscarinic agonists *(pilocarpine* and *cevimeline)* have recently been approved as secretagogues for the treatment of symptoms of xerostomia in Sjögren's syndrome (SS) [54]. These agents stimulate the M1 and M3 receptors present on salivary glands, leading to increased secretory function.

Cevimeline —
Cevimeline (Evoxac®) is a derivative of acetylcholine with a higher affinity for muscarinic M1 and M3 receptors on the lacrimal and salivary epithelium than for receptors on heart tissue [7]. It is also known in the literature as (±)-cis-2-Methylspiro[1, 3-oxathiolane-5, 3′-quinuclidine, SN-201 and AF106[16]. It has been shown to significantly increase saliva flow and patient oral "quality of life" in two double blind US studies[17, 18]. Doses of 30 or 60 mg three times daily alleviate the symptoms of dry mouth, dry eyes, and stimulate salivary flow; the 30 mg dose is nearly as effective as the higher dose and is better tolerated [8].

The efficacy of cevimeline was illustrated in a study that randomly assigned 197 patients with either primary or secondary SS to cevimeline or placebo [9]. Patients' global assessments of dryness were improved significantly more often by cevimeline 30 mg three times daily than by thrice daily doses of 15 mg or

placebo (65, 32, and 35 percent, respectively). It has also been reported in double blind studies in other countries including Japan[19, 20] and China[21].

Major side effects of cevimeline include excessive sweating, nausea, rhinitis, diarrhea, and visual disturbances. It is contraindicated in patients with intractable asthma, narrow-angle glaucoma, and active iritis, as these patients were excluded from the clinical trials.

Cevimeline (also known in neuropharmacology literature as AF102) was originally developed for treatment of Alzheimer's disease (where M1 agonist activity is neuroprotective) and found to increase salivation through its M1 and M3 agonist activities [55]. It was subsequently shown effective in increasing saliva flow and symptom improvement in SS [9].

In addition to simply increasing saliva flow, Cevimeline induced changes in the protein content of saliva, including the release of aquaporin 5 (AQP5) with lipid rafts, amylase, mucin, and lysozyme[20, 22]. Changes in saliva AQP5 levels after cevimeline administration occurred simultaneously with changes in saliva flow rates. Aquaporins selectively conduct water molecules in and out of the cell, while preventing the passage of ions and other solutes.

Also known as **water channels,** aquaporins are integral membrane pore proteins and AQP5 has been implicated in both salivary/lacrimal glands[23-26] and in brain[27, 28] as an important regulator of water transport after cholinergic stimulation.

Pilocarpine —
(Salagen®), a muscarinic agonist that stimulates predominantly muscarinic M3 receptors used at doses of 5 mg three or four times daily, can significantly increase aqueous secretions in patients with residual salivary gland function [3,4]. Unfortunately, side effects (sweating, abdominal pain, flushing, increased urination) may limit its use. Pilocarpine was initially used for treatment of radiation xerostomia and subsequently for SS [55,56].

The longest reported study of pilocarpine in SS evaluated 20 patients taking 10 to 30 mg/day for one year.

- Six patients complained of sweating and four of abdominal cramps [5]. None of the patients chose to discontinue taking pilocarpine because of these side effects.
- The subjective benefit in oral comfort did not correlate closely with objective changes in salivary flow, indicating the importance of mucin in forming a water/mucin gel that lowers friction associated with movement of the buccal mucosal surfaces and the tongue.

In addition to effects upon xerostomia, pilocarpine may improve symptoms of ocular dryness, although without any objective change in tear production [6].

In our experience, *pilocarpine* has a shorter onset of action but also a shorter duration of action with suggesting dosing four times a day. This leads to a narrow window between efficacy and side effects of sweating. Several reports have suggested benefit from time release preparations of pilocarpine as buccal inserts[29, 30] or as transdermal application[31].

Cevimeline is generally used three times a day. However, we recommend gradually increasing the dose and taking it about 30 minutes before meals. Initially, patients may have some increased symptoms of gastric acidity (also stimulated by the muscarinic receptors), but this can be minimized by use of a proton pump inhibitor while initiating therapy.

Pilocarpine and cevimeline (both muscarinic agonists) do more than increase the flow of water. Studies of saliva from treated patients show changes in the types of small molecules termed defensins and alterations in post-translational modification (particularly glycosylation) in saliva [32-34].

Numoisyn—
Numoisyn is a newly available product that appears to be the same as Salinum[35], a linseed oil extract that is available as a liquid and as a throat lozenge. It has been reported in patients with oral dryness related to radiation.

Oral interferon alpha-- was reported as promising in early studies [10,11]. However in the pivotal trial [12], the salivary flow rates in the interferon-treated group and the placebo group were not statistically significant. Neither were there significant differences in the changes in self-reported oral comfort or symptoms of oral dryness, throat dryness, or difficulty swallowing dry food.

F. **Oral hygiene**

It is extremely important that the SS patient regularly:

1. *floss* their teeth after meals,
2. *receive regular professional dental hygiene treatments* including fluoride treatments (discussed below) at frequent intervals such as every three months [33], and recognition that certain fluoride treatments might discolor dental enamel or denture material.
3. *recognize the role of dietary factors* with respect to the correlation between sucrose intake and caries [34].
4. *maintain the use of particular uniquely beneficial toothpastes*. Most commercial toothpastes have the detergent sodium lauryl sulfate (SLS) which may be irritating. Thus, other toothpastes are available that use other detergents such as: Biotene®, Tom's of Maine®, and Spry Toothpaste® with xylitol (many products are listed on the website www.dentist.net with selection of the dry mouth section of products.

Although frequently grouped together, it is important to consider dental caries as distinct from periodontal disease.

Development of dental caries is a major problem in subjects with dry mouth. Avoidance of this complication in subjects with SS follows the same principles as in the rest of the population and these include:

1. *meticulous oral hygiene* with frequent flossing,
2. *frequent visits to the dentist* (at least every six months), and
3. *plaque control*.

A common problem is that cosmetic dentists may place "full veneer" crowns over small carious regions resulting in these areas are no longer being accessible to intensive dental care. As a result, the carious tooth may progress until the tooth is lost and crowns fail.

Again, toothpastes specifically designed for dry mouth are available (e.g., *Biotene*® toothpaste, Laclede Labs, Gardena, CA). These lack the detergents present in many toothpastes that can irritate the dry mouth.

Additional recommendations:

a) *Toothbrushes with special features* include interdental brushes (for cleaning between teeth)
b) *electric toothbrushes* (for patients, such as those with arthritis, who are unable to use a normal brush effectively).
c) *Use of dental floss*
d) *fluoride* either as toothpaste or mouth rinses and *fluoride varnishes* [14].

Oral candidiasis —

A dry mouth is not necessarily a painful mouth, but may become a painful mouth if the patient develops oral candidiasis, and patients with SS are at greater risk of developing this complication [1]. Thus, patients can have dry mouth for many years and only present to the clinician when the mouth becomes painful. Also, there may be a change in the sense of taste and examination reveals a decrease in the number of papillae on the tongue.

Oral candidiasis is particularly frequent following antibiotic treatment or the use of glucocorticoids. Affected patients present with mouth pain, erythematous or white patches on the mucosal surfaces, and loss of tongue papillae. A common clue to the presence of oral candida is angular cheilitis and atrophic changes of the buccal mucosa[36].

The appearance of erythematosus candidiasis (one of the most common presentations) on the roof of the mouth is small red petechial lesions[37]. This appearance is different than the plaque like candida infection that clinicians are used to looking for in patients with severe immunosuppression.

Another presentation of low grade candidiasis in the SS patient is leukoplakia-like lesions, especially in the buccal recesses. The candida infection can occur despite a careful program of regular dental hygiene[38] Treatment of this low grade erythematosus candida is a slow process that involves:

a) *treatment of the angular cheilitis with topical chlortrimazole cream* twice a day for at least 2 weeks;

b) *special cleaning treatment of the dentures* (if being used by patient) at night by cleaning in solutions that will disinfect the denture without discoloring the materials (0.2% chlorhexidine solution is often used) and additionally using nystatin powder to "brush" the dentures after they have soaked overnight in the cleaning solution.

c) *use of oral mouth rinses* 3 to 4 times per day with a solution that contains "Mylanta" as the vehicle (since most other oral rinses contain alcohol based dilutents; 300 ml of Mylanta can be added to nystatin exlixir solution (20ml), benadryl liquid (20 ml, to serve to decrease pain) and doxycycline 100 mg. (In past editions of UpToDate, the vehicle was "peptobismal" but the formulation of this compound has recently been changed, so now we recommend "Mylanta" as the vehicle.) This mouth rinse is available in many pharmacies where it is known as "Stanford Radiation Therapy Mouth Rinse®" or as "XYZ Mouth Rinse®" as patients use it with severe oral dryness after radiation to head and neck. In our clinic, we have the pharmacy simply dispense the components, as this is much less expensive than having the pharmacy "compound" the mixture.

d) *nystatin 200 mg tablets* (1 per day) for 5 days; in some patients, the yeast may be resistant to nystatin or chlortrimazole and topical amphotericin may be required[39].

e) nystatin vaginal suppositories (sucked like lozenges) or amphotericin B lozenges used daily; they are taken with sips of water for periods and used once or twice a day for up to 6 weeks [1].

Prevention of dental caries —
The loss of teeth in SS patients results from a combination of low oral pH that facilitates loss of dental calcium and the alterations of oral flora that lead to accelerated decay [35-39]. These problems have been recently reviewed [40,41].

For individuals with very low to no salivary production, the amount of phosphate and calcium ions available for incorporation onto the tooth surface and enhancement of the remineralization process may be limited. These individuals could possibly benefit from the exogenous addition of calcium phosphate ions commercially available as toothpaste, in specialized chewing gums, and as a solution.

A double-blind clinical trial examined the efficacy of a dentifrice containing calcium phosphate and found modest benefit in the prevention of root caries in SS, but no benefit on coronal caries was noted [41]. These findings are consistent with the observation that individuals with salivary dysfunction are prone to root and incisal caries, rather than coronal caries.

Caphosol® is one of the more common prescription preparations that is a supersaturated calcium phosphate rinse.

Another clinical trial examined the caries preventive effect of a mouth rinse containing casein derivatives coupled to calcium phosphate in patients with Sjögren's syndrome and dry mouth secondary to radiation therapy [42]. The mouthwash failed to show complete efficacy [41]. The majority of studies supporting the addition of calcium and phosphate as an aid to remineralization have been primarily short-term studies in animals and humans. There is currently no agreed-upon formulation/concentration of calcium phosphate or consensus on how often exposure should occur which could influence the results of any clinical trial. Definitive proof would require large long-term clinical trials, which are notoriously difficult and expensive [43].

Artificial sweeteners that are not fermentable by acid-producing bacteria have also been suggested to aid remineralization process [44]. Initial data primarily from studies done with children has shown that certain natural sweeteners such as xylitol and sorbitol (usually in a chewing gum formulation) have a significant anti-caries effect. There has been some suggestion that the caries-preventative effect of xylitol/sorbitol is due to the effect of chewing alone, via the production of saliva [40,41]. But other mechanisms have been suggested including:

a) the growth inhibition of caries-inducing bacteria,
b) the selection of xylitol-resistant strains with a resultant shift to less virulent and cariogenic strains, and
c) the binding of xylitol to surface receptors on Strep. mutans species modulating their function [44].

The mainstay in the prevention of dental caries remains fluoride [45]. A high dose 5 percent sodium fluoride varnish is currently available in the United States, but apparently not as widely used in the United States as in Europe where it was developed and tested primarily in children.

Topical fluoride

Two mechanisms by which **topical fluoride** promotes remineralization include:

1) the development of a crystalline protective veneer at the site of demineralization; and,
2) inhibition of bacterial metabolism, and thus reduction of their acid production.

The theoretical advantage of using the varnish is not only in the higher level of fluoride, but also in the sustained release delivery system.

One *in-vitro* study determined that a single application of the varnish could release fluoride for up to six months [41]. Varnish application is fast and easy and does not necessarily require professional prophylaxis prior to application, and can be applied directly to the root and incisal surfaces that are most vulnerable to decay in the SS patient population [46,47].

Chlorhexidine (CHX) is a topical antimicrobial agent that is used to decrease the intra-oral bacterial load thought to contribute to periodontal disease and caries [48]. In addition, CHX has an antifungal effect that is relevant to the SS population. In our experience, the available CHX oral rinses have not been well tolerated by the SS patient group. Chlorhexidine is now being developed in the varnish format and as a chlorhexidine-fluoride combination varnish that may be more acceptable to the SS population.

Dentures and Implants —
As teeth are lost, there is some concern as to whether patients with SS have more difficulty wearing dentures because of the decreased moisture in the mouth. No systematic clinical trials have addressed this question.

In general, dentures cannot replicate the efficiency and comfort of having your own teeth. There are scattered case reports regarding the ability of patients with SS to handle implants. The majority of reported cases where patients with SS received implants appears favorable, but does not provide long-term follow-up [38].

A rational approach to whether implants are feasible for a patient with SS should be determined on a case-by-case basis, which includes the possibility of the influence of a systemic disease. This topic is well discussed in an article on implants and the dry mouth patient by James Scuibba. http:/www.sjogrens.org/syndrome/reading.html

Two new products to brighten teeth have been released and are available over-the-counter for home application [41]. Both are fairly acidic at pH~5.0 and pH~4.5, respectively:

- One is a polyethylene strip containing peroxide;
- The other is a peroxide-containing gel [41].

In a data sheet provided by Colgate Pharmaceuticals, their product is "non-recommended" for "almost any medical condition" and advises that the individual consult their doctor/dentist prior to using. In the patient with the most severe salivary dysfunction, there would be a theoretical concern about an increased contact time of the product to the mucosa and to the tooth surface. With

professionally applied whitening processes, these variables can be better controlled.

A remineralizing solution containing calcium phosphate and a fluoride treatment may be considered in conjunction with a bleaching treatment. Again, the use of a whitening agent should be decided on a case-by-case basis in consultation with a professional familiar with the products. It should be noted that the majority of studies on tooth whitening have focused on efficacy rather than safety.

Genetically engineered acid-free bacteria are being developed to compete with the intra-oral caries causing bacteria with the ultimate outcome of a population shift to a non-caries promoting bacterial population [49,50]. A caries vaccine has been in development for several years but not yet approved for use [50]. Clinical trials are also underway to test the oral topical application of an engineered tobacco plant secretory IgA specific to a surface protein and other recombinant products on strep mutans ability to adhere to dental enamel [51-53].

In denture wearers, a form of ***oral candidiasis***, characterized by petechial lesions on the palate, may be visible only after the removal of the dentures.

IV. Contributing Factors to Dry Mouth

Nasal dryness, sinus blockage by tenacious secretions and associated "mouth breathing" —
Nasal dryness should be considered in conjunction with xerostomia, since blocked nasal passages increase mouth breathing and exacerbate oral dryness. Saline nasal sprays are available and should be used frequently.

In many patients, the use of humidifiers followed by gentle nasal lavage to remove encrusted secretions may be helpful. The paradoxical finding of rhinitis in a patient with SS may be due to vasomotor rhinitis and often will respond to nasal lavage followed by a topical inhaled nasal glucocorticoid and/or albuterol. Also, humidification can be achieved using products such as *Ocean Spray*®. Additional causes of nasal blockage, including nasal polyps and sinus infection, should be sought and treated appropriately.

At our clinic, we have found that "**nasal lavage**" may prove helpful in treatment of dry nose as well as dry mouth. The patients may irrigate their sinuses using a nasal syringe or use more automated methods of sinus lavage commercially available (www.hydromedonline.com). The general procedure is to first achieve humidification of the sinus (either a warm shower or use of a cool mist humidifier), followed by nasal lavage and then a topical corticosteroid spray.

Also of use are products for the dry nose such as Ayr Saline Nasal Gel®, Breathe Right Saline Nasal Spray®, Ocean Nasal Spray® (and the newly available Ocean Plus®), Pretz Spray®, and Xlear Nasal Wash with Xylitol®.

Laryngotracheal reflux —
It is common for SS patients to exhibit symptoms of recurrent sinusitis, or allergy such as "post-nasal" drip or frequent "throat clearing" with mucus [15]. Many patients with these complaints have acid reflux that results in laryngotracheal irritation, that stimulates vagal responses that mimic sinusitis. If reflux and laryngotracheal irritation are not suspected, and treatment with antibiotics is initiated for sinusitis, the result is likely to be oral candidiasis.

Treatment approaches for laryngotracheal irritation due to acid reflux include twice daily use of a proton pump inhibitor, three times daily use of liquid alginate *(Gaviscon®),* and avoidance of late night meals and caffeine. In some patients, promotility agents may be required and the assistance of an otolaryngologist with experience in distinguishing sinusitis and tracheal reflux is helpful in both diagnosis and therapy. (See "Medical management of gastroesophageal reflux disease in adults.")

Vaginal Dryness is a problem that is prevalent but not often discussed with the rheumatologist due to patient embarrassment. However, the patient should be encouraged to discuss with their gynecologist a variety of suitable lubricants are available:

- Astroglide®
- Estrace Vaginal Cream®
- Feminaease®
- Lubrin Vaginal Inserts®
- Premarin Vaginal Cream®
- Replens Long-Lasting Vaginal Moisturizer®

X. Summary

The treatment of dryness of eyes and mouth, as well as nasal and vaginal symptoms, is important for the symptomatic relief of the SS. However, in the “real” world of rheumatology where time per patient is limited and more “life threatening issues” must be assessed—a good approach is to refer the patient to printed material (such as a print copy of UpToDate suggestions) or to relevant websites.

The composition of tears and saliva are both quite complex, so much more is involved than simply replacement of “water.” Indeed, the stability of tear film and its evaporative rate may be governed by mucins and lipids. This is the reason that patients’ complaints of dry eyes or mouth correlate poorly with tear flow (Schirmer’s test) or saliva flow. The patient is telling us that the problem is the increased “friction” or “viscosity” as they move the lid over the orbit or the tongue around the mouth.

Treatment depends on a combination of measures to preserve existing tears/saliva, replacement of the tear/saliva, and new methods to create improve lubricating vehicles. The section on systemic therapies will concentrate on methods to decrease the inflammatory response that serves as the cause of the glandular dysfunction.

TABLE OF PARTIAL LIST OF AVAILABLE PRODUCTS

- Dry eye products updated on dryeye.com website and Dr. Paul Michelson (Scripps)
- Dry mouth products largely courtesy of Dr. John Weston (Scripps), Athena Pappas (Boston University) and our friend Dona Frosio
- Preparations available in the United States for treatment of dry mouth and dry eyes

Oral moisturizers (available on amazon.com)

Trade name Supplier
Salivart (spray) Gebauer Co, Cleveland, OH
Mouthkote (spray) Scandipharm Inc, Birmingham, AL
Oral Balance (gel) Laclede Prof Prod, Gardena, CA
Xerolube Scherer Labs Inc, Ball Ground, GA
Optimoist (solution and spray) Colgate Oral Pharm, Canton MA
Orex (spray) Young Dental, Maryland Hts, MO
Orajel
ACT products
Xylamelts

Preparations for tear deficiency (dryeye.com and visit “shop”)
Do not use preserved tears more than 4 times per day (use preservative free tears if needed)

- May need lotemax transiently if on airplanes
- May need lotemax when starting Restasis
- New Artificial tears (Liftegraf, Shire) at FDA
- Must Treat blepharitis before Artificial Tears work
- Systane seems better when blepharitis in our cliic

Trade name Active ingredient Preservative
Artificial tears

Trade name Active ingredient Preservative
Liquifilm (2) Polyvinyl alcohol 1.4 percent Benzalkonium
Hypotears (5) Polyvinyl alcohol 1 percent Benzalkonium
Tears Plus (2) Polyvinyl alcohol 1.4 percent, povidone 0.6 percent Chlorbutanol

Murine Tears (8) Polyvinyl alcohol 0.5 percent, povidone 0.6 percent Benzalkonium
Moisture Drops (4) Hypromellose 0.5 percent, povidone Benzalkonium
Tears naturale (1) Dextran 70, hypromellose 0.5 percent Benzalkonium
Tears nat.II (1) Dextran 70 0.1 percent, hypromellose 0.5 percent Polyquad
Genteal (5) Hypromellose Sodium perborate
Refresh (2) Polyvinyl alcohol 1.4 percent, povidone 0.6 percent None
Refresh Plus (2) Carboxymethylcellulose 0.5 percent None
Celluvisc (2) Carboxymethylcellulose 1.0 percent None
Bion Tears (1) Dextran 0.1 percent, hypromellose 0.3 percent None
Tears Nat.Free (1) Dextran 70, hypromellose 0.5 percent None
Hypotears PF (5) Polyvinyl alcohol 1 percent None
Other replacement tear products include: Adsorbotear (1), Murocel (4), Cellufresh (2), Dry Eye Therapy (4), Theratears ATF (9)
Ocular ointments
Trade name Active ingredient Preservative
Lacrilube (2) Petrolatum, mineral oil, lanolin None
Duolube (4) Petrolatum, mineral oil None
Lacrisert* (7) Hydroxypropylcellulose None
Refresh PM (2) Petrolatum None
Other ocular lubricants include: Duratears (1), Refresh PM (2), Hypo Tears (ointment) (5), Puralube (ointment) (6), Tears Renewed (3), Duratears naturale (1)

This list is intended to provide examples and is not necessarily complete. It is not intended to imply any form of recommendation or endorsement.
* Artificial tear insert.
Suppliers: 1. Alcon Labs, Fort Worth, TX; 2. Allergan, Irvine, CA; 3. Akorn Inc, Abita Springs, LA; 4. Bausch and Lomb, Rochester, NY; 5. Ciba Vision Ophthalmics, Duluth, GA; 6. Fougera and Co, Melville, NY; 7. Merck and Co, West Point, PA; 8. Ross Products, Columbus, OH; 9. Advanced Vision Research, Woburn, MA.

Ancillary Aids for dryness
Humidifier (Amazon)
Air purifier (Hepafilter seems to work best)(Amazon)

Tranquil Eyes (moisturizing eye mask)
Variety of wrap around sunglasses such as Wiley to prevent evaporation
Computer glasses with moisture prevention (Jinn moisturizer) at dryeye.com (can get these with prescription for “computer use” and glare reduction even if you don-t need “correction”

For moderate cases, we still use punctal occlusion
For severe cases, Prose lens by Opthalmologist WITH experience

Punctal occlusion, in this case with a collagen plug, may be performed easily at the slit lamp. This procedure maximizes tear conservation in patients with severe dry eyes by diminishing tear drainage through the lacrimal puncta. Courtesy of M Reza Dana, MD, MPH.

Preparations available in the United Kingdom for treatment of dry mouth and dry eyes

Oral moisturizers
Trade name Active ingredient Supplier
Artificial saliva Hypromellose Dental Practitioner Formulary
Saliva Orthana Gastric mucin (porcine) Nycomed
Salivix pastilles Malic acid Thames Labs
Preparations for tear deficiency
Trade name Supplier Active ingredients Preservative
Artificial tears
Isopto plain 1 Hypromellose 0.5 percent Benzalkonium
Isopto alkaline 1 Hypromellose 1 percent Benzalkonium
Ilube 4 Hypromellose 0.35 percent Benzalkonium
Acetylcysteine 5 percent Benzalkonium
Sno Tears 5 Polyvinyl alcohol 1.4 percent Benzalkonium,
Liquifilm 2 Polyvinyl alcohol 1 percent Benzalkonium
Tears naturale 1 Hypromellose 0.3 percent Benzalkonium
Dextran 70 0.1 percent
Hypotears 3 Polyvinyl alcohol 1 percent Benzalkonium
Minims Artificial Tears 5 Hydroxyethylcellulose 0.44 percent None
Liquifilm PF 2 Polyvinyl alcohol 1 percent None
Ocular ointments
Lacrilube 2 Petrolatum, mineral oil,lanolin None
Lubrifilm 4 Lanolin 10 percent, liquid paraffin None

This list is intended to provide examples and is not necessarily complete. It is not intended to imply any form of recommendation or endorsement.
Suppliers: 1. Alcon Labs (UK), Watford; 2. Allergan Ltd, High Wycombe; 3. Iolab, Bracknell; 4. Cusi Pharmaceuticals (UK), Haslemere; 5. Chauvin Pharmaceuticals, Romford.