Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

atomoxetine 10mg, 18mg, 25mg, 40mg, 60mg, 80mg and 100mg capsules (Strattera®) SMC No. (909/13)

Eli Lilly and Company

04 October 2013

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

ADVICE: following a full submission

atomoxetine (Strattera®) is accepted for use within NHS Scotland.

Indication under review: treatment of attention-deficit/hyperactivity disorder (ADHD) in adults as part of a comprehensive treatment programme. The presence of symptoms that were pre-existing in childhood should be confirmed.

Short term studies in adults have shown that atomoxetine improves symptoms of ADHD compared to placebo.

The economic case for atomoxetine has been demonstrated for a treatment duration of one year.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 11 November 2013

Indication

Treatment of attention-deficit/hyperactivity disorder (ADHD) in adults as part of a comprehensive treatment programme. Treatment must be initiated by a specialist in the treatment of ADHD, such as a psychiatrist. Diagnosis should be made according to current DSM criteria or the guidelines in ICD.

In adults, the presence of symptoms of ADHD that were pre-existing in childhood should be confirmed. Third-party corroboration is desirable and atomoxetine should not be initiated when the verification of childhood ADHD symptoms is uncertain. Diagnosis cannot be made solely on the presence of one or more symptoms of ADHD. Based on clinical judgment, patients should have ADHD of at least moderate severity as indicated by at least moderate functional impairment in two or more settings (for example, social, academic, and/or occupational functioning), affecting several aspects of an individual's life.

Dosing Information

40mg daily for a minimum of seven days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance daily dose is 80mg to 100mg. The maximum recommended total daily dose is 100mg. The safety of single doses over 120mg and total daily doses above 150mg have not been systematically evaluated. It can be administered as a single daily dose in the morning, with or without food. Patients who do not achieve a satisfactory clinical response (tolerability [e.g. nausea or somnolence] or efficacy) when taking atomoxetine as a single daily dose might benefit from taking it as twice daily evenly divided doses in the morning and late afternoon or early evening.

Product availability date

24 May 2013

Summary of evidence on comparative efficacy

Atomoxetine has been available for several years for the treatment of children and adolescents with attention deficit hyperactivity disorder ADHD and those diagnosed and treated as children who transition into adulthood.[1,2] It has been accepted by the Scottish Medicines Consortium (SMC) for restricted use by physicians with expertise in ADHD in patients who do not respond to stimulants or in whom stimulants are contra-indicated or not tolerated. [3] The marketing authorisation for atomoxetine has recently been extended to allow treatment to be initiated in adults diagnosed with ADHD. This submission relates to the initiation of atomoxetine treatment for ADHD when diagnosed in adults.

Two identical 10-week US phase III studies (LYAA and LYAO) and a similar phase II/III Asian study (LYEE) recruited adults with attention deficit hyperactivity disorder (ADHD) as defined by Diagnostic and Statistical Manual version IV (DSM-IV) in childhood who currently had symptoms of moderate severity, defined as a score of at least 2 on at least 6 items of either the inattentive or hyperactive subscales of the Conners' Adult ADHD rating scale-Investigator rated: screening version (CAARS-Inv: SV) with a total score of at least 20 and a Clinical Global Impression-ADHD severity (CGI-ADHD-S) score of at least 4. The US studies included a two-week placebo lead-in, after which only patients who maintained initial severity criteria were randomised. In all studies, patients were randomised equally to double-blind treatment with placebo or atomoxetine flexibly dosed to achieve CGI-ADHD-S<3 without tolerability issues.

Three phase IV double-blind studies (LYBY, LYDQ and LYDZ) recruited adults aged at least 18 years, or the minimum legal drinking age in study LYBY, but not exceeding 30 years in LYDZ or 65 years in LYDQ. They had ADHD as defined by DSM-IV-text revision (DSM-IV-TR) and symptoms of moderate severity, defined as a CGI-ADHD-S score of at least 4 in LYDZ and LYDQ, and ADHD Investigator Symptom Rating Scale (AISRS) of at least 20 in LYBY. In study LYDQ, patients met the DSM-IV-TR criteria for social anxiety disorder and had a Liebowitz Social Anxiety Scale (LSAS) total score of 50 at screening with a decrease of less than 30% at randomisation. In study LYBY, patients had alcohol abuse disorder as defined by DSM-IV-TR. Patients were randomised equally in studies LYDZ and LYBY to 12 weeks' and in study LYDQ to 16 weeks' double-blind treatment with placebo or atomoxetine flexibly dosed to control ADHD symptoms without tolerability issues.[4,9-14]

Three similar 6-month phase IV double-blind studies (LYCU, LYCW and LYBV) recruited adults with ADHD as defined by DSM-IV-TR and moderate symptoms, defined as a CGI-ADHD-S of at least 4. They were randomised in a 1:1 ratio, except in study LYCW (1:2 ratio), to double-blind placebo or atomoxetine flexibly dosed to control ADHD symptoms without tolerability issues.[4,15-20]

The primary outcome measure was CAARS-Inv: SV total ADHD symptom score (i.e. sum of inattention and hyperactivity/impulsivity subscales) in all studies, except studies LYCU and LYBY where it was AISRS, and LYBV where it was Endicott Work Productivity Scale (EWPS).[4-20] A diverse range of statistical analyses was employed across the studies to calculate primary treatment effect, and some of these were presented in the published papers. The UK Medicines and Healthcare products Regulatory Agency (MHRA) review of this new licence noted last observation carried forward (LOCF) analyses and these are presented in the summary of product characteristics (SPC), although these may not have been the primary analysis in all of the studies. These are therefore presented in table below.[1,4]

In all studies except LYBV, mean reductions from baseline to endpoint in ADHD symptoms, assessed by CAARS-Inv: SV total ADHD symptom score or (in LYCU) AISRS and CGI-ADHD-S, were significantly greater with atomoxetine compared with placebo. In studies LYEE, LYDZ, LYDQ and LYCU, but not LYBV, mean Adult ADHD Quality of Life scale (AAQoL) increased from baseline to endpoint significantly more in the atomoxetine group compared to the placebo group.[4-20]

In study LYDQ, mean reduction from baseline to endpoint in LSAS total score was significantly greater with atomoxetine compared with placebo: -22.9 versus -14.4. There were no significant differences between atomoxetine and placebo in study LYBY for time to relapse to heavy drinking, or in study LYBV, for change from baseline to endpoint in EWPS: -16.2 versus -15.6.

Table: Mean change from baseline to study endpoint (LOCF) in patients with baseline and at least one post-baseline measurement.[1,4-20]

Study	Treatment	N	CAARS -Inv:SV*	CGI-S	AAQoL
10-week studies in patients without comorbidities					
LYAA	Atomoxetine 60mg to 120mg	133	-9.5	-0.8	
	Placebo	134	-6.0	-0.4	
LYAO	Atomoxetine 60mg to 120mg	124	-10.5	-0.9	
	Placebo	124	-6.7	-0.5	
LYEE	Atomoxetine 40mg to 120mg	191	-14.3	-1.3	12.8
	Placebo	195	-8.8	-0.8	8.2

12-week (LYDZ and LYBY) and 16-week (LYDQ) studies in patients with comorbidities					
LYDZ	Atomoxetine 40mg to 100mg	192	-10.7	-1.1	15.8
	Placebo	198	-7.2	-0.7	11.0
LYDQ	Atomoxetine 40mg to 100mg	171	-8.7[Q]	-0.8[Q]	14.9
	Placebo	158	-5.6[Q]	-0.6[Q]	11.1
LYBY	Atomoxetine 25mg to 100mg	72	-13.6	-1.0	
	Placebo	75	-8.3	-0.7	
6-month studies					
LYCW	Atomoxetine 60mg to 100mg	264	-14.3	-1.2	
	Placebo	232	-8.3	-0.7	
LYCU	Atomoxetine 25mg to 100mg	214	-13.2	-1.2	13.1
	Placebo	216	-10.2	-0.9	8.6
LYBV	Atomoxetine 40mg to 100mg	185	-11.6	-1.0	13.9
	Placebo	109	-11.5	-0.9	11.2

CAARS-Inv: SV* = Connor's Adult ADHD rating scale – Investigator rated: screening version total ADHD symptom score (range 0 to 54) or, in study LYBY, ADHD Investigator Symptom Rating Scale (AISRS) total score (range 0 to 54); CGI-ADHD-S = Clinical Global Impression-ADHD-Severity (range 1 to 7); AAQoL = Adult ADHD Quality of Life (range 0 to 100). Q = analyses are in "qualified" patients, who had <25% change in Liebowitz Social Anxiety Scale total score during placebo run-in (Within all randomised patients in the atomoxetine and placebo groups mean changes from baseline to endpoint for CAARS-Inv: SV total ADHD symptom score were -8.4 versus -4.9 and CGI-ADHD-S were -0.76 versus -0.6)

A double-blind phase III study (LYDO) with the same inclusion criteria as LYAA and LYAO recruited 2,017 patients who underwent 12-weeks open-label treatment with atomoxetine 80mg to 100mg daily, which was then continued for 12 weeks of double-blind treatment. From 12 to 24 weeks, 524 patients continually achieved response criteria, defined as at least 30% reduction from baseline in CAARS-Inv: SV total ADHD symptom score and CGI-ADHD-S of 3 or less and were then randomised equally to double-blind placebo or continuation of atomoxetine. The primary outcome was the proportion of patients in the intention-to-treat population who maintained this response throughout the 6-month post-randomisation treatment phase. This was significantly greater in the atomoxetine group compared with the placebo group: 64% (171/266) versus 50% (129/258), difference 14% (95% confidence interval (CI): 5.9 to 22.7).[21,22]

In an open-label continuation study (LYAR), 385 patients who had completed studies LYAA or LYAO received atomoxetine 50mg to 160mg daily and those who achieved a response, defined as CGI-ADHD-S<3 at 6 weeks, could continue to receive this open-label treatment for up to three years. The study was primarily designed to assess long-term safety. The primary efficacy assessment, CAARS-Inv: SV total ADHD symptom score, was significantly reduced compared to baseline at study endpoint at up to 221 weeks by -8.9, as was CGI-ADHD-S, -1.1.[23,24]

Summary of evidence on comparative safety

Atomoxetine has previously held a marketing authorisation for use in children and adolescents, allowing continuation of treatment into adulthood. It has been approved in some countries for use in adults with ADHD since 2002 and there is extensive post-marketing experience with about 10 million patients treated (up to August 2011), including approximately 3 million adults. The adverse effect data in the clinical studies are in line with the established adverse effect profile, which includes tolerability issues such as insomnia, decreased appetite, nausea, vomiting and headache. It also includes rarer but potentially more serious events: suicide-related behaviour, increases in aggression and hostility, psychotic or manic symptoms and sudden death in patients with pre-existing cardiac abnormalities.[4] A

recent extensive review of haemodynamic adverse effects indicated that atomoxetine was associated with increases in blood pressure and heart rate. These cardiovascular adverse effects may be of greater concern in adults than in children and adolescents.[25]

Summary of clinical effectiveness issues

No other medicines are licensed for the initiation of treatment for ADHD in adults. Methylphenidate, atomoxetine and dexamfetamine are licensed for use in children with ADHD. Methylphenidate has been widely used off-label for treatment of ADHD in adults and is recommended by NICE as the first choice treatment for adults with moderate to severe ADHD.[2] Atomoxetine and dexamfetamine should be considered in patients who fail to respond to, or cannot tolerate, methylphenidate.[2] SMC clinical experts advise that off-label methylphenidate is the current first-line treatment for adult ADHD.

The UK Public Assessment Report (UKPAR) notes that atomoxetine has a modest effect on symptoms of ADHD and functional outcomes compared with placebo.[4] In all short-term and six-months studies, except LYBV, there were improvements in ADHD symptoms over placebo of up to 5 points on the 54-point CAARS-Inv: SV total ADHD symptom score or (in LYCU) AISRS, and up to 0.5 point on the 7-point CGI-ADHD-S scale. Functional improvements were demonstrated on AAQoL in studies LYEE, LYDZ, LYDQ and LYCU, but not LYBV.[4-20]

Across the studies, a variety of different statistical analyses were employed. In some studies, the primary analysis was analysis of covariance (ANCOVA) with LOCF. However, in other studies, a mixed-model repeated measures (MMRM) model was used for the primary analysis. It is not clear how these models handle missing data, which is important as the rates of discontinuation in some studies were substantial and differed between the treatment groups. The MMRM analyses, some of which were the pre-specified primary outcome analysis and presented in published papers, give different estimates of treatment effect size compared to the LOCF analysis. As the results of LOCF analyses are presented in the SPC, these have also been used in this document.[4-20]

Some studies employed methods to limit the proportion of patients in the study population most susceptible to a placebo response. Studies LYAA and LYAO had a two-week placebo lead-in and only patients who maintained symptom severity after this were randomised. Study LYDZ excluded patients with a >25% decrease in symptoms as measured by CAARS-Inv: SV total ADHD symptom score between screening and randomisation. The analysis of study LYDQ was conducted only in "qualified" patients who had less than a 25% decrease in social anxiety symptoms during a 2-week placebo run-in.[5-7,9,10,13,14] The magnitude of treatment effects in these selected populations may differ from what would be observed in the general population treated in clinical practice.

There are no studies designed primarily to compare atomoxetine with an active comparator in adults with ADHD. A study in these patients of a new drug in development (bavisant) included placebo, atomoxetine and sustained-release methylphenidate-OROS (osmotic release oral system) (Concerta XL®), as control arms.[26] Results from this study and placebo-controlled studies[5-12,27-34] were included in a network meta-analysis comparing atomoxetine and methylphenidate-OROS in adults with ADHD. This suggested that there was no difference between these in efficacy or tolerability, assessed by discontinuation rates overall and adverse effects. However, this analysis is limited by differences across the included studies in duration, methodology, statistical analyses and patient populations.

No comparison was made to other formulations of methylphenidate. Analysis of 2012/13 Scottish prescribing data shows that around 30% of 1651 patients aged 18 and over dispensed methylphenidate receive prescriptions for an immediate release formulation and about 10% of patients are dispensed both immediate release and extended release formulations of methylphenidate.

Methylphenidate is a controlled drug under the Misuse of Drugs Regulations 2001 but atomoxetine is not. Some SMC clinical experts advise that atomoxetine can be given to patients at risk of drug misuse or diversion in place of first-line treatment with methylphenidate. Patients who abuse drugs were excluded from the atomoxetine clinical studies described above so there is no evidence of efficacy or tolerability of atomoxetine in this patient group. Similarly, although NICE recommends atomoxetine for adults who do not respond to or are intolerant of methylphenidate, no data have been presented within this patient group.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing atomoxetine with methylphenidate-OROS (Concerta XL®) for the treatment of moderate to severe ADHD in adults. The analysis was carried out over a one-year time horizon.

The relative 12-week efficacy and safety of atomoxetine compared to methylphenidate-OROS was estimated based on an indirect comparison between the two medicines which indicated equivalent efficacy and safety. Comparable efficacy between treatments was assumed for the remainder of the time horizon.

The results of the analysis are based upon a comparison of the relative drug acquisition costs of atomoxetine and methylphenidate-OROS, which in turn are based upon the daily doses required to achieve clinical response, i.e. the maintenance dose for atomoxetine (80 or 100mg/day) and methylphenidate-OROS (base case assumed off-label dose of 72mg/day). Other than a pharmacy dispensing fee for controlled drugs, no other costs were included in the analysis.

The annual cost of atomoxetine per patient is £1,086, compared to an annual cost per patient of £1,055 for methylphenidate-OROS.

A key concern was therefore that atomoxetine and methylphenidate are assumed to be comparable in terms of efficacy and safety but atomoxetine may not be cost saving. In their submission, the company suggested that the use of atomoxetine may require fewer contacts with the health service compared to methylphenidate-OROS on the basis that fewer dose titration steps are needed. The company provided some sensitivity additional analysis to address this aspect. Accounting for lower doses of both medicines used in the titration phase, the costs associated with clinician time for titration visits and controlled dispensing fees, the results indicated annual costs of £1,349 for methylphenidate-OROS versus £1,248 for atomoxetine 80mg or £1,340 for atomoxetine 100mg. Although SMC expert responses indicate that it may be reasonable to assume fewer contacts with atomoxetine during the titration phase, it is worth noting that any saving here would only apply to the first year of treatment.

Other uncertainties are as follows;

- Methylphenidate is a stimulant, and may not be suitable for patients with co-morbidities, for example, patients with a history of alcohol or drug abuse. Thus, for a proportion of the ADHD population, methylphenidate may not be the appropriate comparator and there is no evidence regarding the cost effectiveness of atomoxetine in the patient group who cannot receive methylphenidate.

- Although methylphenidate-OROS is not licensed for the management of ADHD diagnosed in adults, it is the most commonly used medicine for this patient group based on SMC clinical expert responses, NHS National Service Scotland prescription data, and clinical guidelines. As

such, methylphenidate-OROS appears to be an appropriate comparator. However, the prescription data also show that methylphenidate immediate release makes up 30% of the methylphenidate prescriptions. The SMC experts were invited to comment on the relative use of the immediate release and methylphenidate-OROS, and their responses highlighted the possibility that some patients maintained on methylphenidate-OROS might also be taking some immediate release methylphenidate as a 'top-up' at the beginning or end of the day. As such, the company's base case analysis may be considered conservative, since only the costs of methylphenidate-OROS are included in the comparator arm. The company provided some further analysis to address this aspect by assuming 20% of methylphenidate-OROS patients would also receive methylphenidate immediate release. When this was incorporated into the sensitivity analysis presented above, this increased the annual cost of methylphenidate-OROS to £1,371 and therefore increased potential savings with atomoxetine.

Given the additional analysis provided by the company to address the issues with the base case analysis, the economic case has been demonstrated.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Addressing The Balance
- Add Information Services (ADDISS)

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) clinical guideline number 72, Attention Deficit Hyperactivity Disorder: Diagnosis and Management in Children, Young People and Adults was published in September 2008 and updated in March 2013. This recommends that drug treatment is the first-line treatment for adults with ADHD with either moderate or severe levels of impairment. Drug treatment should be started only under the guidance of a psychiatrist, nurse prescriber specialising in ADHD, or other clinical prescriber with training in the diagnosis and management of ADHD. Drug treatment for adults should always form part of a comprehensive treatment programme that addresses psychological, behavioural and educational or occupational needs. Following a decision to start drug treatment in adults with ADHD, methylphenidate is the first-line drug. Atomoxetine or dexamfetamine should be considered in adults unresponsive or intolerant to an adequate trial of methylphenidate (this should usually be about 6 weeks). Caution should be exercised when prescribing dexamfetamine to those likely to be at risk of misuse or diversion. When starting treatment, adults should be monitored for side effects. In particular, people treated with atomoxetine should be observed for agitation, irritability, suicidal thinking and self-harming behaviour, and unusual changes in behaviour, particularly during the initial months of treatment, or after a change in dose. They should be warned of potential liver damage in rare cases (usually presenting as abdominal pain, unexplained nausea, malaise, darkening of urine or jaundice). Younger adults aged 30 years or younger should also be warned of the potential for atomoxetine to increase agitation, anxiety, suicidal thinking and self-harming behaviour in some people, especially during the first few weeks of treatment.[2]

Additional information: comparators

No other medicines are licensed for initiation of treatment for ADHD in adults. Methylphenidate, atomoxetine and dexamfetamine are licensed for use in children with ADHD. Methylphenidate has been widely used for treatment of ADHD in adults and is recommended by NICE as the first choice treatment for patients with moderate to severe ADHD symptoms.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Atomoxetine	**40mg to 100mg daily**	**812 to 1,083**
Methylphenidate*	10mg to 100mg daily	67 to 663
Methylphenidate m/r (Medikinet XL®)*	10mg to 100mg daily	292 to 1,517
Methylphenidate OROS m/r (Concerta XL®)*	18mg to 108mg daily	379 to 1,545
Methylphenidate m/r (Equasym XL®)*	10mg to 100mg daily	303 to 1,577

Doses are for general comparison and do not imply therapeutic equivalence. Costs are from eVadis on 05 August 2013. * Methylphenidate is not licensed for initiation of treatment in adult ADHD, however, dose ranges for this unlicensed indication are detailed in the British National Formulary. m/r = modified release.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 937 in year one rising to 1,031 in year five, with an estimated uptake rate of 14% in year one and 27% in year five. The gross impact on the medicines budget was estimated to be £140k in year one and £298k in year five. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £6.8k in year one and £112k in year five.

References

The undernoted references were supplied with the submission. The references shaded in grey are additional to those supplied with the submission.

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This assessment is based on data submitted by the applicant company up to and including 13 September 2013.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.