Scottish Medicines Consortium

Re-Submission

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

Eli Lilly and Company Ltd

10 June 2005

The Scottish Medicines Consortium (SMC) 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 re-submission

Atomoxetine (Strattera®) is accepted for restricted use within NHS Scotland for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children of 6 years and older or in adolescents. It is restricted to use in patients who do not respond to stimulants or in whom stimulants are contraindicated or not tolerated. It is restricted to use by physicians with appropriate knowledge and expertise in treating ADHD. This advice concerns use in children and adolescents only and does not cover use in adults

Atomoxetine (Strattera) it is not a Controlled Drug under the Misuse of Drugs regulations 2001.

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

Atomoxetine 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+	£78-£156
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 £312 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.

Atomoxetine increases synaptic concentrations of nor-adrenaline by inhibiting pre-synaptic transporter mechanisms. The pathophysiology of ADHD is thought to involve several neurotransmitters including adrenaline, nor-adrenaline and dopamine.

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.

In the 6-week acute phase of a randomised double-blind comparison of atomoxetine up to 1.8 mg/kg/day and prolonged-release methylphenidate up to 54 mg/day, the primary end-point was a test for non-inferiority between atomoxetine and methylphenidate in terms of the proportion of patients achieving response defined as ≥40% reduction in the ADHD-RS score. Patients could be included if they had received stimulant therapy but the study excluded patients who had responded poorly to stimulants, could not tolerate them or in whom they were contra-indicated. There was separate analysis of stimulant-naive patients and those who had previously been exposed (stimulant responders).

Overall, 61% of patients had been treated with stimulants, leaving 39% in the stimulant naive group. Methylphenidate prolonged-release (PR) was associated with a significantly larger response rate than atomoxetine overall and in the stimulant-responder group, but there was no significant difference in the stimulant-naive group.

Other data were also assessed but remain commercially confidential.*

Atomoxetine (ATX) vs methylphenidate-PR (MPH): percentage of patients classified as responders (defined as ³40% reduction in ADHD-RS score)

	ATX n/N (%)	MPH n/N (%)	Placebo n/N (%)	p-value ATX vs MPH
All patients	95/213 (45%)	119/211 (56%)	16/68 (24%)	0.016
Stimulant naive	45/79 (57%)	54/84 (64%)	7/28 (25%)	0.42
Stimulant responders	50/134 (37%)	65/127 (51%)	9/40 (22%)	0.026

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

Patients resistant to stimulants

In an extended phase of the comparison with prolonged-release methylphenidate, all patients who had been receiving methylphenidate were switched to atomoxetine, with randomisation according to whether they were responders or non-responders in the double-blind phase. Only preliminary data are available, but 29/64 (45%) of patients who had not responded to methylphenidate in the initial treatment phase became responders when switched to atomoxetine. Also, 76/100 (76%) of patients who had responded to methylphenidate in the first phase maintained the response with atomoxetine in the second phase. The manufacturer submitted further data, provided in confidence, concerning the efficacy of atomoxetine in patients who were recruited as unresponsive to or intolerant of stimulants.

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, anxiety, depression or oppositional defiant disorder. In some cases, there was 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 to placebo in both morning and evening scores in a questionnaire designed specifically to differentiate between morning and evening symptoms of ADHD.

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 methylphenidate. One study suggests that abrupt discontinuation, without tapering of the doses, did not result in an acute withdrawal syndrome and was well tolerated.

Following very rare reports of liver toxicity, the prescribing information has been amended to include a warning that it should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted.

In the comparative trial with prolonged-release methylphenidate, both drugs are reported to be well tolerated, with greater insomnia related to methylphenidate (13.2% methylphenidate vs 6.3% atomoxetine, $p<0.05$) and greater somnolence related to atomoxetine (6.3% atomoxetine vs 1.8% methylphenidate, $p<0.05$). Weight loss was greater during the 6-week comparator phase for patients on methylphenidate prolonged-release (0.9kg compared to 0.6kg atomoxetine). Heart rate increase was slightly greater with atomoxetine (atomoxetine 6.4 bpm, methylphenidate 3.0 bpm). Discontinuations for adverse events/completion rates were similar to placebo for both drugs (atomoxetine 2.3%/84%, methylphenidate 2.3%/82%, placebo 2.7%/77%).

Summary of clinical effectiveness issues

In the comparative study with prolonged-release methylphenidate, patients were excluded if they had failed to respond to prior administration of stimulants or if stimulants were poorly tolerated or contra-indicated. This may have biased the response rates in favour of methylphenidate.

Data were presented for patients who were non-responders to methylphenidate in the first phase of this trial and were re-assigned to atomoxetine. Because stimulant-resistant patients were excluded from the original recruitment, this may not be fully representative of resistant patients within the ADHD population. However, the manufacturer submitted further data, in confidence, on patients unresponsive to or intolerant of stimulants.

Summary of comparative health economic evidence

An 18-state Markov model of 1-year duration was used, to perform a cost-utility analysis (Incremental Cost-Effectiveness Ratio). The model evaluated the cost-effectiveness of atomoxetine as the first line therapy choice within a 4-line therapy sequence and compared this with the current standard Scottish practice considering up to 3rd line therapy, for various different sub-populations.

The model discriminated between atomoxetine and methylphenidate based on drug cost, utilities, response and transition probabilities for insomnia adverse events. It did not specifically consider differential transition probabilities for the higher incidence of gastrointestinal and somnolence adverse events observed for atomoxetine.

The daily cost of medication assumed that 10% of patients receive a twice-daily atomoxetine dosing regimen. The clinical evidence included in the model for the Tourette syndrome and anxiety subgroups was based on all patients receiving a twice-daily dosing regimen. Thus the daily cost of medication may be underestimated.

As only drug costs were included in the model, zero costs were assumed for the 'No treatment' comparator.

The utility values for the two health states 'responder with side effects' and 'responder without side effects' were treatment-dependent, patients on atomoxetine being assigned a higher utility value than those receiving methylphenidate. Justification for the difference in responder utilities was limited.

Noting these limitations of the model, it suggests that the costs per QALY for the stimulant medication contraindicated subgroups are in the range £12,000-£13,200. The costs per QALY reported for the stimulant failure population are in the range £16,000-£18,400, for varying response criteria. As atomoxetine has higher acquisition costs than methylphenidate with no overall greater benefit, its use cannot be recommended as first-line treatment for ADHD. The economic case has been made for its use in patients in whom stimulants are contraindicated or not tolerated and for patients who do not respond to stimulant drugs.

Patient and Public involvement

Patient Interest Group Submission: ADD It Up

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

Budget impact

The budget impact analysis assumes there are 9,350 children and adolescents diagnosed in Scotland with ADHD and that 20% suffer from co-morbidities for which stimulant medications are contra-indicated (1,870 patients). If 80% of these patients are then treated with atomoxetine it will result in 1,496 patients being treated.

It is assumed that of the 80% not suffering from co-morbidities for which stimulant medications are contra-indicated, that 80% of these patients are currently being treated with stimulant medication ie 5,948 patients. It is expected that 30% of these patients will not respond to stimulants and therefore could possibly be treated with atomoxetine (1,795 patients).

Thus combining the two groups, the estimated maximum number of patients who would be treated with atomoxetine is 3,291 patients.

The estimated daily drug cost of £2.15, assumes that 90% of patients will receive 1 capsule per day and 10% will receive 2 capsules per day, over a period of 249 days per year.

The budget impact for the maximum number of patients e.g. all 3,291 possible patients are treated with atomoxetine, is £1.7 million in 2005. The budget impact for varying assumptions of yearly uptake is presented below. It should be noted that these assumptions of yearly uptake may be underestimated, given that there is no alternative therapy for the patients considered.

	2005	2006	2007	2008	2009
Yearly uptake (% of eligible patients)	4	11	17	23	29
Number of patients	131	362	559	757	955
Total Drug Cost (£)	70,130	193,780	299,260	405,260	511,250

Guidelines and protocols

Scottish Intercollegiate Guideline Network (SIGN) guidelines on *attention deficit and hyperkinetic disorders in children and young people (SIGN 52)* published June 2001.

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 19 May 2005.

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

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:* http://www.scottishmedicines.org.uk/

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

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Michelson D. B4Z-MC-LYBI: A double-blind, placebo-controlled comparison of atomxetine, Oros® methylphenidate, and placebo. Conference presentation 2004 supplied by Eli Lilly.