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: July 2006

1. Purpose of Application

The re-submission requested the PBS listing of atomoxetine hydrochloride as an authority required item for the treatment patients diagnosed with attention deficit hyperactivity disorder (ADHD) between the ages of 6 and 18 years.

2. Background

This was the fourth submission to the PBAC for listing for the treatment of ADHD. The first application was to the March 2004 meeting, a second was considered at March 2005.

A submission to list atomoxetine hydrochloride ('atomoxetine') capsules on the PBS for attention deficit hyperactivity disorder (ADHD) was rejected by the PBAC at its March 2004 meeting. The PBAC rejected the submission 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.

The March 2005 submission was rejected because the conclusion from the trial evidence for atomoxetine was that it was non-inferior, rather than superior, to the stimulants in terms of clinical benefits overall and therefore atomoxetine was of uncertain but unacceptable cost-effectiveness due to its increased costs.

The third was to 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.

This re-submission presented the same positioning, supportive data and economic analyses as presented in the previous submission (PBAC meeting November 2005) but focused specifically on providing information to address concerns raised in the evaluation of that submission.

3. Registration Status

Atomoxetine is TGA registered for marketing in Australia for the 'treatment of Attention Deficit Hyperactivity Disorder (ADHD) as defined by DSM-IV criteria in children 6 years of age and older, adolescents and adults.'

The TGA approved Product Information has recently been amended to include a boxed warning to highlight to physicians the importance of monitoring for the emergence of suicidal related behaviours.

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 10 mg 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 10 mg 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 10 mg 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.

The PBAC's view was that the requested restriction was appropriate and that most of its previous concerns had been addressed in this submission.

5. Clinical Place for the Proposed Therapy

The sponsor proposed that atomoxetine had a clinical place where dexamphetamine sulfate or methylphenidate were either contraindicated, resulted in a worsening of associated conditions, or resulted in adverse events necessitating permanent treatment withdrawal.

6. Comparator

Placebo as previously agreed by the PBAC.

7. Clinical Trials

No changes had been made to the trial data presented in the previous submissions. See Public Summary Document from November 2005 PBAC meeting.

8. Results of Trials

The key results were based on a meta-analysis of ten randomised placebo controlled trials using the outcomes of the Attention Deficit Hyperactivity Disorder Rating Scale 4th Parent Version:Investigator administered and scored (ADHDRS-IV-Parent:Inv). The ADHDRS-IV-Parent:Inv-Parent:Inv is an 18-item scale based on semi-structured interview between a patient's parent (or primary caretaker and a clinician experienced in working with children with ADHD). According to the meta-analysis using this outcome measure, atomoxetine was associated in the re-submission's meta-analysis with a superior statistically significant change from baseline to endpoint compared with placebo. The results of this meta-analysis were derived from individual patient data (IPD). The results for proportion of responders (≥40% decrease from baseline to endpoint ADHDRS Total score) were slightly changed from the previous re-submission in favour of atomoxetine.

The PBAC had previously noted that mean changes in ADHDRS-Parent: Inv were similar between the overall meta-analysis and those individual trials in sub-types of patients who are more representative of the populations for whom listing was requested. This conclusion was addressed by comparing the proportions of patients with particular co-morbidities recruited into certain trials with the ensuing results of these trials against the results of the meta-analysis, with specific emphasis on anxiety (LYBP), depression (LYAX), and tic disorders or Tourette's syndrome (LYAS). This suggested that there was no evidence of treatment effect modification across these different patient groups. The PBAC thus considered it was reasonable to accept that the results of the meta-analysis are generalisable to those populations for whom listing was sought.

No new toxicity data were presented in the re-submission because of its inclusion in the previous submission. Since the previous 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.

9. Clinical Claim

The submission claimed 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 re-submission claimed that an updated preliminary economic evaluation was not presented. However, the value assumed for a number of variables had changed from the previous re-submission. These included a slight increase in the incremental effectiveness, the average treatment duration which had decreased (reducing drug costs), the average daily dose which had increased (increasing drug costs) and lower drug costs which had

been updated to reflect the new requested dispensed price from July 2006. Only drug costs were included in the analysis.

The trial-based incremental cost per extra patient with ≥40% reduction from baseline in ADHD-RS total score over 56.21 days (mean daily dose 54.78mg/day) was < $1,000.

An updated modelled economic evaluation was presented. Although the structure of the model remained the same, some of the values of variables were changed. The base case modelled incremental discounted cost per extra discounted QALY was in the range of $45,000 - $75,000 over 104 weeks.

As with the model presented in the previous re-submission, the model presented in the current submission, on the basis of data from the LYBI trial, assumed that 50.4% of non-responders to atomoxetine at 10 weeks will develop a delayed response after up to 8 months of continued treatment and also assumed that 0% of non-responders to atomoxetine at 10 weeks will develop a delayed response after up to 8 months of continued treatment on the grounds that there is absence of evidence to suggest that patients treated with placebo will experience a delayed response. The LYBI trial did not include a placebo arm in the relevant phase of the trials used by the re-submission to permit assessment of 'delayed response' in patients who continue therapy despite response not being achieved at 8 weeks. Thus, the concern raised previously that the assumption with respect to proportion of non-responders to placebo developing a delayed response after up to 8 months of continued treatment being 0% (where it was assumed to be 50.4% for non-responders to atomoxetine) was poorly supported remained unaddressed.

The PBAC noted that a key concern with the previous submission, the application of the TTO methodology to elicit utilities remained. The ESC advised the key issue with the elicitation of utilities is that a time trade off (TTO) approach in which a subject is asked to trade off someone else's life is not comparable with a standard time trade off approach because it does not have the same basis in utility. A QALY weight is a person's individual preference ranking about health states for themselves. Even if an adult is asked to imagine that she was a child, it is the adult who then has to answer how much she wants to trade-off the child's life whereas in standard TTO the adult would be asked how much of her own life she would trade off. Implicitly the utility function which has the adult's survival, and the adult's quality of life is then taken as the child's utility function.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was in the range of 10,000 – 50,000 in Year 4 under both treatment scenario 1 (where stimulant therapy is standard of care) and under treatment scenario 2 (based on a treatment algorithm for patients with co-morbid conditions).

The financial cost per year to the PBS (excluding co-payments) minus any savings in use of other drugs was in the range of $10 – 30 million in Year 3 for treatment scenario one and in the range of $30 – 60 million in Year 3 for treatment scenario two. As previously, the submission proposed entering into price/volume agreement negotiations.

12. Recommendation and Reasons

The PBAC considered that the requested restriction was appropriate and that most of its previous concerns had been addressed in this submission and by the Pre-Sub-Committee and Pre-PBAC Responses. Further, it was reiterated at the hearing that the sponsor is willing to enter into a risk-sharing arrangement to account for any doses greater that 1.3 capsules per day. The outstanding issues about the economic model, which led to uncertainty about the reliability of the base-case incremental cost-effectiveness ratio, concerned the assumption about the delayed response at 8 months of non-responders to atomoxetine at 10 weeks compared to non-responders to placebo at 10 weeks, the assumption about a difference in relapse rates between the atomoxetine and placebo arms of the model and utilities.

As with the model presented in the previous resubmission, this submission's model, on the basis of data from the LYBI trial, assumed that 50.4% of non-responders to atomoxetine at 10 weeks will develop a delayed response after up to 8 months of continued treatment. It also assumed that 0% of non-responders to placebo at 10 weeks will develop a delayed response after up to 8 months of continued treatment on the grounds that there is absence of evidence to suggest that patients treated with placebo will experience a delayed response. The LYBI trial did not include a placebo arm after the initial 10 weeks period to permit assessment of 'delayed response' in patients who were initially non-responders while on placebo. The PBAC agreed with the ESC that, in the absence of evidence that non-responders in the atomoxetine arm have different subsequent response rates in comparison with non-responders in the placebo arm, the most conservative approach in the model would have been to assume no difference between the atomoxetine and placebo arms of the model for this parameter. By assuming a differential effect the model biases the results in atomoxetine's favour.

The PBAC noted that the model was less sensitive to assumptions about the relapse rates than those in relation to delayed response rates.

The PBAC accepted that it would be difficult to design a methodologically sound utility study in ADHD and acknowledged the attempts made by the sponsor to address this problem. However, the PBAC agreed with the ESC that the key issue with the elicitation of utilities is that a time trade off approach in which a subject is asked to trade off someone else's life is not comparable with a standard time trade off approach because it does not have the same basis in utility theory. The time trade off approach only provides a QALY weight if specific assumptions are made about the form of the utility function for the individual, which would exclude consideration of another individual's survival and quality of life. Thus, it is not appropriate to derive utility values by using a method in which an individual (adult) is trading off the life of another individual (child).

The PBAC recalled there were other issues raised by the ESC and PBAC in regard to elicitation of utilities assumed in the model presented with the previous re-submission. The utility values assumed in the model presented in the current re-submission are the same as assumed in the model presented in the previous re-submission. These issues include the use of a 70-year time horizon for the time trade off survey which is likely to lead to lower utility weights because of respondents' time preferences; derivation of the final health states using visual analogue scales for health states, and asking respondents to extrapolate from a child health state to the adult health state, particularly for health states

that relate to developmental/learning outcomes. The PBAC noted that the model is most sensitive to assumed utility weights of the various health states in the model. As noted above the model is also sensitive to the assumptions about the delayed response by non-responders. Given the concerns about the assumptions about these two factors in the model, there was uncertainty about the base-case modelled incremental cost-effectiveness ratio, which between $45,000 and $75,000 was considered high, and would likely be higher, given the above concerns. The PBAC therefore rejected the submission because of 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

Eli Lilly Australia is disappointed with this outcome, but remains committed to finding a means to provide equitable access to Strattera® treatment for patients who need a treatment for ADHD that is not amphetamine-based. With regards to Utility analysis, we acknowledge that there are methodological issues, however, the results were not inconsistent with the outcomes of the trials. The new guidelines appear to have been taken some step to address this methodological issue.