PUBLIC SUMMARY DOCUMENT

Product: Atomoxetine Hydrochloride, capsules, 10 mg, 18 mg, 25 mg, 40 mg and 60 mg, Strattera®

Sponsor: Eli Lilly Australia Pty Ltd

Date of PBAC Consideration: November 2006

1. Purpose of Application

The resubmission sought an authority required PBS listing for atomoxetine for the treatment of patients with attention deficit hyperactivity disorder (ADHD) diagnosed between the ages of 6 and 18 years by a paediatrician or psychiatrist who meet certain criteria.

The resubmission sought to address the concerns of the PBAC from the July 2006 meeting.

2. Background

At the March 2004 and March 2005 meeting, the PBAC rejected the submissions to list atomoxetine hydrochloride ('atomoxetine') capsules on the PBS for ADHD because the conclusion from the trial evidence for atomoxetine was that it is non-inferior, rather than superior, to the stimulants in terms of clinical benefits overall and thus atomoxetine is of uncertain but unacceptable cost-effectiveness due to its increased costs.

At the November 2005 meeting, the application was rejected on the basis of unacceptable and uncertain cost-effectiveness. The PBAC's principal concern about the submission was reliability of the economic model and thus its results were considered uncertain.

At the July 2006 meeting, the fourth re-submission presented the same positioning, supportive data and economic analyses as presented in the November 2005 submission but focused specifically on providing information to address concerns raised in the evaluation of that submission. The PBAC rejected the submission because of uncertain cost-effectiveness.

3. Registration Status

Atomoxetine is TGA registered for marketing in Australia for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) as defined by Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria in children 6 years of age and older, adolescents and adults.

4. Listing Requested and PBAC's View

Authority Required

Initial treatment of patients with attention-deficit hyperactivity disorder (ADHD) diagnosed between the ages of 6 and 18 years by a paediatrician or psychiatrist according to the DSM-IV criteria where:

- Treatment with dexamphetamine sulfate or methylphenidate 10mg poses an unacceptable medical risk due to the following contraindications to immediate-release stimulant treatment as specified in the TGA-approved product information:
- The patient has a history of substance abuse or misuse (other than alcohol); and/or
- The patient has comorbid motor tics or Tourette's Syndrome; and/or
- The patient has comorbid severe anxiety diagnosed according to the DSM-IV.

OR
Treatment with dexamphetamine sulfate or methylphenidate 10mg has resulted in the development or worsening of a comorbid mood disorder (diagnosed according to the DSM-IV criteria i.e. anxiety disorder, obsessive compulsive disorder, depressive disorder) of a severity necessitating permanent stimulant treatment withdrawal; or where the combination of stimulant treatment with another agent would pose an unacceptable medical risk of a severity necessitating permanent stimulant treatment withdrawal.
OR
Treatment with dexamphetamine sulfate AND methylphenidate 10mg has resulted in the development of adverse reactions of a severity necessitating permanent treatment withdrawal:

- Adverse effects on growth and weight
- Adverse effects on sleep including insomnia
- Adverse effects on appetite including anorexia

Authority Required
Continuing treatment where the patient has previously been issued with an authority prescription for this drug.

See Recommendation and Reasons for the PBAC's view.

5. Clinical Place for the Proposed Therapy

The PBS-listing of atomoxetine would provide appropriate specialist clinicians with a therapy when treating patients aged between 6 and 18 years suffering from ADHD who are unable to use the short acting stimulants dexamphetamine sulfate 5 mg and methylphenidate hydrochloride 10 mg because of an unacceptable medical risk to the patient.

6. Comparator

The submission nominated placebo as the main comparator. This had previously been accepted by the PBAC as the appropriate comparator for second-line therapy.

7. Clinical Trials

The submission presented 3 longer term clinical trials, studies LYAF, LYBI and LYAC, which included a randomised, blinded treatment phase within the trials as supportive evidence in the re-submission. Study LYAF included a placebo-comparator. The submission presented these data to support delayed responder rates among acute treatment non-responders and relapse prevention analysis to determine robustness of response in atomoxetine patients and placebo patients.

Study LYAF was published at the time of the submission as follows:

Trial/First author	Publication title	Publication citation
Michelson D et al (2004)	Relapse prevention in pediatric patients with ADHD treated with atomoxetine: a randomized, double-blind, placebo-controlled study.	Journal of the American Academy of Child & Adolescent Psychiatry, 43(7): 896-904

8. Results of Trials

The submission presented the same meta-analysis as the July 2006 submission for the estimation of acute treatment effects. This had been previously reported in the July 2006 Public Summary Document (PSD). However, since the November 2005 re-submission, the

TGA has implemented the need to monitor all patients for suicidal ideation and behaviour by inclusion of a boxed warning in the revised product information. Also included in this revised product information was the need to exercise caution when prescribing atomoxetine in patients who have a history of seizures and the rare cases of QT prolongation that have occurred when atomoxetine has been given in conjunction with fluoxetine, paroxetine or quinidine.

Aspects about the toxicity of atomoxetine were noted, but although there were some concerns about the possible incidence of suicidal ideation and hepatotoxicity, the Committee also noted that these adverse events are rare. Further, the PBAC's concerns had been addressed adequately by the submission documents and the information provided at the sponsor's hearing.

9. Clinical Claim

No new clinical claim was made. The July 2006 submission had previously claimed that atomoxetine had significant advantages in effectiveness over placebo but was more toxic. This claim of advantage over placebo had previously been accepted by the PBAC.

10. Economic Analysis

The submission presented a preliminary economic evaluation which calculated the incremental cost of atomoxetine per patient achieving a response at 10 weeks using the same approach used in the July 2006 submission but updated to reflect the change in the proposed price.

In the base-case cost-effectiveness analysis, the submission estimated the incremental cost per responder to be < $1,000. When the mean number of capsules per patient per day was increased to 1.3, there was little difference in the incremental cost per responder, which remained < $1,000.

A cost-utility analysis was presented using the modelled evaluation from the November 2005 submission and updated to reflect 1.3 capsules per patient per day at a cost of $4.05 per capsule. Costs and QALYs were modelled over a 104 week (2 year) treatment period.

The incremental cost per QALY was estimated to be in the range $15,000 - $45,000.

11. Estimated PBS Usage and Financial Implications

The submission presented the financial implications based on the model presented in the July 2006 submission. Using the revised price and based on epidemiological estimates of 7.5% prevalence and over 40% diagnosis rates of ADHD in Australia, under the assumption that current clinical practice parameters of 'stimulant treatment first' would continue (Scenario 1), the submission estimated the number of patients to be in the range 10,000 – 50,000 in year 4 of listing.

The submission estimated the mean cost per annum to the PBS for the first four years to be < $10 million, assuming 1.3 capsules per day.

Under the assumption that the PBS-listing of atomoxetine hydrochloride would change treatment patterns in line with the proposed restriction (Scenario 2), the number of patients was estimated to be in the range 10,000 – 50,000 in year 4 of listing.

The submission estimated the mean cost per annum to the PBS for the first four years to be in the range $10 – 30 million.

The submission proposed a risk sharing arrangement if recommended for listing, which had 3 key elements, including the price, population and potential penalty (rebate).

The submission also proposed a Quality Use of Medicine (QUM) Program to encourage appropriate use within the eligible population where cost-effectiveness has been accepted by the PBAC and outlined 3 main QUM opportunities for atomoxetine:

- Appropriate patient;
- Safety awareness
- Appropriate dosing.

12. Recommendation and Reasons

The PBAC recommended listing on a cost effectiveness basis over placebo at the new price proposed. The PBAC accepted that there is a clinical need for this product and that the restriction appropriately targets those patients most likely to benefit from treatment.

The Committee accepted that it was unlikely that any new utility study would address the uncertainties around these values. However the substantial reduction in the price to pharmacist offered in this submission resulted in a lower, and more acceptable, incremental cost per quality adjusted life year (QALY) of $15,000 to $45,000. The Committee further considered that it was unlikely that the worst case incremental cost per QALY would be as high as the upper estimate ($75,000 - $105,000) estimated in sensitivity testing.

The PBAC noted that the sponsor has agreed to enter into a risk sharing agreement with the Government.

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

Recommendation

Restriction: <u>Authority Required</u>

Initial treatment of attention-deficit hyperactivity disorder (ADHD) diagnosed between the ages of 6 and 18 years inclusive, by a paediatrician or psychiatrist according to the DSM-IV criteria where:

- Treatment with dexamphetamine sulfate or methylphenidate poses an unacceptable medical risk due to the following contraindications as specified in the TGA-approved product information:
- The patient has a history of substance abuse or misuse (other than alcohol); and/or
- The patient has comorbid motor tics or Tourette's Syndrome; and/or
- The patient has comorbid severe anxiety diagnosed according to the DSM-IV.

OR

Treatment with dexamphetamine sulfate or methylphenidate has resulted in the development or worsening of a comorbid mood

disorder (diagnosed according to the DSM-IV criteria i.e. anxiety disorder, obsessive compulsive disorder, depressive disorder) of a severity necessitating permanent stimulant treatment withdrawal; or where the combination of stimulant treatment with another agent would pose an unacceptable medical risk of a severity necessitating permanent stimulant treatment withdrawal.
OR
Treatment with dexamphetamine sulfate AND methylphenidate has resulted in the development of adverse reactions of a severity necessitating permanent treatment withdrawal:

- Adverse effects on growth and weight
- Adverse effects on sleep including insomnia
- Adverse effects on appetite including anorexia

Authority Required
Continuing treatment where the patient has previously been issued with an authority prescription for this drug.

Maximum quantity:	56
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

Eli Lilly Australia welcomes the decision by the Pharmaceutical Benefits Advisory Committee (PBAC) to issue a positive recommendation for Strattera (atomoxetine HCl) to be placed on the Pharmaceutical Benefits Scheme (PBS).