PUBLIC SUMMARY DOCUMENT

Product: Topiramate, tablets, 25 mg and 50 mg, Topamax®

Sponsor: Janssen-Cilag Pty Ltd

Date of PBAC Consideration: July 2006

1. Purpose of Application

The application sought to add to the current listing for epilepsy, an authority required listing for the prophylactic treatment of migraine.

2. Background

Topiramate was first listed on the PBS in August 1997 with an authority required listing for the treatment of partial epileptic seizures which are not controlled satisfactorily by other anti-epileptic drugs. The restriction was amended in March 2000 to include primarily generalised tonic-clonic epileptic seizures and seizures of the Lennox-Gastaut syndrome.

3. Registration Status

Topiramate tablets (25 mg, 50 mg, 100 mg, and 200 mg) and sprinkle capsules (15 mg, 25 mg and 50 mg) are registered by the TGA for prophylaxis of migraine headache in adults.

4. Requested Listing and PBAC's view

Authority required
Prophylaxis of migraine in adults who are experiencing an average of three or more migraines per month, and who:
(a) have failed to achieve an adequate response to beta-blockers at the recommended dose, for a period of at least 3 months, where adequate response is defined as a reduction in migraine frequency of at least 50%; or
(b) have experienced treatment-limiting adverse effects with a beta-blocker; or
(c) have one or more of the contraindications listed in the TGA-approved Product Information for beta-blockers;
AND
(d) have failed to achieve an adequate response to pizotifen at a dose of at least 1.5 mg/day, for a period of at least 3 months, where adequate response is defined as a reduction in migraine frequency of at least 50%; or
(e) have experienced treatment-limiting adverse effects with pizotifen; or
(f) have one or more of the contraindications listed in the TGA-approved Product Information for pizotifen.

For PBAC's view, see Recommendation and Reasons.

5. Clinical place for the proposed therapy:

For use in migraine prophylaxis in patients who have failed or are unable to tolerate other treatments.

6. Comparator

The submission nominated placebo as the comparator. The PBAC agreed the comparator was appropriate.

7. Clinical Trials

The submission presented two randomised trials (Silberstein et al 2004 and Brandes et al 2004) as key evidence, in which topiramate 50 mg/day, 100 mg/day and 200 mg/day were compared with placebo respectively in migraine patients over 26 weeks. Another trial (Silvestrini et al 2003) was also provided as key evidence, comparing topiramate 50 mg/day with placebo in patients who failed at least four prior prophylactic therapies over a 9-week period.

The trials were published at the time of the submission as follows:

Trial/First author	Publication title	Publication citation
Silberstein JD	A randomized, double-blind, placebo-controlled, parallel group, dose-response study to evaluate the efficacy and safety of topiramate in the prophylaxis of migraine	Archives of Neurology, 2004:61, no. 4;490-495.
Brandes JL	A randomized, double-blind, placebo-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of topiramate in the prophylaxis of migraine.	Journal of the American Medical Association,2004:291, no. 8;965-973.
Silvestrini M	"Topiramate in the treatment of chronic migraine	Cephalalgia, 2003:23, no. 8; 820-824.

8. Results of Trials

The submission pooled analysis demonstrated a statistically significant difference in responder rate comparing the recommended topiramate dose of 100 mg /day with placebo.

Although from the Silberstein et al 2004 and Brandes et al 2004 trials, topiramate seems to have significant treatment effects over placebo, the applicability of these results to the intended population for topiramate on the PBS was uncertain. It was not clear whether the patients who failed two or more prior prophylactic medications (the PBS intended population) would demonstrate similar treatment effects to those patients who had received (including both failed and responded) one or two prior prophylactic medications

Across all topiramate treatment groups, the most commonly reported adverse events were related to the central and peripheral nervous system (i.e., neurologic) or were psychiatric in nature. Paresthesia was the most frequently occurring adverse event in patients receiving topiramate, with higher incidence (35%-51%) than in the placebo group (6%). Other common neurologic or psychiatric adverse events that were reported at least twice as frequently in all topiramate dose groups compared with the placebo group included language problems (6.5%-8.0% vs. 1.9%), anorexia (9%-15%% vs. 6%), difficulty with memory (7%-11% vs. 2%), anxiety (4%-6% vs. 2%), mood problems (3%-7% vs. 2%),

difficulty with concentration/attention (3%-12% vs. 2%), and nervousness (3.6%-4.8% vs. 1.9%).

9. Clinical Claim

The submission described topiramate as having significant advantages in effectiveness over placebo but having more toxicity.

For PBAC's views see Recommendation and Reasons.

10. Economic Analysis

A preliminary economic evaluation was presented. The resources included were the costs of topiramate, acute migraine attack treatment medications (rescue medications), and the administration of rescue medications.The outcomes were response rate, defined as the proportion of subjects who had a 50% or greater reduction in their average monthly migraine period rate from baseline, and the number of migraine days.

The trial-based incremental cost per extra responder gained was estimated to be <$15,000. The trial-based incremental cost per extra migraine day avoided was estimated to be <$15,000.

A modelled economic evaluation was presented using a cost-utility approach. The base case modelled incremental cost per additional QALY was estimated to be in the range $15,000 - $45,000.

11. Estimated PBS Usage and Financial Implications

The submission stated that the likely number of patients per year is in the range 10,000 to 50,000 in Year 5 of listing. The PES commentary advised that this is a likely under-estimate in the submission.

The submission estimated that the financial cost/year to the PBS was < $10 million in Year 5.

12. Recommendation and Reasons

The PBAC noted that the submission requested a listing in patients who have either failed or developed intolerance to beta-blockers and pizotifen, or in whom these agents are contra-indicated.

Although from the Silberstein et al 2004 and Brandes et al 2004 trials , topiramate seems to have significant treatment effects over placebo, the appropriate comparator for last line therapy, the PBAC considered that the applicability of these results to the intended population for topiramate on the PBS is uncertain, since the trials explicitly excluded the patients who had failed more than two prior migraine prophylactic medications, while the requested restriction on the PBS requires that patients have failed or are contraindicated for at least 2 migraine prophylactic medications. Therefore the PBAC expressed the view that overlap between the trial population and the population for whom PBS listing is sought is likely to be minimal.

The PBAC noted that there were a number of issues with the modelled economic evaluation in addition to the use of response rates from a trial which was not representative of the patient group for whom listing was sought.

The PBAC thus rejected the submission because of uncertain benefit in the population in whom listing was requested and the resulting uncertain cost-effectiveness.

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

Due to the strong clinical need for an additional prophylactic treatment in migraine, Janssen-Cilag has engaged in discussions with the PBAC and clinicians to clarify and address issues raised by the Committee with a view to ensuring access to topiramate for migraine prophylaxis through the PBS.