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New dry eye products

Some exciting new therapeutic agents for dry eye and related disorders have been released in the USA. They are Systane (Alcon), Restasis (Allergan) and Refresh Endura (Allergan). Systane is now available in Australia.

Systane is a sterile multi-dose aqueous tear solution. It contains HP Guar (hydroxypropyl guar) derived from guar, a form of gum, and is preserved with Polyquad, a relatively non-cytotoxic preservative. When HP-guar combines with physiological tears, it crosslinks with borate, forming a network with a gel-like consistency. The crosslinked HP-guar and borate in Systane binds to the hydrophobic ocular surface, especially to damaged epithelial cells, so the dwell time (the length of time it remains on the ocular surface) of this gel network is claimed to be longer than those of other artificial tears, maintaining a protective shield across the ocular surface. It is claimed that the protective shield allows natural healing of the cornea and conjunctiva to occur. According to data provided by Alcon, Systane significantly reduces some symptoms of dryness and conjunctival staining (www.systane.com). Systane will be available on the PBS from 1 November 2003 as a Restricted Benefit (1 + 5 repeats).

Restasis (Allergan), cyclosporine ophthalmic emulsion 0.05%, was launched in the USA in May 2003. It has a role in controlling inflammation, especially in severe steroid-resistant atopic keratoconjunctivitis. It has been successfully used in tear deficient patients, both autoimmune and non-autoimmune, in whom tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Topical cyclosporine improves tear secretion, reduces ocular surface staining and inflammation, reduces the rate of ocular surface cellular turnover and restores goblet cells in eyes with moderate to severe keratoconjunctivitis sicca. No significant ocular or systemic side effects have been reported with long-term use. Transient ocular burning and irritation on instillation are common side effects. It is contraindicated in patients with active ocular infection. In Federal Drug Administration trials, the lacrimogenic effect of cyclosporine did not occur in patients already taking anti-inflammatory drugs or in patients with punctal plugs. Interestingly, only 15 per cent of patients had improved Schirmer wetting compared to five per cent in the vehicle treated group and it took six months to improve Schirmer strip wetting. Further studies are required to identify patients who are most likely to benefit and test parameters that are best to identify and monitor patients' responses to the medication.

Refresh Endura (Allergan) is derived from the ophthalmic emulsion vehicle for Restasis. In FDA Phase 2 and 3 trials, this emulsion vehicle was found to reduce symptoms of ocular irritation by stabilising the tear film and reducing tear evaporation. On application to the eye, the electrolytes in the tear film dissolve the polymer matrix, releasing the emulsion components. When the components separate, the oil floats to the lipid layer, the water enhances the aqueous volume, and the ocular lubricant combines with the mucin layer. Refresh Endura is packaged in the USA in a non-preserved unit dose form.

Sources and further references

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Preservative and antibiotic toxicity to the ocular surface

Commercially available multidose topical medications contain preservatives, stabilisers and other additives. These compounds supply stability and retard microbial contamination and growth, thus ensuring a longer shelf life. The most common preservatives are benzalkonium chloride (BAK: 0.005–0.02%), chlorbutanol (0.5%) and thimerosal (0.001–0.005%). BAK is the preservative in most cases. At these concentrations, these agents may be toxic to the corneal epithelium, stroma and endothelium when used more than four times per day. Preservative toxicity is always a consideration in long-term, high-dose use of ocular medications and can mask the signs of the condition being treated.

Antibiotics may also be toxic to the ocular surface and delay wound healing. Aminoglycoside toxicity is well recognised, with neomycin and gentamicin being the most cytotoxic. Clinical signs include punctate keratitis, injection in the inferior cul-de-sac and a weepy erythema and

oedema of the eyelid tissues. These responses are usually not serious and occur mostly after the drug is used for longer than one or two weeks. Tobramycin (another aminoglycoside) and chloramphenicol do not appear to retard wound healing[1-3] but excessive dosing (for example, more than four times per day) or prolonged dosing can be cytotoxic to the corneal epithelium.[4,5] Excessive dosing of ciprofloxacin (Ciloxin, Alcon) and, to a lesser extent, ofloxacin (Ocuflox, Allergan) is also cytotoxic to the corneal epithelium[4] and can retard epithelial wound healing.[6] Co-administration of a non-preserved lubricant and an antibiotic has a beneficial effect on the recovery of the ocular surface.[7] This study compared the effects of three different treatments, each applied six times per day, on corneal epithelial wound healing and haze in 18 myopic patients who had PRK surgery. The treatments were ciprofloxacin, ofloxacin, and a combination of ofloxacin with carboxymethyl cellulose lubricant (Refresh Plus, Allergan).

Eyes treated with ciprofloxacin were significantly more prone to impaired or delayed epithelial wound healing and to the development of stromal haze than those treated with either ofloxacin and Refresh Plus or ofloxacin alone. The ofloxacin and Refresh Plus combination delayed healing less than ofloxacin alone.[7]

Drug group	Generic brand	Premium brand	Price reduction over premium brand
Antibiotic			
Fluoroquinolone	CiloQuin	Ciloxan	$2.48
Anti-glaucoma			
Topical Beta antagonist	Tenopt/Optimol	Timoptol	$0.99
Parasympathomimetic	Pilopt/Isopto Carpine	PV Carpine	$1.71
Artificial tears			
Paraffin	Polyvisc/Lacrilube	Duratears	$1.24
Hypromellose	In-a-wink Moisturising	Genteal	$2.00

Source: schedule of Pharmaceutical Benefits May 2002 Commonwealth of Australia P: 229-235

Table 1. Generic drugs: categories of brand equivalents

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Generic drugs

Generic medications or brand equivalents are medications that can be supplied in place of that written on the prescription, usually at a lower cost. In the case of brand equivalents for topical ocular medications, all have been shown to be therapeutically equivalent so it would be expected that they would have the same clinical effect as the premium brand. If a prescription specifies 'no substitution', the exact brand of medication as specified in the prescription must be supplied.

There are relatively few brand equivalents of topical ophthalmic drugs in Australia, which can be supplied at a lower cost. The Table 1 shows the three categories of brand equivalents.

Optometrists' therapeutic prescribing habits

Since January 2003, Optometrists Association Victorian Division has been surveying therapeutically qualified optometrists within Victoria. The e-mail survey looks at the medications prescribed and whether it was necessary to involve a general medical practitioner in the process to allow the medication to be prescribed via the Pharmaceutical Benefits Scheme (PBS). About 30 per cent of therapeutically qualified optometrists have responded to the survey. In the the nine months to September 2003, the survey respondents had written 507 prescriptions for 25 medictions. The five most common medications prescribed by therapeutically qualified optometrists were:

- chloramphenicol (various brands)
- fluorometholone (Flucon, FML)
- fluorometholone acetate (Flarex)
- prednisolone acetate (Prednefrin Forte)
- lodoxamide trometamol (Lomide)

On 41 occasions in the nine months to September 2003, the optometrists had involved the patient's GP to allow the prescription to be prescribed via the PBS.

Contributions

The authors welcome comments or contributions from readers, including optometrists and pharmaceutical manufacturers.

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