PUBLIC SUMMARY DOCUMENT

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

Sponsor: Janssen-Cilag Pty Ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application

This re-submission sought to add to the current listing for epilepsy, an authority required listing for the prophylactic treatment of migraine for the 25 mg and 50 mg strengths only.

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.

A submission for an authority required listing for the prophylactic treatment of migraine in patients who had tried beta-blockers and pizotifen was considered by the PBAC at its July 2006 meeting. The PBAC rejected the submission because of uncertain benefit in the population in whom listing was requested and the resulting uncertain cost-effectiveness. The PBAC was concerned that overlap between the trial population and the population for whom PBS listing was sought was likely to be minimal.

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. Listing Requested and PBAC's View

Authority required
Initial treatment
Prophylaxis of migraine in an adult who has experienced an average of three or more migraines per month over a period of at least six months, and who:
(a) has a contraindication to beta-blockers, as described in the relevant TGA-approved Product Information; OR
(b) has experienced intolerance of a severity necessitating permanent withdrawal during treatment with a beta-blocker; AND
(c) has a Body Mass Index (BMI) >30 kg/m^2; OR
(d) has experienced intolerance of a severity necessitating permanent withdrawal during treatment with pizotifen.
Details of the contraindication and/or intolerance(s) and/or BMI must be provided at the time of application.

Continuing treatment

Continuing treatment for patients who have previously received PBS subsidised treatment with topiramate for prophylaxis of migraine.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

For use in migraine prophylaxis in patients who are unable to take other treatments (beta blockers and pizotifen).

6. Comparator

The submission nominated placebo as the comparator and this was previously agreed by the PBAC at its July 2006 meeting.

7. Clinical Trials

The submission presented the same two randomised trials as in the previous submission (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.

The re-submission removed the trial Silvestrini et al (2003), as the population who have failed previous prophylactic medications was no longer applicable to the requested restriction in this re-submission.

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

Trial/First author	Protocol title/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.

8. Results of Trials

The pooled analysis of the primary efficacy outcome, change in average monthly migraine period rate showed that topiramate 100 mg/day was statistically significantly superior to placebo.

The average monthly migraine period rate was defined as the total number of migraine periods during a phase, divided by the total duration of that phase (in days), times 28. Migraine periods were defined as the length of time between the onset and cessation of painful migraine symptoms. The duration of this period could last up to, but no longer than 24 hours. If symptoms ended and recurred within 24 hours of the onset, they were considered part of the initial migraine period. Any symptoms lasting beyond 24 hours of the initial onset were considered to be part of a new, distinct migraine period.

9. Clinical Claim

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

See Recommendation and Reasons for PBAC's view.

10. Economic Analysis

An updated preliminary economic evaluation was presented. The approach in the preliminary economic evaluation remained unchanged.

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

An updated modelled economic evaluation was presented. The approach and structure of the modelled economic evaluation were unchanged from the previous submission.

The base case modelled incremental cost/extra 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/year would be in the range 10,000 to 50,000 in Year 5 of listing. The PBAC considered that this is a likely under-estimate in the submission.

The submission estimated that the financial cost/year to the PBS would be up to between $10 million to $30 million in Year 5 of listing.

12. Recommendation and Reasons

The PBAC recommended listing on the basis of acceptable cost-effectiveness compared to placebo for migraine prophylaxis in patients unable to take a beta-blocker and/or pizotifen.

The PBAC was concerned about the risk of use beyond the requested restriction to first line therapy for migraine prophylaxis and to neuropathic pain and that this presented a high degree of financial risk for government. The PBAC thus considered that an authority required listing would be appropriate.

Recommendation

TOPIRAMATE, tablets, 25 mg and 50 mg
Authority required
Initial treatment
Prophylaxis of migraine in a patient who has experienced an average of three or more migraines per month over a period of at least six months, and who:

(a) has a contraindication to beta-blockers, as described in the relevant TGA-approved Product Information; OR

(b) has experienced intolerance of a severity necessitating permanent withdrawal during treatment with a beta-blocker;
AND
(c) is overweight (as defined by body mass index of $\geq$30 kg/m^2); OR
(d) has experienced intolerance of a severity necessitating permanent withdrawal during treatment with pizotifen.
Details of the contraindication and/or intolerance(s) and/or body mass index must be provided at the time of application.

Continuing treatment
Continuing treatment for patients who have previously received PBS subsidised treatment with topiramate for prophylaxis of migraine.

Maximum Quantity: 60 (tablets 25 and 50 mg only)
Repeats: 5

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

The sponsor welcomes this decision by the PBAC to provide access to an alternative migraine prophylactic agent.