PUBLIC SUMMARY DOCUMENT

Product: Ciprofloxacin, ear drops, 3 mg per mL (0.3%), 5 mL Ciloxan®

Sponsor: Alcon Laboratories (Australia) Pty Ltd

Date of PBAC Consideration: July 2006

1. Purpose of Application

The submission requested an authority required listing for the treatment of chronic suppurative otitis media (CSOM).

2. Background

A submission for ciprofloxacin ear drops had not been considered previously by the PBAC, although ciprofloxacin eye drops are PBS listed (Authority required for bacterial keratitis) and a combination ear drop of ciprofloxacin with hydrocortisone is listed on the Repatriation PBS (Restricted benefit for acute bacterial otitis externa where first-line treatment has failed or is inappropriate).

A central issue in the consideration of these earlier submissions had been the public health concern over adding to antibiotic resistance in the community. General advice from the Expert Advisory Group on Antimicrobial Resistance was that it was prudent to limit topical use of antibiotics to those products that are not used systemically.

The EAGAR's advice to the Committee for ciprofloxacin ear drops, was that the group remains reluctant to support widespread use of quinolones to treat ear infections. The EAGAR also raised the issue of limited topical options for the treatment of CSOM. Those which are available are based on aminoglycosides and these are problematic in perforated membranes, particularly for those patients in whom the condition frequently relapses. The EAGAR advice concluded that if the PBAC were inclined to list, use be restricted to the Aboriginal and Torres Strait Islander (ATSI) population population.

3. Registration Status:

Ciprofloxacin ear drops (Ciloxan) was registered by the TGA on 17 May 2006 for the treatment of chronic suppurative otitis media caused by organisms susceptible to ciprofloxacin in adults and children 1 month and older. The product is identical to the currently registered eye drop formulation.

4. Requested Listing and PBAC's view

Authority required
Treatment of chronic suppurative otitis media.

The PBAC's view was that, taking into account the clinical data, the prevalence of the condition in the ATSI population, the advice from EAGAR, and noting also the 2004-05 Budget measure "Improving the capacity of the PBS to meet the needs of Indigenous

Australians", a recommendation restricting treatment to the ATSI population was more appropriate.

5. Clinical place for the proposed therapy

An alternative treatment for chronic suppurative otitis media (CSOM).

6. Comparator

The submission nominated Sofradex® (dexamethasone with framycetin sulfate and gramicidin = DFG) as the main comparator and oral antibiotics as a secondary comparator.

7. Clinical trials

The submission presented a single randomised trial (Couzos et al. 2003) comparing ciprofloxacin 0.3% with Sofradex 5 drops/day for 9 days in 8 Aboriginal communities in children under 15 years with CSOM in Western Australia and Queensland. The trial was published at the time of the submission, as follows:

First author	Publication title	Publication citation
Couzos et al	Effectiveness of ototopical antibiotics for chronic suppurative otitis media in Aboriginal children: A community-based, multicentre, double-blind randomised controlled trial	*Medical Journal of Australia*, 2003. 179(4): p. 185-190.

Also presented were 19 supplementary trials of ciprofloxacin vs other comparators and other doses of ciprofloxacin, and two Cochrane reviews: MacFayden (2006) Systemic antibiotics versus topical treatments for chronically discharging ears with underlying eardrum perforations (9 trials) and; MacFayden (2005) Topical antibiotics without steroids (quinolone, non-quinolone) for chronically discharging ears with underlying eardrum perforations (14 trials).

8. Results of Trials

There was a statistically significant difference in the proportion with clinical cure, favouring ciprofloxacin in the key trial's primary analysis. There were no statistically significant differences in the secondary outcomes, including perforation and hearing impairment, between treatments. There was no association between clinical cure and any assessed confounders: age, sex, history of exposure to cigarette smoke inside dwellings, crowding, other children with CSOM in household, duration and grade of discharge, prior ear infection, swimming, and number of visits by the Aboriginal Health Worker. Children who were not cured (31 of the 83 with baseline audiometry) were more likely to be those with poor hearing at baseline (average hearing threshold, 36.2dB compared with 23.7dB p=0.01).

In general, there were no major adverse events associated with ciprofloxacin.

9. Clinical Claim

The submission claimed that ciprofloxacin had significant advantages in effectiveness (clinical cure of discharge at 1-2 weeks) over topical DFG (Sofradex) and oral antibiotics and had similar or less toxicity. This was considered acceptable by the PBAC.

10. Economic Analysis

The submission presented a preliminary economic evaluation. The choice of the cost-effectiveness approach was considered valid. The resources included were drug costs. Two modelled economic evaluations were presented. Model 1: ciprofloxacin compared to Sofradex in rural settings for 2 treatment courses (~20 days). A patient can have up to 2 courses of Sofradex® or ciprofloxacin. If unsuccessful, 5% of patients are hospitalised. Only includes direct medical costs associated with GP visits, specialist visits, audiograms, drug costs and hospitalisation. Model 2: ciprofloxacin compared to systemic antibiotics in urban settings. A patient can have up to 2 courses of systemic antibiotics or ciprofloxacin. If unsuccessful, then treated with 1 course of Sofradex. If Sofradex treatment then fails, 5% of patients are hospitalised.

The incremental cost-effectiveness ratios are $10.30 saved per week of earlier resolution gained and $23.40 saved per week of earlier resolution in the rural and urban environments, respectively.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was between 100,000 – 200,000 in Year 3 (some patients will have bilateral disease), while the financial cost per year to the PBS in Year 3 was < $10 million.

12. Recommendation and Reasons

The PBAC recommended listing on clinical and cost-effectiveness grounds for use in chronic suppurative otitis media (CSOM) in an Aboriginal and Torres Strait Islander (ATSI) person.

The key evidence in the submission came from a single randomised trial (Couzos et al. 2003) comparing ciprofloxacin 0.3% with Sofradex (DFG) in ATSI children under 15 years with CSOM. Ciprofloxacin was statistically significantly better than Sofradex in the proportion with clinical cure [RD 24.6% (95%CI 15.8, 33.4)]. Although the ESC advised that this difference declines to 16% (p=0.06) when an ITT analysis is conducted, the PBAC considered it was not inappropriate to accept the data as presented in view of the difficulty in conducting such trials in the population studied.

The Committee also noted that the prevalence of CSOM in the ATSI population is extremely high at approximately 15%, compared to approximately 1% in the non-indigenous population. The PBAC also noted that there was a higher chronicity and relapse rate in the ATSI population with a greater potential for hearing loss.

Although, the sponsor has stated that it will conduct a post-listing evaluation of the development of resistant strains, the Committee noted that the use of fluoroquinolones in other indications has previously been restricted on advice from the Expert Advisory Group on Antibiotic Resistance (EAGAR). This has been done in an attempt to limit the

potential for the development of resistant strains which could limit the usefulness of these agents. EAGAR's advice to the Committee for ciprofloxacin ear drops, was that that group remains reluctant to support widespread use of fluoroquinolones to treat ear infections. EAGAR also raised the issue of limited topical options for the treatment of CSOM. Those which are available are based on aminoglycosides and are problematic in perforated membranes, particularly for those patients in whom the condition frequently relapses. The EAGAR advice concluded that if the PBAC is inclined to list, use be restricted to the ATSI population.

The Committee considered that economic analysis provided in the submission is adequate to provide confidence that the product would be of acceptable cost effectiveness. If the product is restricted to the ATSI population, then the total cost is anticipated to be less than $1million.

Taking into account the clinical data, the prevalence of the condition in the ATSI population, the advice from EAGAR, and noting also the 2004-05 Budget measure "Improving the capacity of the PBS to meet the needs of Indigenous Australians", the Committee considered that a recommendation restricting treatment to the ATSI population was appropriate.

The Committee requested that the DUSC monitor usage.

The PBAC recommended the 20 day safety net rule should not apply.

Recommendation

Ciprofloxacin**,** ear drops, 3 mg per mL (0.3%), 5 mL

Restriction: Authority required
Treatment of chronic suppurative otitis media in an Aboriginal and Torres Strait Islander person aged one year and older.

Maximum quantity: 1
Repeats: 1

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

In view of the limitations of other available therapies, Alcon will be working towards making Ciloxan Ear Drops accessible to all Australians with CSOM. Alcon did not believe there was adequate justification that the only medicine approved in Australia for CSOM should not be re-imbursed for non-ATSI Australians.