Scottish Medicines Consortium

atomoxetine capsules 10 mg to 60 mg (Strattera®) No. (153/05)

Eli Lilly and Company Ltd

4 February 2005

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Atomoxetine (Strattera®) is not recommended for use within NHS Scotland for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children of 6 years and older or in adolescents. This advice concerns use in children and adolescents only and does not cover use in adults.

Atomoxetine is no more effective than a stimulant preparation against which it has been assessed. Tolerability was similar, though with some differences in the individual adverse events reported. Unlike the available stimulant preparations, it is not a Controlled Drug under the Misuse of Drugs regulations 2001 and there is evidence that it lacks abuse potential. However, the economic case has not been demonstrated.

The licence holder has indicated their decision to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Atomoxetine capsules
10 mg - 60 mg
(Strattera®)

Licensed indication under review

Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children of 6 years and older and in adolescents as part of a comprehensive treatment programme. Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10. It should be initiated only by or under the supervision of a physician with appropriate knowledge and experience in treating ADHD.

Dosing information under review

Strattera should be initiated at a total daily dose of approximately 0.5mg/kg/day, maintained for a minimum of 7 days then titrated upwards. The recommended maintenance dose is approximately 1.2mg/kg/day. No additional benefit has been demonstrated for doses higher than 1.2mg/kg/day and the safety of doses over 1.8mg/kg/day has not been systematically evaluated.

UK launch date June 2004

Comparator medications

Methylphenidate, dexamphetamine.

Cost per treatment period and relevant comparators

The costs below represent the range between the starting dose and the highest recommended maintenance dose. For weight-based dosing the lowest dose is based on a child weighing 20 kg and the highest is based on a 70 kg adolescent. Those doses may have been rounded according to the strengths available.

Preparation	Daily dose range	Annual cost range
Atomoxetine (Strattera)	**10 mg to 60 mg*(>60mg to120mg)**	**£710 (£1420)**
Dexamphetamine (Dexedrine)	10 mg to 20 mg+	£50-£100
Methylphenidate (generic)	5 mg to 60 mg	£34 - £363
Methyphenidate m/r (Concerta XL	18 mg to 54 mg	£328 - £774

* Up to 100 mg at a cost of £1420 for adolescents over 70 kg
+ Up to 40mg at a cost of £200 for older children
Costs from Practitioner Services Division, National Services Scotland except for dexamphetamine from Monthly Index of Medical Specialities.

Summary of evidence on comparative efficacy

ADHD is one of the most commonly diagnosed behavioural disorders amongst children and adolescents. Common features include developmentally inappropriate levels of activity and impulsivity, an impaired ability to sustain attention and a combination of both.

Primary endpoints

Most trials involving atomoxetine used the Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) as the basis for the primary end-point. This scale has 18 questions, each on a 4-point scale (0-3) giving a maximum score of 54 (most severe). It can be separated into assessment of hyperactivity/impulsivity and inattention symptoms. The questions are rated by the investigator following interviews with the parent or teacher and sometimes the child.

A number of placebo-controlled trials reported ADHD-RS as t-scores that relate the raw scores to age and gender normative values. In three trials, the scores at 6-8-week end-point for patients treated with atomoxetine at target doses in the range 1-1.8 mg/kg/day were equivalent to 1.6-1.7 standard deviations (SD) above the age and gender norm. For placebo, end-point scores corresponded to about 2.5 SD and the differences were significant. In a fourth trial, the end-point scores after 10 weeks' treatment were equivalent to 0.8 SD and 0.6 SD for atomoxetine and methylphenidate respectively, with no significant difference between them.

In a crossover study involving 44 patients aged 6-14years, patients on atomoxetine showed a shorter time to sleep onset and a more restful pattern than during methylphenidate administration.

Time to protocol-defined relapse was significantly longer with continued treatment with atomoxetine for up to 18 months than with placebo in patients aged 6-15 years who had achieved an initial response to atomoxetine up to 1.8 mg/kg/day for 10 weeks.

Secondary endpoints, sub-group analysis and uncontrolled trials

Core efficacy (based on ADHD-RS) has been demonstrated in patients with co-morbid tics or Tourette syndrome, affective disorder and oppositional defiant disorder. In each case, there was some evidence of reduction in the severity of the co-morbidity in atomoxetine-treated patients.

Atomoxetine has also been associated with significantly better responses than placebo for secondary measures including ADHD-specific clinician-rated global impression, parent-rating scales and the psychosocial component of a parent-rated health questionnaire.

Once-daily dosing of atomoxetine was associated with significant benefit compared with placebo in both morning and evening scores in a questionnaire designed specifically to differentiate between morning and evening symptoms of ADHD. Additional data were used to assess atomoxetine. However these data are commercial in confidence.

Summary of evidence on comparative safety

Gastro-intestinal adverse events, including loss of appetite, are the most common adverse event with atomoxetine and vomiting was significantly more common than with methyphenidate. One study suggests that abrupt discontinuation, without tapering of the doses, did not result in an acute withdrawal syndrome and was well tolerated. Additional data was used to assess atomoxetine however this data are commercial in confidence.

Summary of clinical effectiveness issues

In three placebo-controlled trials of 6-8 weeks duration, t-scores for ADHD RS at end-point were significantly lower than with placebo but were just above the threshold for inclusion in the trials (1.5 SD above norm). In a fourth placebo-controlled trial, end-point scores were equivalent to 0.8 SD above norm, and did not differ significantly from methylphenidate. Additional data were used to assess atomoxetine. However, these data are commercial in confidence

Summary of comparative health economic evidence

A Markov model using atomoxetine first line for some populations was submitted. The model had a 1-year time frame, which is considered short, as patients may receive atomoxetine from childhood through to adolescence. The health economic model included specific adverse effects, in particular insomnia, but the estimates used in the model did not consider the results of the six week active comparator trial. In addition, adverse events observed for atomoxetine, such as somnolence and gastrointestinal disturbance were not considered in the model. As a result it was concluded that the health economic case was not convincingly demonstrated.

Budget impact

The budget impact assumes that 931 patients will be treated with atomoxetine for the remaining of 2005/2006 rising to approximately 3,270 patients in the year 2008/2009. This gives rise to an estimated annual budget impact of approximately £0.5M in 2005-6 and £1.75M in 2008-9. After considering potential cost savings, the net cost of atomoxetine is estimated at £0.45M for 2005-6 rising to £1.6M for the year 2008-9.

Guidelines and protocols

Scottish Intercollegiate Guideline Network (SIGN) guidelines on *attention deficit and hyperkinetic disorders in children and young people.*

Additional information

Atomoxetine is not a Controlled Drug, unlike methylphenidate and dexamphetamine, which are subject to the requirements of the Misuse of Drugs Regulations 2001 for prescription writing, dispensing in instalments, storage and recording.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 14 January, 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The key references are listed below. Those shaded grey are additional to those supplied with the submission.

Summary of Product Characteristics. Atomoxetine (Strattera). November 2004. Eli Lilly and Co.

Scottish Intercollegiate Guidelines Network. Attention deficit and hyperkinetic disorders in children and young people. A national clinical guideline. No. 52. June 2001. Edinburgh.

Spencer T. Heiligenstein JH. Biederman J. Faries DE. Kratochvil CJ. Conners CK. Potter WZ (2002) Results from 2 proof-of-concept, placebo-controlled studies of atomoxetine in children with attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry. 63(12):1140-1147*

Michelson D. Faries D. Wernicke J. Kelsey D. Kendrick K. Sallee FR. Spencer T (2001) Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: A randomized, placebo-controlled, dose-response study. *Pediatrics 108(5):E83*

Michelson D. Allen AJ. Busner J. Casat C. Dunn D. Kratochvil C. Newcorn J. Sallee FR. Sangal RB. Saylor K. West S. Kelsey D. Wernicke J. Trapp NJ. Harder D (2002) Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: A randomized, placebo-controlled study. *American Journal of Psychiatry. 159(11):1896-1901*

Kelsey D, Sumner C et al (2004) Once-daily atomoxetine treatment for children with ADHD, including an assessment of evening and morning behaviour: A double-blind, placebo controlled trial. *Pediatrics 114 (1) e1-e8*

Kratochvil CJ. Heiligenstein JH. Dittmann R. Spencer TJ. Biederman J. Wernicke J. Newcorn JH. Casat C. Milton D. Michelson D (2002) Atomoxetine and methylphenidate treatment in children with ADHD: A prospective, randomized, open-label trial. *Journal of the American Academy of Child & Adolescent Psychiatry. 41(7):776-784*

Sangal RB et al (2004) Effects of atomoxetine and methylphenidate on sleep in children with ADHD. *Poster presented at Associated Professional Sleep Societies Meeting, Philadelphia June 2004*

Michelson D, Buitelaar JK, Danckaerts M, Gillberg C, Spencer TJ, Zuddas A, Faries DE, Zhang S, Biederman J (2004) Relapse prevention in pediatric patients with ADHD treated with atomoxetine: a randomised, double-blind, placebo controlled study. J Am Acad Child Adolesc Psychiatry 43(7): 896-904

Buitelaar JK, Michelson D, Danckaerts M et al (2004) Continued atomoxetine in paediatric patients with ADHD after 1 year of treatment. *Poster presented at CINP Paris 2004*

Allen AJ, Kurlan RM et al (2003) Atomoxetine treatment in children with ADHD and comorbid tic disorders. *Poster presented at ACNP, San Juan, Puerto Rico Dec 2003.*

Kratochvil (2003) Atomoxetine for comorbid ADHD and affective symptoms. *Poster presented at AACAP Miami, Oct 2003.*

Newcorn et al (2003) Atomoxetine treatment in child/adolescent ADHD with co-morbid ODD. *European Society for Child and Adolescent Psychiatry (ESCAP) 12th International Congress, 28 September - 1 October 2003, Paris, France*

Wernicke JF. Adler L. Spencer T. West SA. Allen AJ. Heiligenstein J. Milton D. Ruff D. Brown WJ. Kelsey D. Michelson D. (2004) Changes in symptoms and adverse events after discontinuation of atomoxetine in children and adults with attention deficit/hyperactivity disorder: a prospective, placebo-controlled assessment. *Journal of Clinical Psychopharmacology. 24(1):30-5*

Gillberg C, Lothgren M, Fitzgerald P, Cottrell S, Burridge J and Aristides M (2003) Atomoxetine versus methylphenidate as a treatment for ADHD in children and adolescents: a meta-analysis of safety data incorporating active comparator and placebo controlled trials. *European Society for Child and Adolescent Psychiatry (ESCAP) 12th International Congress, 28 September - 1 October 2003, Paris, France*

Patient Interest Group Submission: ADD It Up

Patient Interest Group Submission: The National Attention Deficit Disorder Information and Support Service (ADDISS)