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 2005

1. Purpose of Application

This re-submission proposed a more targeted patient population for the Authority Required listing to restrict use in the treatment of attention deficit hyperactivity disorder (ADHD) to patients unable to take dexamphetamine sulfate or methyl phenidate 10 mg.

2. Background

This is the third submission to list atomoxetine on the PBS. Applications were rejected by the PBAC at the March 2004 and March 2005 meetings.

The March 2004 submission was rejected because of uncertain cost-effectiveness, but also because of the applicability of the randomised trials to the proposed population and the impractical restriction proposed.

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.

3. Registration Status

Atomoxetine was registered on 27 January 2004 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.

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 sulphate 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 co-morbid motor tics or Tourette's Syndrome; and/or
    - The patient has co-morbid severe anxiety diagnosed according to the DSM-IV.

OR

Treatment with dexamphetamine sulphate or methylphenidate 10mg has resulted in the development or worsening of a co-morbid mood disorder (diagnosed according to the DSM-IV criteria i.e. anxiety disorder, obsessive compulsive disorder, depressive disorder and psychosis) 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 sulphate AND methylphenidate 10mg has resulted in the development of adverse reactions of a severity necessitating permanent treatment withdrawal:

- Seizures
- 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 Recommendations and Reasons for PBAC's view on restriction.

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

The submission, as with previous submissions, proposed placebo as the most appropriate comparator. The PBAC accepted this as appropriate.

7. Clinical Trials

The submission presented a meta-analysis of ten randomised trials- HFBD, HFBK, LYAC, LYAT, LYBG, LYAS, LYBI (Phase II), which were all presented in previous submissions, and LYCC, LYAX and LYBP, which were newly presented in this re-submission. Two of these ten trials recruited subjects with co-morbid conditions contraindicated to stimulant therapy as specified in the PI. These were LYAS (tics and Tourette's syndrome) and LYBP (anxiety). Trial LYAX included subjects with depression, but did not specifically recruit patients whose depression had been worsened by stimulant therapy.

List of included trials

Trial	Protocol title	N	Duration	In previous submissions
Trials in children/adolescents				
HFBD	A randomised, double-blind parallel study of atomoxetine, methylphenidate hydrochloride, and placebo in paediatric outpatients with ADHD	127	9 weeks	√ §
HFBK	A randomised, double-blind parallel study of atomoxetine, methylphenidate hydrochloride and placebo in paediatric outpatients with ADHD	126	9 weeks	√ §
LYAC	A phase III randomised, double-blind, parallel, placebo-controlled efficacy and safety comparison of fixed-dose ranges (mg/kg/day) of atomoxetine with placebo in child and adolescent outpatients with ADHD, aged 8-18 years	297	8 weeks	√
LYAS	A randomised, double-blind parallel study of atomoxetine and placebo in paediatric outpatients with ADHD and co-morbid tic disorders	148	18 weeks	§
LYAT	A multi-centre, randomised, double-blind, placebo-controlled parallel trial of the efficacy, tolerability, and safety of once-daily atomoxetine versus placebo in children with ADHD	171	6 weeks	√
LYAX	A randomized, double-blind, placebo-controlled parallel trial of atomoxetine in adolescents with ADHD and co-morbid depressive disorder. (The randomised period lasted 9 weeks followed by two open-label phases of up to 9 months	142	9 weeks	

	assessments. The trial discontinued early because of slower than anticipated enrolment - the original protocol planned to recruit approximately 240 patients.)			
LYBG	A multi-centre randomised, double-blind, placebo-controlled parallel trial of once daily atomoxetine hydrochloride to evaluate efficacy in the treatment of ADHD in children ages 6-12 with an assessment of evening behaviour	197	8 weeks	√ §
LYBI	A multi-centre randomized, double-blind, parallel, comparison of atomoxetine, slow release methylphenidate hydrochloride and placebo in paediatric outpatients with DSM-IV ADHD	516	6 weeks	§
LYBP	A randomized, double-blind, placebo-controlled parallel, trial of atomoxetine in children and adolescents with ADHD and Co-morbid Anxiety	176	12 weeks	
LYCC	A placebo-controlled double-blind assessment of morning-dosed or evening-dosed atomoxetine. Evaluation of Continuous Symptom Treatment of ADHD. (Only the morning-dose efficacy data are included in the re-submission.)	288	6 weeks	
LYAW	*Double-blind, placebo-controlled trial of atomoxetine hydrochloride to evaluate efficacy in the school setting in children ages 8 to 12 years with Attention-Deficit/ Hyperactivity Disorder*	*153*	*7 weeks*	√
Trials in adults				
LYAA	A phase III randomised, double-blind comparison of placebo and atomoxetine in adult outpatients with DSM-IV ADHD	280	10 weeks	√ §
LYAO	A phase III randomised, double-blind comparison of placebo and atomoxetine in adult outpatients with DMS-IV ADHD	256	10 weeks	√ §
Spencer et al, 1998	*Randomised, double-blind crossover trial of atomoxetine in the treatment of adults with childhood-onset and persistent ADHD*		*3 weeks*	√ §
Supportive evidence - long-term trials				
LYBI	A randomised, double-blind comparison of atomoxetine hydrochloride, slow-release methylphenidate and placebo in children with ADHD			§
LYAF	A multi-centre, randomised, double-blind relapse prevention study of atomoxetine versus placebo			§
LYAC	A phase III, multi-centre, double-blind, placebo-controlled efficacy and safety comparison of fixed-dose ranges (mg/kg/day) of atomoxetine with placebo in child and adolescent outpatients with ADHA, aged 8-18 years			√ §
Supportive evidence - long-term safety studies				
LYAB	A phase II open-label safety and efficacy study of atomoxetine in outpatients with ADHD, ages 6-18 years			√
HFBF	Long-term, open-label safety study of atomoxetine in patients, 6 years and older			√ §

√ presented in original submission to March 2004 PBAC meeting
§ presented in re-submission to March 2005 PBAC meeting

8. Results of Trials

The key result, using the Attention Deficit Hyperactivity Disorder Rating Scale 4th Parent Version :Investigator administered and scored (ADHDRS-IV-Parent:Inv), from the re-submission's meta-analysis are summarised in the table below. The ADHDRS-IV-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 this measure, atomoxetine was associated with a superior statistical significant change from baseline to endpoint compared with placebo in all ten trials.

In this submission, a meta-analysis of ten trials was conducted. In the meta-analysis a treatment responder was defined as a participant achieving a ≥40% reduction in ADHDRS-IV-Parent:Inv scores from baseline. Using this definition, atomoxetine was associated with a

superior statistical significant proportion of responders compared with placebo.

The pooled data set used in the meta-analysis confirmed the claim that atomoxetine is associated with more adverse events than placebo.

The PBAC noted that the TGA-approved Product Information stated that post-marketing reports indicated that atomoxetine can cause severe liver injury in rare cases. Further, on the 29 September 2005, the United States Food and Drug Administration (FDA) issued a Public Health Advisory to alert clinicians of the risk of suicidal thinking in children and adolescents treated with atomoxetine. The FDA advised that children and adolescents being treated with atomoxetine should be closely monitored for clinical worsening, as well as agitation, irritability, suicidal thinking or behaviours, and unusual changes in behaviour, especially during the initial few months of therapy or when the dose is changed.

For PBAC's comments, see Recommendations and Reasons.

9. Clinical Claim

The submission claimed that atomoxetine had significant advantages in effectiveness over placebo, but was more toxic. A claim of advantage over placebo has been accepted previously by the PBAC.

10. Economic Analysis

The submission presented an updated preliminary (trial-based) economic evaluation for a population of adolescents and children. Only drug costs were included in the analysis. Outcomes were based on the results of the re-submission's meta-analysis.

The trial-based incremental cost/extra patient with ≥40% reduction from baseline in ADHD-RS total score over 57 days (mean daily dose 52.95 mg/day) was <$1,000.

An updated modelled economic evaluation was presented. It differed from the previous model in terms of structure; the model presented was an Excel-based decision-analytic cost-utility model. At 2 years, the time horizon was longer than the previous model. A new approach was used to develop health states descriptors for eliciting utility values and a time trade-off approach was used to elicit utility values. Modifications to assumptions made in the re-submission's model were made during the evaluation.

The base case modelled incremental discounted cost/extra discounted QALY gained over 104 weeks was between $15,000 to $45,000. However, the PBAC noted that with modification of five assumptions, the incremental discounted cost per extra discounted QALY gained over 104 weeks could increase to over $115,000.

The PBAC had a number of concerns with the economic model (see Recommendations and Reasons).

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year was estimated to be between 10,000 and 50,000 in Year 4 of listing.

The submission estimated that the financial cost/year to the PBS would be up to

$10 to $25 million Year 4 of listing.

12. Recommendation and Reasons

Although supportive of its overall objective, the PBAC expressed some concerns about whether the requested restriction would achieve the intention of reserving atomoxetine to patients for whom stimulants are not a therapeutic option. However, although enforcing the restriction to help limit atomoxetine use within the intent of the restriction could pose difficulties for Medicare Australia, the PBAC noted that the sponsor had indicated it would be prepared to enter a price/volume arrangement and this would help manage the cost to government of use beyond the restriction.

The PBAC noted that a 40% or more decrease in ADHDRS Total Score in the meta-analysis represented a clinically relevant outcome and accepted that the post hoc analysis was both generally consistent with the analysis of the primary outcome of the majority of the trials and helpful in interpreting the treatment effect of atomoxetine. Further, the mean change in ADHDRS-Parent: Inv was similar between the overall meta-analysis and the individual trials in patients who are more representative of the populations for whom listing was requested. 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.

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.

The PBAC's principal concern about the submission was reliability of the economic model and thus its results were considered uncertain. The PBAC noted that there was uncertainty about the elicitation of the utilities. In particular, the utility valuations of the health states by those who had children with ADHD were all higher than the valuations by those who did not have children with ADHD, which, despite the small numbers in the sample, lends some support to the likelihood that other health impacts are being inferred by respondents beyond the standard information provided

Further concerns about the model were as follows:

- the use of the 70-year time horizon in the utility analysis was likely to introduce a significant discounting effect,
- the extrapolation from a child health state to the adult health state,
- the assumption in the model that a high proportion (or more than half) of non-responders at 10 weeks will respond to atomoxetine at 8 months, and
- the dosing assumptions.

The PBAC noted that with modification of five assumptions as presented in the PES Commentary, the incremental discounted cost per extra discounted QALY gained over 104 weeks could increase to over $115,000.

The PBAC therefore rejected the submission because of unacceptable and 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 acknowledges the need to address some of the uncertainties raised in the submission, particularly in relation to data supporting assumptions used in the modeled evaluation which lead to an unfavourable sensitivity analysis. We have discussed these assumptions with both the Chair of the PBAC and the PBB. We are currently planning to resubmit an application for PBS listing for atomoxetine.