Part 1   Summary of Recommendations

As a result of this review of the ophthalmological preparations (Section 21), of which two products have been reviewed as single-medicines and reported previously, it is recommended that six of the products currently listed in the WHO Model List of Essential Medicines should be retained, five should be deleted and one new product added (see table for details). The ophthalmological products for retention are acetazolamide, gentamicin, prednisolone, tetracaine, tetracycline and timolol. The products recommended for deletion are atropine, epinephrine (adrenaline), idoxuridine, pilocarpine and silver nitrate eye drops. Atropine eye drops are effective, but it is more logical to use the alternative product tropicamide, which is also effective for the same indications but has a shorter duration of action and fewer unwanted effects. Epinephrine (adrenaline) eye drops are no longer required as timolol has fewer unwanted effects for the same indication. Idoxuridine should be deleted as a treatment of keratitis or kerato-conjunctivitis caused by herpes simplex, as aciclovir eye ointment, which is more effective for this indication, is recommended for inclusion. Pilocarpine eye drops are no longer required as, for the same indication, timolol is cheaper. Finally silver nitrate eye drops are no longer required as tetracycline can be used for the same indications with fewer unwanted effects.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Status</th>
<th>Product</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>retain</td>
<td>250mg tablets. 0.25-1g daily in divided doses.</td>
<td>used as an adjunct in the treatment of chronic open-angle glaucoma; secondary glaucoma; and as part of the pre-operative treatment of acute angle-closure glaucoma.</td>
</tr>
<tr>
<td>Aciclovir</td>
<td>include</td>
<td>Aciclovir eye ointment 3%. 5 times daily (continue for at least 3 days after complete healing).</td>
<td>antiviral drug, used for keratitis or keratoconjunctivitis caused by herpes simplex.</td>
</tr>
<tr>
<td>Atropine</td>
<td>delete</td>
<td>Atropine eye drops 0.1%, 0.5%, 1%. For cycloplegic refraction, the recommended adult doses are: 1 drop (1%) twice daily for 1-2 days before procedure or a single application of 1 drop (1%) 1 hour before procedure. In children the doses are: 3 months – 1 year (0.1%), 1-5 year (0.1-0.5%); over 5 year (0.5-1%), 1 drop is applied twice daily for 1-3 days before procedure with a further dose given 1 hour before procedure. It is not recommended for children aged under 3 months because of the risk of systemic effects. For iritis or uveitis, the recommended dose for adults is 1 drop (0.5 or 1%) up to 4 times daily; for children, 1 drop (0.5 or 1%) up to 3 times daily.</td>
<td>long-acting anti-cholinergic mydriatic agent for iritis, uveitis, and cycloplegic refraction procedures.</td>
</tr>
<tr>
<td>Epinephrine (adrenaline)</td>
<td>delete</td>
<td>epinephrine hydrochloride eye drops, 0.5% or 1%. For chronic open-angle glaucoma, it is given by installation into the eye, 1 drop (0.5% or 1%) 1-2 times daily.</td>
<td>sympathomimetic drug, used for chronic open-angle glaucoma, ocular hypertension.</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>retain</td>
<td>Gentamicin sulphate eye drops, 0.3% solution. 1 drop every 2 hours, reducing frequency as infection is controlled, continue 48 hours after healing.</td>
<td>broad spectrum topical antibacterial preparation for blepharitis and bacterial conjunctivitis.</td>
</tr>
<tr>
<td>Idoxuridine</td>
<td>delete</td>
<td>eye drops (0.1%). For herpes simplex keratitis, it is given by instillation into the eye, 1 drop every hour during daytime and every 2 hours at night-time, reducing frequency as infection is controlled to 1 drop every 2 hours during daytime and every 4 hours at night-time, then continued for 3-5 days after healing is complete.</td>
<td>antiviral drug, used for keratitis or keratoconjunctivitis caused by herpes simplex.</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>delete</td>
<td>pilocarpine hydrochloride eye drops, 2% or 4%; or pilocarpine nitrate 2% or 4%. For chronic open-angle glaucoma, it is given by installation into the eye, 1 drop (2% or 4%) up to 4 times daily. For acute angle-closure glaucoma, before surgery, it is given by installation into the eye, 1 drop (2%) every 10 minutes for 30-60 minutes, then 1 drop every 1-3 hours until intra-ocular pressure subsides.</td>
<td>miotic drug, used for chronic open-angle glaucoma, ocular hypertension; emergency treatment of acute angle-closure glaucoma; to antagonize effects of mydriasis and cycloplegia following surgery or ophthalmoscopic examination.</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>retain</td>
<td>Prednisolone sodium phosphate eye drops, 0.5% solution. 1 drop every 1-2 hours, reducing frequency as inflammation is controlled.</td>
<td>topical corticosteroid used for short-term local treatment of inflammation of the eye; inflammatory and allergic reactions.</td>
</tr>
<tr>
<td>Silver nitrate</td>
<td>delete</td>
<td>drops solution (1%). 2 drops into each eye.</td>
<td>topical anti-infective agent, for prophylaxis of neonatal conjunctivitis (ophthalmia neonatorum) due to Neisseria gonorrhoea.</td>
</tr>
<tr>
<td>Drug</td>
<td>Status</td>
<td>Product Description</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>----------</td>
<td>-------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Tetracaine</strong> (sub-section 21.3)</td>
<td>retain</td>
<td>Tetracaine hydrochloride eye drops, 0.5% solution. 1 drop.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>INDICATIONS: short-acting local anaesthetic which can be used for anaesthesia of the cornea and conjunctiva.</td>
<td></td>
</tr>
<tr>
<td><strong>Tetracycline</strong> (sub-section 21.1)</td>
<td>retain</td>
<td>Tetracycline hydrochloride 1% eye ointment. Superficial bacterial infection: 1 application 3-4 times daily. Prophylaxis of neonatal conjunctivitis: 1 application into each eye. Trachoma: 1 application into each eye either twice daily for 5 days or once daily for 10 days, every month for 6 consecutive months each year.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>INDICATIONS: antibacterial agent used for superficial bacterial infection of the eye, treatment of trachoma in endemic areas; prophylaxis of neonatal conjunctivitis (ophthalmia neonatorum) due to Neisseria gonorrhoea or Chlamydia trachomatis.</td>
<td></td>
</tr>
<tr>
<td><strong>Timolol</strong> (sub-section 21.4.2)</td>
<td>retain</td>
<td>Timolol maleate eye drops, 0.25% or 0.5% solution. 1 drop twice daily.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>INDICATIONS: ocular hypertension; chronic open-angle glaucoma, aphakic glaucoma, some secondary glaucoma.</td>
<td></td>
</tr>
</tbody>
</table>
Part 2  Individual Product Reviews

2.1  Products to be retained

2.1.1  Acetazolamide

Introduction
Acetazolamide is an oral carbonic anhydrase inhibitor and diuretic, used as an adjunct in the
treatment of chronic open-angle glaucoma; secondary glaucoma; and as part of the pre-
operative treatment of acute angle-closure glaucoma.

Product and Dosage
Acetazolamide, 250mg tablets. Chronic open-angle glaucoma, secondary glaucoma, 0.25-1g
daily in divided doses.

Evidence of value
Chronic open-angle glaucoma
Topical beta-blockers have traditionally been the mainstay of initial treatment. They have
excellent pressure-lowering efficacy, long duration of action, and relatively few ocular adverse
effects. Other drugs, if needed, include the oral carbonic anhydrase inhibitor acetazolamide,
which can be used in severe cases.1

Acute angle-closure glaucoma
In the acute situation, oral (or intravenous) administration of a carbonic anhydrase inhibitor
can be used to reduce intraocular pressure.1

Recommendation
Acetazolamide tablets should be retained in the WHO Model List of Essential medicines.

References
1. Prodigy guidance glaucoma: Primary open-angle glaucoma. Last revised December 2002.
2.1.2 Gentamicin

Introduction
Gentamicin is a broad spectrum topical antibacterial preparation for blepharitis and bacterial conjunctivitis.

Product and Dosage
Gentamicin sulphate eye drops, 0.3% solution. 1 drop every 2 hours, reducing frequency as infection is controlled, continue 48 hours after healing.

Evidence of value
Topical antibacterial preparations are recommended in most cases of infective conjunctivitis.\(^1\) It is clinically difficult to distinguish between viral and bacterial infection. Bacterial superinfection may occur in cases of viral conjunctivitis. Treatment should be considered to reduce the risk of spreading infection. Aminoglycosides such as gentamicin should be reserved for treatment once the sensitivity of the infecting organism is known. Incomplete coverage of *Streptococcus* and *Staphylococcus* species rule out aminoglycosides as first-line therapy. A relatively higher incidence of toxicity to the corneal epithelium has been recorded with prolonged use of aminoglycosides. Gentamicin should be reserved for more serious ocular infections and as second-line treatments when the sensitivity is known.\(^2\)

For people with culture-positive bacterial conjunctivitis, one randomised control trial (156 children) compared three treatments: trimethoprim–polymyxin, gentamicin, and sulfacetamide (sulphacetamide). It found no significant difference in clinical cure rate between any of the treatments (84% with trimethoprim–polymyxin vs. 88% with gentamicin vs. 89% with sulfacetamide; p>0.1) or in microbiological cure rate (83% with trimethoprim–polymyxin vs. 68% with gentamicin vs. 72% with sulfacetamide; p>0.1) after 2–7 days. Another randomised control trial found no significant difference between topical netilmicin and topical gentamicin in the rate of adverse reactions (redness, itching, and burning).\(^3\)

Prices for a bottle of antibacterial eyedrops may vary 3-fold. Gentamicin is one of the cheapest drugs.\(^4\)

Recommendation
Gentamicin should be retained in the WHO Model List of Essential Medicines

References
2.1.3 Prednisolone

Introduction
Prednisolone is a topical corticosteroid used for short-term local treatment of inflammation of the eye; inflammatory and allergic reactions.

Product and Dosage
Prednisolone sodium phosphate eye drops, 0.5% solution. 1 drop every 1-2 hours, reducing frequency as inflammation is controlled.

Evidence of value
A brief course of topical corticosteroids may be helpful for eyelid or ocular surface inflammation.13

Recommendation
Prednisolone should be retained in the WHO Model List of Essential Medicines

References
2.1.4 Tetracaine

Introduction
Tetracaine hydrochloride is a short-acting local anaesthetic which can be used for anaesthesia of the cornea and conjunctiva.

Product and Dosage
Tetracaine hydrochloride eye drops, 0.5% solution. 1 drop.

Evidence of value
There is no general consensus on which topical local anaesthetic eye drop provides the best analgesia. Tetracaine, amethocaine, proparacaine, lignocaine and bupivacaine have all been used successfully in a variety of different concentrations.¹

Recommendation
Tetracaine should be retained in the WHO Model List of Essential Medicines

References
2.1.5 Tetracycline

Introduction
Tetracycline is an antibacterial agent used for superficial bacterial infection of the eye, treatment of trachoma in endemic areas, prophylaxis of neonatal conjunctivitis (ophthalmia neonatorum) due to Neisseria gonorrhoea or Chlamydia trachomatis.

Product and Dosage
Tetracycline hydrochloride 1% eye ointment. Superficial bacterial infection: 1 application 3-4 times daily. Prophylaxis of neonatal conjunctivitis: 1 application into each eye. Trachoma: 1 application into each eye either twice daily for 5 days or once daily for 10 days, every month for 6 consecutive months each year.

Evidence of value
Face washing plus tetracycline drops significantly reduced the proportion of children with trachoma after 3 months compared with no intervention (215/312 [69%] with face washing plus topical tetracycline vs 160/211 [76%] with no intervention; regression analysis, P < 0.05).2

Strategies for the control of gonococcal infection include eye prophylaxis in the newborn at birth. Eye prophylaxis by the instillation immediately after birth of 1% tetracycline eye ointment is very effective. This reduces the gonococcal ophthalmia neonatorum (GCON) incidence by 80% to 95% and is highly cost-effective, particularly in high-risk settings.3

1% silver nitrate solution and 0.5% erythromycin ointment are approximately comparable in efficacy, but tetracycline is more cost-effective than silver nitrate. There is good evidence to support the use of universal ocular prophylaxis for gonococcal ophthalmia neonatorum, at least in the absence of universal prenatal screening for gonorrhoea. Prophylaxis should be administered as soon as possible (within 1 hour) after birth.4

Recommendation
Tetracycline should be retained in the WHO Model List of Essential Medicines

References
2.1.6 Timolol

Introduction
Timolol is a beta-blocking drug that is used for the treatment of ocular hypertension, chronic open-angle glaucoma, aphakic glaucoma, and some secondary glaucomas.

Product and Dosage
Timolol maleate eye drops, 0.25% or 0.5% solution. 1 drop twice daily.

Evidence of value
Ocular hypertension
A randomised controlled trial of timolol vs. placebo in patients with ocular hypertension found that after 1 month, the mean intraocular pressure reduction compared with baseline was 6.8mmHg in the timolol group and 2.0mmHg in the placebo group, and the mean difference between treatment groups was 4.0mmHg (p<0.0001).1

Primary open-angle glaucoma
Eye drops generally are the initial treatment of choice (timolol or pilocarpine).2 Topical beta-blockers have traditionally been the mainstay of initial treatment. They have excellent pressure-lowering efficacy, long duration of action, and relatively few ocular adverse effects. Several preparations can be used (betaxolol, carteolol, levobunolol, and timolol) - all are equally effective and are given once or twice daily.3

Recommendation
Timolol should be retained in the WHO Model List of Essential Medicines

References
2.2 Products recommended for deletion

2.2.1 Atropine

Introduction
Atropine is a potent long-acting anti-cholinergic mydriatic agent which, as eye drops, is listed in the WHO Model Formulary for use for: iritis, uveitis, and cycloplegic refraction procedures. Tropicamide eye drops, which have a similar action, are also listed in the Formulary, but to be used for shorter-lasting procedures.

Product and dosage
Atropine eye drops are available in strengths of 0.1%, 0.5%, 1%. For cycloplegic refraction, the recommended adult doses are: 1 drop (1%) twice daily for 1-2 days before procedure or a single application of 1 drop (1%) 1 hour before procedure. In children the doses are: 3 months – 1 year (0.1%), 1-5 year (0.1-0.5%); over 5 year (0.5-1%), 1 drop is applied twice daily for 1-3 days before procedure with a further dose given 1 hour before procedure. It is not recommended for children under 3 months because of the risk of systemic effects. For iritis or uveitis, the recommended dose for adults is 1 drop (0.5 or 1%) up to 4 times daily; for children, 1 drop (0.5 or 1%) up to 3 times daily.

Evidence of value
Topically applied atropine solution is an effective mydriatic. However, it is contraindicated in glaucoma or in people with a tendency towards glaucoma (e.g. a narrow anterior chamber angle) as it can precipitate glaucoma. Chemical conjunctivitis is not uncommon. The ocular effects of topically applied atropine are prolonged: accommodation and pupillary reflexes may not fully recover for 7 - 12 days.

Tropicamide is shorter-acting than atropine (it is given three times a day; its effects reverse in around 30-60 minutes after application), which is an advantage if a long duration of action is not required. This preparation can be used for iritis in the same way as atropine. It has a similar range of unwanted effects to atropine but these are less likely to occur.

Recommendation
It is recommended that atropine eye drops be deleted from the WHO Model List of Essential Medicines. Although it is effective, it is more logical to use the alternative product tropicamide, which is effective when used for the same indications and has a shorter duration of action and fewer unwanted effects.

References
2.2.2 Silver nitrate

Introduction
Silver nitrate is a topical anti-infective agent, listed in the 2004 WHO Model Formulary to be used for prophylaxis of neonatal conjunctivitis (ophthalmia neonatorum) due to Neisseria gonorrhoea, if tetracycline is not available. Other drugs listed for the same indication are gentamicin, tetracycline.

Product and dosage
Silver nitrate is available as eye drops solution (1%). For prophylaxis of neonatal conjunctivitis, it is given by installation of 2 drops into each eye at birth after cleansing the eyes with sterile gauze.

Evidence of value
Strategies for the control of gonococcal ophthalmia neonatorum (GCON) include eye prophylaxis in the newborn at birth, by the instillation of either 1% silver nitrate eye drops or 1% tetracycline eye ointment. This procedure which reduces the GCON incidence by 80% to 95% respectively, is cost-effective, particularly in high-risk settings. Instillation of 1% silver nitrate solution or 1% tetracycline ointment into the conjunctival sac of the newborn within 1 hour after birth have comparable efficacy in preventing gonococcal infection, but tetracycline is more cost-effective than silver nitrate. There is good evidence to support the use of universal ocular prophylaxis for GCON, at least in the absence of universal prenatal screening for gonorrhoea. Water from the silver nitrate solution can evaporate and allow the solution to become more concentrated, which can lead to a severe chemical conjunctivitis when it is then applied to the eye.

Recommendation
It is recommended that silver nitrate eye drops be deleted from the WHO Model List of Essential Medicines as tetracycline (already listed) can be used for the same indications with fewer unwanted effects.

References
2.2.3 Idoxuridine

Introduction
Idoxuridine is an antiviral drug, used for keratitis or keratoconjunctivitis caused by herpes simplex. No other drugs are listed for the same indication.

Product and dosage
Idoxuridine is available as eye drops (0.1%). For herpes simplex keratitis, it is given by instillation into the eye, 1 drop every hour during daytime and every 2 hours at night-time, reducing frequency as infection is controlled to 1 drop every 2 hours during daytime and every 4 hours at night-time, then continued for 3-5 days after healing is complete. The maximum length of treatment is 21 days.

Idoxuridine is also available as eye ointment (0.2%). For herpes simplex keratitis, it is given by application to the eye, 1 application of ointment every 4 hours during daytime and once at night-time (5 applications), then continued for 3-5 days after healing is complete. The maximum length of treatment is 21 days.

Evidence of value
A recent systematic review examining treatments for ocular herpes simplex found that topical idoxuridine increased healing after 14 days compared with placebo, but that aciclovir increased healing compared with idoxuridine after 7 and 14 days. A randomised controlled trial found that 3% aciclovir ointment was more effective than 1% idoxuridine (cure rate 90% vs. 60%) with a shorter healing time (8.5 days vs. 13.4 days). In addition, unwanted effects (follicular conjunctivitis, epithelial keratopathy and stinging) were more frequent among patients treated with idoxuridine than in those given aciclovir.

Recommendation
It is recommended that the Expert Committee requests that an application for the deletion of idoxuridine eye drops be prepared for consideration at the next Expert Committee Meeting in 2007, provided that the product aciclovir has been added to the list (see entry below under 'aciclovir').

References
2.2.4 Pilocarpine

Introduction
Pilocarpine is a miotic drug which acts as a muscarinic acetylcholine receptor agonist and so as a parasympathomimetic. It is used for the treatment of chronic open-angle glaucoma, ocular hypertension; emergency treatment of acute angle-closure glaucoma; to antagonize effects of mydriasis and cycloplegia following surgery or ophthalmoscopic examination. The other drug listed for the same indication is timolol.

Product and dosage
This product is available as pilocarpine hydrochloride eye drops, 2% or 4%; or pilocarpine nitrate 2% or 4%. For chronic open-angle glaucoma, it is given by installation into the eye, 1 drop (2% or 4%) up to 4 times daily. For acute angle-closure glaucoma, before surgery, it is given by installation into the eye, 1 drop (2%) every 10 minutes for 30-60 minutes, then 1 drop every 1-3 hours until intra-ocular pressure subsides.

Evidence of value
Pilocarpine and timolol have around the same level of effectiveness in lowering intraocular pressure and range of adverse effects. However, pilocarpine is more expensive ($170 for 100 x 2% 10mls, which is approximately twice as expensive as Timolol from India or the Netherlands.

Recommendation
It is recommended that the Expert Committee requests that an application for the deletion of pilocarpine eye drops be prepared for consideration at the next Expert Committee Meeting in 2007.

References
2.2.5 Epinephrine (adrenaline)

Introduction
Epinephrine (adrenaline) is a sympathomimetic drug, used for chronic open-angle glaucoma, ocular hypertension. Other drugs listed for the same indication: timolol.

Product and Dosage
It is available as epinephrine hydrochloride eye drops, 0.5% or 1%. For chronic open-angle glaucoma, it is given by installation into the eye, 1 drop (0.5% or 1%) 1-2 times daily.

Evidence of value
Epinephrine has a similar level of effectiveness in lowering intraocular pressure as timolol. However, epinephrine has many unwanted effects including tachycardia, hypertension and arrhythmias.

Recommendation
It is recommended that the Expert Committee requests that an application for the deletion of epinephrine eye drops be prepared for consideration at the next Expert Committee Meeting in 2007.

References
2.3 Product recommended for addition

2.3.1 Aciclovir

Introduction
Aciclovir is an antiviral drug, used for keratitis or keratoconjunctivitis caused by herpes simplex.

Product and Dosage
Aciclovir eye ointment 3%; apply 5 times daily (continue for at least 3 days after complete healing).

Evidence of value
A recent systematic review examining treatments for ocular herpes simplex found that topical idoxuridine increased healing after 14 days compared with placebo, but that aciclovir increased healing compared with idoxuridine after 7 and 14 days.¹

Recommendation
It is recommended that the Expert Committee requests that an application for the inclusion of aciclovir eye ointment be prepared for consideration at the next Expert Committee Meeting in 2007. If aciclovir is added, it is recommended that it should replace idoxuridine eye drops currently listed for the same indication (see entry above under ‘idoxuridine’).

References
Part 3  Search Strategy

The medical literature was searched to identify guidelines, systematic reviews or meta-analyses related to products used for the treatment of ophthalmic conditions. Below is a list of electronic databases, websites and journals searched (date of search: 10 June 2004)

Sources Searched
The Cochrane Library
Clinical Evidence
Scottish Intercollegiate Guidelines Network
National Institute for Clinical Excellence
Prodigy
Drug and Therapeutics Bulletin
eTG complete (Therapeutic Guidelines)
British Medical Journal
Lancet

Jacoby Patterson, Drug and Therapeutics Bulletin, UK (January 2005)