Application for the inclusion of Aciclovir eye ointment in the WHO list of essential medicines.

WHO therapeutic group 21.1

1. Summary statement of the proposal for inclusion, change or deletion

This is a proposal for the inclusion of the anti-viral medication aciclovir (ACV) eye ointment in the ophthalmological preparations section of the WHO essential medicines list. ACV eye ointment is used for the treatment of ocular surface disease caused by herpes simplex virus (HSV).

This is also a proposal to replace the use of topical idoxuridine (IDU, currently the WHO recommended drug for herpetic ocular surface disease) with ACV eye ointment.

ACV is a potent antitherpetic agent when phosphorolated into its active form by the virus specific enzyme thymidine kinase. It is selective and thus relatively non toxic to humans. The oral form has been added to the core list in 1998 for use in the treatment of primary genital herpes and disseminated varicella-zoster in immunocompromised patients.

In June 2006 a meeting of the Ophthalmological preparations section of the WHO essential medicines committee recommended deletion of IDU 0.1% eye drops and 0.2% eye ointment from the list.¹

2. Name of the focal point in WHO submitting application

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3. Name of the organisation consulted and supporting the application

a.) Cochrane Eyes and Vision Group www.cochraneeyes.org
b.) International Centre for Eye Health, London School of Hygiene and Tropical Medicine, Keppel St, London, UK.
c.) V2020 technology working group

Point of contact:
Dr Shaheen Shah, MBBS MRCOphth MSc, International Centre for Eye Health, London School of Hygiene and Tropical Medicine, Keppel St, London, UK.
E mail: Shaheen.shah@lshtm.ac.uk
4. International Nonproprietary Name (INN, generic name) of the medicine

Aciclovir ointment, chemically denoted 9-(2-Hydroxyethoxymethyl) guanine) ²

5. Formulation proposed for inclusion

Aciclovir 3.0% W/W ointment
FOR OPHTHALMIC USE ONLY

6. International availability – sources, manufactures

Zovirax ® eye ointment is a registered trademark of the GlaxoSmithKline group of companies.
Other international sources include:
IDA Foundation
Missionpharma
Durbin

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Individual medicine

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Herpes simplex is probably the most common virus acquired by humans. It is usually acquired in early life, one study finding antibodies against the virus in 50% of subjects with high socioeconomic status and in 80% of people with low socioeconomic status by the age of 30 years.³ Humans are the only natural host and reservoir for the virus and antiviral drugs do not eliminate latent virus. Thus blindness due to herpes virus remains a significant public health problem. The incidence of ocular HSV is estimated at 21 to 31 per 100,000 people per year ⁴,⁵ and worldwide, up to 10 million people are thought to have a history of ocular HSV.⁶ Data from a long term study in Rochester, MN, USA, suggested that approximately 400,000 Americans have had ocular herpes and that approximately 50,000 episodes of new and recurrent ocular HSV in the USA occur annually.⁵

Ocular surface disease occurs predominantly in two forms. Dendritic epithelial keratitis is virtually pathognomonic of HSV whereas geographic epithelial keratitis,
the macroulcerative form, is less common. Combined, Herpes Simplex Keratitisis (HSK) accounts for approximately 70 to 80 per cent of all cases of ocular HSV.

HSK is a result of infection predominantly with the HSV type 1 (HSV-1) virus. The prevalence of HSK is estimated to be 149/100,000 in developed countries. Recurrent reactivation of latent virus is the principal cause of visual loss and the reactivation principally takes the form of dendritic involvement. The majority of HSK cases occur in the working age group population, the mean age ranging between 29 and 49 years. Although predominantly a unilateral disease, bilateral cases, occurring in 1.2-12%, tend to be more severe and occur in younger ages. This may be particularly acute for low/middle income countries where lack of access to medical care is compounded by presence of malnutrition which lowers the resistance to HSV virus.

The main impact on vision is through corneal scarring, thinning and neovascularization, particularly through recurrent attacks. Although the prognosis of visual loss subsequent to HSK has improved recently with the introduction of antiviral agents, it remains one of the leading causes of corneal opacities in high income countries and is one of the most common causes of corneal keratoplasty in these countries. In low and middle income countries HSK is also a leading cause of corneal blindness and can account for up to 10% of workload in corneal clinics.

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

Dosage regimen
Application of 1cm (approximately ½ inch) of ointment to the inside of the lower lid on the affected side. The medicine should be applied 5 times a day.

Duration
Lesions typically heal after 5-9 days. The ointment is normally used for a minimum of 3 days after the lesions have healed and the cornea has fully re-epithelialised.

Storage
This medication should be kept in a safe place below 25°C. The ointment should not be used if more than one month has passed since the tube was first used.

Treatment Facilities
No special facilities are required.

Diagnostic
Approximately 90% of the studies detailed in this proposal utilized special corneal stains (either fluorescein or rose-Bengal) to detect corneal epithelial status for diagnosis of lesions and/or outcome assessment. Thus we recommend the use.
of corneal staining techniques for diagnosis and follow up of patients with herpetic ocular surface disease.

Shelf Life
5 years

10. Summary of comparative effectiveness in a variety of clinical settings

- Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

As part of a comprehensive literature search, we identified a recent Cochrane systematic review entitled “Therapeutic Interventions for herpes simplex virus epithelial keratitis”. This review included controlled clinical trials that assessed the effects of one or more therapeutic interventions on the corneal epithelial healing of participants with presumed herpes simplex virus epithelial keratitis. The latest literature search (strategy outlined below) for this systematic review was conducted on 1 August 2006 and will be published in 2007 [Issue 5]. The literature search date for the most recent published review of the work was 2003 [Issue 4] the results of which were neatly summarised by Barker. Other sources of literature searched included PubMed, Drugs and Therapeutic Bulletin, NICE, Scottish Intercollegiate Guidelines Network and Prodigy.

Literature reviewed

The Cochrane review systematically searched for studies in CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) on The Cochrane Library, MEDLINE and EMBASE. LILACS (Latin American and Caribbean Literature on Health Sciences), BIOSIS, and JICT-EPlus were also searched up to 2005. To identify randomised controlled trials, this search was combined with the Cochrane Highly Sensitive Search Strategy phases one, two and three as contained in the Cochrane Handbook for Systematic Reviews of Interventions. Manual searching included Index Medicus from 1960 through 1965 and Excerpta Medica Ophthalmology from 1960 to 1973. Titles and abstracts of meetings held between 1980 and 2006 of the Association for Research in Vision and Ophthalmology (ARVO), the American Academy of Ophthalmology (AAO), the Ocular Microbiology and Immunology Group, and the International Conference on Herpetic Eye Diseases were searched for clinical studies of herpetic keratitis.

- Summary of available data (appraisal of quality, outcome measures, summary of results)

Outcome Measures
The primary outcome was the proportion of participants healed at seven days after study entry. To evaluate that the speed of healing correlated with overall treatment effectiveness, the secondary outcome was the proportion healed at 14 days after study entry.
Selection of Studies
Studies were selected that had an unbiased allocation of two or more interventions to participants with herpes simplex virus (HSV) epithelial keratitis and that reported the status of participants by seven or 14 days after study entry.

Assessment of methodological quality of included studies
Studies were assessed for internal validity, as noted in the Cochrane Handbook for Systematic Reviews of Interventions. Each study was rated by the degree of plausible biases. The level of possible bias was based on three criteria: the use of concealed randomised allocation of the intervention, the use of masking of participants and providers, and the use of slit-lamp biomicroscopy for determining eligibility and outcome.

The searches identified 161 different clinical trials of herpes simplex virus (HSV) epithelial keratitis. Sixty-three trials were excluded for methodological reasons or applicability. Ninety-eight trials, published between 1963 and 2006, were retained for data analysis. Of the 98 included trials 70% took place in Europe and only one took place in Africa. 78% of the trials were published in the English language.

Nearly 70% of the included studies specifically mentioned the use of a randomized allocation scheme. Attrition bias was uncommonly encountered as the primary endpoint occurred within two weeks of enrolment. A total of 5211 participants were enrolled and analyzed in the 98 trials. 34 trials assessing ACV eye ointment were identified. (Appendix Table 1)

- Summary of available estimates of comparative effectiveness

The results of the meta-analysis showed that all nucleoside antiviral medications were significantly better than placebo. ACV eye ointment was significantly better than idoxuridine at seven days (OR 4.69, 95% CI 3.13 to 7.02) and at 14 days (OR 4.18, 95% CI 2.48 to 7.03). Results from the systematic review [Issue 4, 2006] comparing ACV eye ointment and Idoxuridine are demonstrated in Figure 1. Trifluridine and ACV eye ointment appeared equivalent to one another at seven days and 14 days. Vidarabine was not shown to be better than ACV. Other topical antiviral agents including bromovinyldeoxyuridine, iododeoxyctydine, ganciclovir, foscarnet and cidofovir appeared equivalent in clinical antiviral effectiveness to ACV, but few trials evaluated these comparisons, and those that did were small.

In summary, the meta-analysis found evidence to suggest that compared to idoxuridine, the application of ACV eye ointment, vidarabine or trifluridine generally resulted in a significantly greater proportion of participants healing within one week of treatment. Among these three antiviral agents, no treatment emerged as significantly better for the therapy of dendritic epithelial keratitis.
### Figure 1. Forest plot demonstrating comparison of Aciclovir and Idoxuridine

**Source:** Cochrane review [Issue 4, 2006]  

<table>
<thead>
<tr>
<th>Study</th>
<th>Aciclovir (n/N)</th>
<th>Idoxuridine (n/N)</th>
<th>Odds Ratio (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Odds Ratio (Fixed) 95% CI</th>
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<tr>
<td><strong>01 Healing at 7 days</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Abe 1987</td>
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<td>6.6 [5.0, 8.6]</td>
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<tr>
<td>Albinisk 1987</td>
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<td>1/0</td>
<td>3.4 [2.4, 4.9]</td>
<td>8.00</td>
<td>3.4 [2.4, 4.9]</td>
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<tr>
<td>Collum 1980</td>
<td>20/30</td>
<td>0/30</td>
<td>1.3 [0.7, 2.5]</td>
<td>1.18</td>
<td>1.3 [0.7, 2.5]</td>
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<tr>
<td>Coster 1980</td>
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<td>21/30</td>
<td>18.2 [11.0, 29.9]</td>
<td>2.06</td>
<td>18.2 [11.0, 29.9]</td>
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<tr>
<td>McCulley 1982</td>
<td>19/30</td>
<td>18/34</td>
<td>30.5 [19.5, 48.0]</td>
<td>1.54</td>
<td>30.5 [19.5, 48.0]</td>
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<tr>
<td>Panda 1995</td>
<td>18/20</td>
<td>0/20</td>
<td>0.7 [0.1, 5.4]</td>
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<td>0.7 [0.1, 5.4]</td>
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<td><strong>Subtotal (95% CI)</strong></td>
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<td>173</td>
<td>100.0 [5.33, 8.53]</td>
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<tr>
<td>Total events: 138 (Aciclovir), 65 (Idoxuridine)</td>
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</table>

Test for overall effect Z=5.00, p<0.000001

<table>
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<tr>
<th>Study</th>
<th>Aciclovir (n/N)</th>
<th>Idoxuridine (n/N)</th>
<th>Odds Ratio (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Odds Ratio (Fixed) 95% CI</th>
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<td><strong>02 Healing at 14 days</strong></td>
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<td>90.27</td>
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<td>10.9 [6.4, 18.9]</td>
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<td>43/65</td>
<td>17.3 [10.5, 29.6]</td>
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<td>17.3 [10.5, 29.6]</td>
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<td>Kunch 1987</td>
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<td>13/17</td>
<td>10.0 [5.9, 19.4]</td>
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<td>24.8 [15.8, 39.8]</td>
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<td>3.3 [1.8, 6.3]</td>
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<td><strong>Subtotal (95% CI)</strong></td>
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<td>309</td>
<td>100.0 [3.71, 2.27]</td>
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</tr>
<tr>
<td>Total events: 207 (Aciclovir), 229 (Idoxuridine)</td>
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</tr>
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</table>

Test for overall effect Z=5.21, p<0.000001
In addition, unwanted side effects (follicular conjunctivitis, epithelial keratopathy and stinging) were more common in patients using idoxuridine compared to the use of other topical nucleoside antiviral agents in a randomized double blind study. 15

The question of prevention of ocular HSV disease was addressed by the multicentre randomised controlled trial from the Herpetic Eye Disease Study group.9 703 patients with a history of ocular HSV in the preceding year were randomly assigned to receive oral ACV 400mg (n=357) or placebo (n=346) twice daily for one year. The cumulative probability of a recurrence was 19% in the aciclovir treated group compared to 32% in the placebo group. The study concluded that long term oral prophylaxis is effective in reducing rate of recurrence of ocular HSV. However the question raised that has not been answered to date regarded the duration of prophylaxis required to avert eventual progression of the disease.

11. Summary of comparative evidence on safety

• Estimate of total patient exposure to date

The use of systemic ACV is generally well tolerated and has few side effects.

ACV eye ointment is listed on the Medecins sans Frontieres essential medicines catalogue [date accessed: 27 November 2006] and was added to the order list in 2002. 16

One (4.5g) tube of ACV eye ointment typically contains 135mg of ACV.

• Description of adverse effects/reactions

Contraindications
ACV eye ointment is contra-indicated in patients with a known hypersensitivity to aciclovir or valaciclovir.17

Special warnings and precautions for use
Patients should avoid wearing contact lenses when using ACV eye ointment.

Interaction with other medicinal products and other forms of interaction
No clinically significant interactions have been identified. ACV eye ointment does not contain sucrose, lactose, gluten or tartrazine.

Pregnancy and lactation
Systemic administration of ACV in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rats, rabbits or mice.17 In a non-standard test in rats, foetal abnormalities were observed, but only following such
high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain. A post-marketing ACV pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of ACV. The birth defects described amongst ACV exposed subjects have not shown any uniqueness or consistent pattern to suggest a common cause.

The use of ACV eye ointment should be considered only when the potential benefits outweigh the possibility of unknown risks.

There is no information on the effect of ACV eye ointment on human female fertility. Two-generation studies in mice did not reveal any effect of (orally administered) ACV on fertility. Limited human data show that the drug does pass into breast milk.

**Effects on ability to drive and use machines**
As this medicine may cause vision to blur temporarily after application it is recommended not to drive or operate machinery until this effect has worn off.

**Undesirable effects**
Transient mild stinging immediately following application may occur in a small proportion of patients. Superficial punctate keratopathy has been reported but has not resulted in patients being withdrawn from therapy, and healing has occurred without apparent sequelae. Local irritation and inflammation such as blepharitis and conjunctivitis have also been reported.

The results of a wide range of mutagenicity tests *in vitro* and *in vivo* indicate that aciclovir does not pose a genetic risk to man. ACV was not found to be carcinogenic in long-term studies in the rat and the mouse. Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of ACV greatly in excess of those employed therapeutically. Oral ACV has been shown to have no definite effect upon sperm count, morphology or motility in man.

There have been very rare reports of immediate hypersensitivity reactions including angioedema with ACV eye ointment.

**Overdose**
No untoward effects would be expected if the entire contents of the tube containing 135 mg of ACV were ingested orally. Oral doses of 800 mg five times daily (4 g per day) have been administered for seven days without adverse effects.

Single intravenous doses of up to 80 mg/kg have been inadvertently administered without adverse effects. ACV is dialysable by haemodialysis.
12. Summary of available data on comparative cost and cost effectiveness within the pharmacological class or therapeutic group

- Range of costs of the proposed medicine (Aciclovir 3% ophthalmic ointment ATC Code S01AD03)

Date of access to International Drug Price indicator: 28 November 2006

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<th>Unit Price</th>
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<td>MISSION</td>
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<td>DURBIN</td>
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<td>$23.21</td>
<td>5.1570/G</td>
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Buyers Price

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<td>NAMIBIA</td>
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<td>$5.49</td>
<td>1.2211 /G</td>
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</table>

IDA Foundation is a not-for-profit organization supporting healthcare in low- and medium-income countries by improving access to and delivering high-quality essential medicines and medical supplies. IDA is an independent and self-supporting foundation, distributing more than 3,000 products to over 100 countries worldwide. Orders under Euro 50,000 are charged a handling fee of 1.5%, with a minimum fee of Euro 45. Prices are indicative and may change.

Missionpharma prices are given as an indication only. There are no minimum orders required or service charges.

Durbin supplies pharmaceuticals and medical supplies to doctors, pharmacies, hospitals, pharmaceutical wholesalers and traders, military and government agencies, charities and other relief organizations worldwide.

ETHIOPIA: The Pharmaceutical Administration and Supply Service conducts an annual, international, open tender.

CRSS Costa Rica Social Security conducts an annual, international, closed tender and negotiates contracts for drugs and medical supplies for its own facilities.

NAMIBIA: The Namibia Central Medical Stores conducts an international open tender every two years for pharmaceuticals and medical supplies.

- Comparative cost effectiveness presented as range of cost per routine outcome (e.g. cost per case)

ACV belongs to the nucleoside antiviral group of medicines. The alternatives to ACV eye ointment include; topical vidarabine, topical trifluridine and topical bromovinyldeoxyuridine (BVDU).

Topical trifluridine is manufactured under the brand name Viroptic® 1%. Limited information is available on drug pricing. (see Appendix)

Idoxuridine was removed from market in 1990s due to low demand.6
13. Summary of regulatory status of the medicine (in country of origin, and preferably other countries as well)

N/A

14. Availability of pharmacopoeial standards (British Pharmacopoeia)

Yes listed in major pharmacopoeias including British National Formulary.

15. Proposed (new/adapted) text for the WHO Model formulary

Aciclovir eye ointment 3% W/W ophthalmic preparation

Uses:
FOR OPHTHALMIC USE ONLY
Adults: Herpetic ocular surface disease (dendritic or geographic herpetic epithelial keratitis)
Children: As for adults
Elderly: As for adults.

Interactions:
No clinically significant interactions have been identified.

Contraindications:
Aciclovir is contra-indicated in patients with a known hypersensitivity to aciclovir or valaciclovir. Patients should avoid wearing contact lenses when using the eye ointment.

Precautions:
Systemic administration of aciclovir is internationally accepted; standard tests did not produce embryotoxic or teratogenic effects in rats, rabbits or mice. However, it is suggested that the use of aciclovir eye ointment in pregnancy should be considered only when the potential benefits outweigh the possibility of unknown risks. Limited human data show that the drug does pass into breast milk.

Overdose:
No untoward effects would be expected if the entire contents of the tube containing approximately 135 mg of aciclovir were ingested orally.
References


APPENDIX

Table 1. Studies including acyclovir eye ointment that were included in the Cochrane Systematic Review

<table>
<thead>
<tr>
<th>Study author</th>
<th>Treatments evaluated</th>
<th>Number of patients enrolled</th>
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<tr>
<td>Abe 1987</td>
<td>ACV Idoxuridine</td>
<td>27</td>
</tr>
<tr>
<td>Altinisik 1987</td>
<td>ACV Idoxuridine</td>
<td>19</td>
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<tr>
<td>Carmassi 1993</td>
<td>ACV Interferon</td>
<td>15</td>
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<tr>
<td>Cellini 1994</td>
<td>ACV ACV + Epidermal growth factor</td>
<td>40</td>
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<td>Colin 1981</td>
<td>ACV Idoxuridine</td>
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<tr>
<td>Colin 1983</td>
<td>ACV ACV + Interferon</td>
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<td>Colin 1984</td>
<td>ACV Iododeoxycytidine</td>
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<td>Colin 1987</td>
<td>ACV ACV + Vidarabine</td>
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<td>Colin 1997b</td>
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<td>ACV Vidarabine</td>
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<td>De Koning 1983</td>
<td>ACV ACV + Interferon</td>
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<td>Kumar 1987</td>
<td>ACV + Idoxuridine</td>
<td>36</td>
</tr>
<tr>
<td>La Lau 1982</td>
<td>ACV + Trifluridine</td>
<td>33</td>
</tr>
<tr>
<td>Maychuk 1988</td>
<td>ACV + Idoxuridine</td>
<td>138</td>
</tr>
<tr>
<td>McCulley 1982</td>
<td>ACV + Idoxuridine</td>
<td>64</td>
</tr>
<tr>
<td>Meurs 1985</td>
<td>ACV + Interferon</td>
<td>93</td>
</tr>
<tr>
<td>Panda 1995</td>
<td>ACV + Idoxuridine + Triflu</td>
<td>80</td>
</tr>
<tr>
<td>Pavan-Langston 1981</td>
<td>ACV + Vidarabine</td>
<td>41</td>
</tr>
<tr>
<td>Wilhelmus 1981a</td>
<td>ACV + debridement</td>
<td>50</td>
</tr>
<tr>
<td>Yeakley 1981</td>
<td>ACV + Vidarabine</td>
<td>40</td>
</tr>
<tr>
<td>Young 1982</td>
<td>ACV + Vidarabine</td>
<td>93</td>
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<tr>
<td>Total number of studies</td>
<td></td>
<td>1729</td>
</tr>
</tbody>
</table>

Average retail price quoted by drugstore.com [Date accessed: 28 November 2006]

Viroptic® - 1% Solution 7.5ml Bottle 105 USD per bottle.

Average retail price quoted by 77canadapharmacy.com [Date accessed: 28 November 2006]

Viroptic® - 1% Solution 7.5ml Bottle 53 USD per bottle.