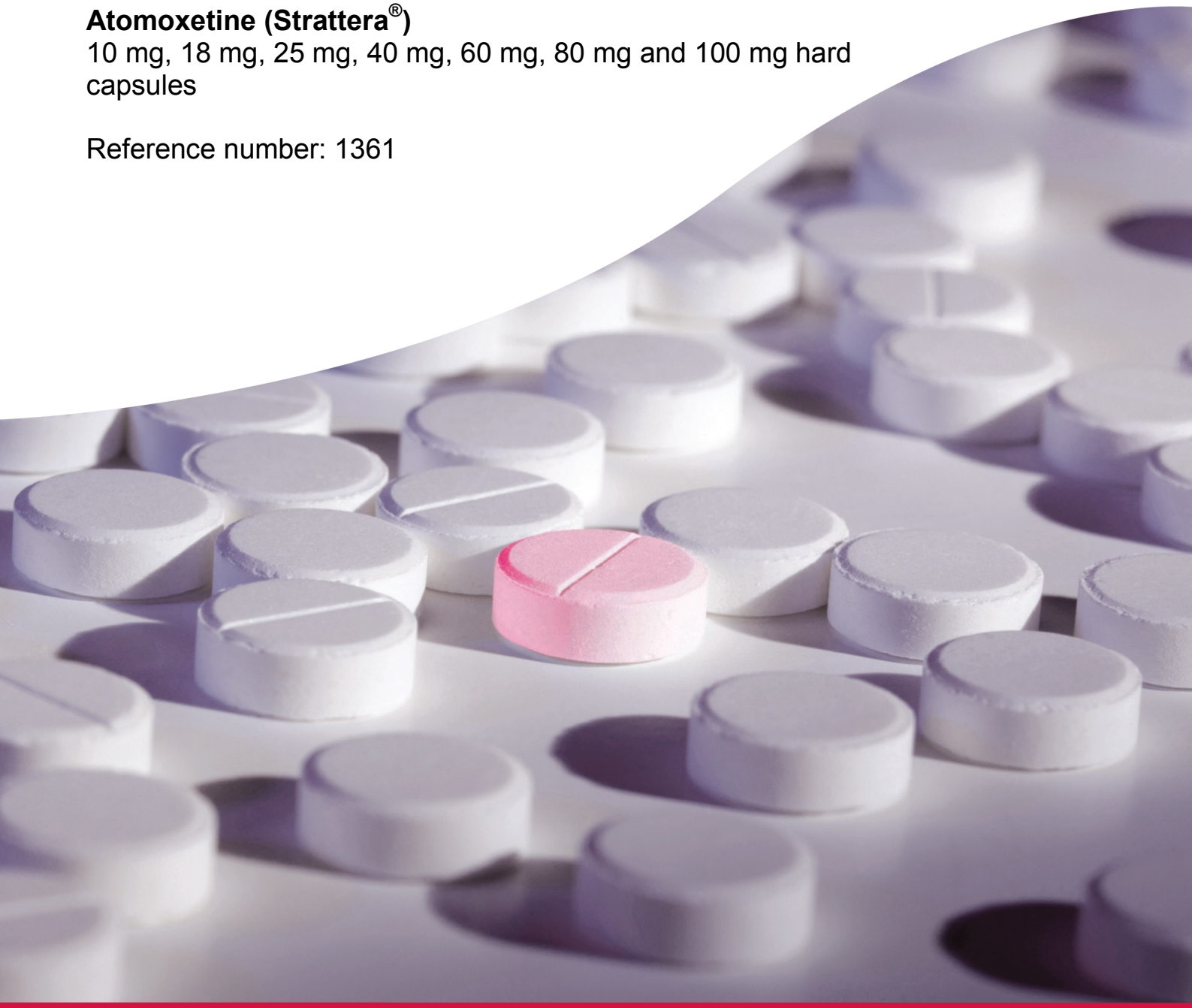
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

# AWMSG SECRETARIAT ASSESSMENT REPORT

**Atomoxetine (Strattera®)**
10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules

Reference number: 1361



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# AWMSG Secretariat Assessment Report
# Atomoxetine (Strattera®)
# 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules

This assessment report is based on evidence submitted by Eli Lilly & Co Ltd on 2 August 2013[1].

## 1.0 PRODUCT DETAILS

| | |
|---|---|
| **Licensed indication under consideration** | Atomoxetine (Strattera®) is indicated for the initiation of treatment in adults with attention deficit hyperactivity disorder (ADHD). Treatment must be initiated by a specialist in the treatment of ADHD, such as a paediatrician, child/adolescent psychiatrist, or psychiatrist. Diagnosis should be made according to current Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria or the guidelines in International Classification of Mental and Behavioural Disorders (ICD).<br><br>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.<br><br>Refer to the Summary of Product Characteristics (SPC) for the full licensed indication[2]. |
| **Dosing** | Atomoxetine should be initiated at a total daily dose of 40 mg. The initial dose should be maintained for a minimum of seven days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance daily dose is 80 mg to 100 mg. The maximum recommended total daily dose is 100 mg. The safety of single doses over 120 mg and total daily doses above 150 mg have not been systematically evaluated.<br><br>Atomoxetine 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.<br><br>Refer to the SPC for further dosing information[2]. |
| **Marketing authorisation date** | 24 May 2013 (licensed for the treatment of ADHD in children of six years and older and in adolescents on 27 May 2009)[2]. |

## 2.0 DECISION CONTEXT

### 2.1 Background

Attention deficit/hyperactivity disorder (ADHD) is a heterogeneous neurobehavioral disorder characterised by impulsivity, hyperactivity and inattention (either alone or in combination)[3,4]. Prevalence of ADHD, defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; see Glossary) is thought to affect about 3–9% of school-age children and young people in the UK, and about 2% of adults worldwide[4]. In general, ADHD is a persisting disorder. Its onset is in early childhood and, in many cases (reports indicate about 50% to 75%), it persists into adolescence and adulthood where it is associated with adverse long-term outcomes in academic and social function[4,5]; high rates of co-existing psychiatric disorders are often associated in adults with ADHD. The presence of ADHD in childhood and adolescence is a prerequisite for the diagnosis to be made in adults[5].

The National Institute for Health and Care Excellence (NICE) Clinical Guideline 72 (CG72) advises pharmacological treatment as the first-line treatment for adults with ADHD with either moderate or severe levels of impairment. Methylphendiate should normally be tried first; however, if methylphenidate is ineffective or unacceptable, atomoxetine or dexamphetamine may be considered[4]. Pharmacological treatment should always form part of a comprehensive treatment programme, which addresses psychological, behavioural and educational or occupational needs[4,5]. If there is residual impairment, despite some benefit from medication, or there is no response to medication, then cognitive behavioural therapy (CBT) may be considered.

Atomoxetine is licensed for the treatment of ADHD in children over six years of age and adolescents, with continuation into adulthood[2]. Atomoxetine represents the first treatment for ADHD which is also licensed for the initiation of treatment in adults. Atomoxetine is a highly selective and potent inhibitor of the pre-synaptic noradrenaline transporter, which shows minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors[2]. It does not affect dopamine transporters[2], although its main metabolite shows modest inhibition of the serotonin reuptake transporter[5].

### 2.2 Comparators

The comparator included in the company submission was methylphenidate hydrochloride prolonged-release tablets (Concerta® XL).

### 2.3 Guidance and related advice

- NICE CG72. Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people and adults (2013)[4].
- NICE Quality Standard 39. Attention deficit hyperactivity disorder (July 2013)[6].
- British Association for Psychopharmacology. Evidence-based guidelines for management of attention-deficit/hyperactivity disorder in adolescence in transition to adult services and in adults: recommendations from the British Association for Psychopharmacology (2007)[7].

## 3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company included information on 12 clinical trials, which were either of short- or long-term duration: ten trials were placebo controlled, one trial was non-placebo controlled and one trial had an open-label design[1]. In the absence of any direct data comparing atomoxetine with Concerta® XL, the company performed an indirect analysis to evaluate the comparative efficacy of atomoxetine versus Concerta® XL. The efficacy results of the longer term, placebo-controlled, pivotal study, LYDO, is used to support the indirect analysis[8,9]. The remaining trials will not be discussed further as they do not inform the comparison of atomoxetine with methylphenidate; however, safety information is included in Section 3.3.

### 3.1 LYDO study

LYDO was a randomised, multicentre, double-blind, placebo-controlled trial, which was designed to assess the maintenance of efficacy and safety of atomoxetine in adult patients with ADHD. Patients must have met DSM-IV-TR criteria for current ADHD (at least moderate severity) as well as met criteria for a historical diagnosis of ADHD during childhood. The study consisted of three study periods: an initial washout and screening period, a three month open-label short-term treatment period; and a nine month double blind period during which patients continued to receive atomoxetine for three months; responders were then randomly assigned to receive atomoxetine or placebo for a six month randomised withdrawal maintenance treatment period. A total of 2,017 patients, were enrolled in the study; however, 1,493 patients discontinued during the open-label phase prior to randomisation. Patients (n = 524) were randomised to receive either atomoxetine 80 mg–100 mg per day (n = 266) or placebo (n = 258) for 25 weeks. The primary efficacy endpoint was the percentage of patients who maintained a satisfactory response (defined as a ≥ 30% reduction in patient baseline Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS Inv:SV) total ADHD symptom score and a score of ≤ 3 on the Clinical Global Impression (CGI)-ADHD score, except ≤ 2 non-executive excursions [worsening in CGI-ADHD score rating by one, not to exceed a score of four]) at the end of the double-blind treatment (during the randomised withdrawal maintenance treatment period). A statistically significant greater proportion of patients receiving atomoxetine maintained a satisfactory response compared to placebo (64.3% versus 50%, $p < 0.001$). Additionally, the time to relapse (defined as two consecutive visits with a CGI-ADHD score ≥ 4points, and a return to ≥ 80% of patient's baseline CAARS Inv:SV total ADHD symptom score) was significantly longer for atomoxetine than placebo-treated patients (log-rank test p-value = 0.004). Compared to placebo, patients treated with atomoxetine demonstrated a statistically significant higher improvement on the Adult ADHD quality of life (AAQoL) total score at the three month interval ($p = 0.003$) and six month interval ($p = 0.002$)[9].

### 3.2 Indirect analysis of atomoxetine versus Concerta® XL

In their submission, the applicant company included details of an indirect analysis (model-based meta-analysis), which evaluated the efficacy and safety of atomoxetine versus Concerta® XL in adults with moderate to severe ADHD. The systematic literature review identified 225 studies. A total of 14 eligible randomised, placebo-controlled trials were included in the indirect analysis; no comparable Concerta® XL studies over 12 weeks were identified and hence only studies which were up to 12 weeks in duration for both atomoxetine and Concerta® XL were included. All 14 trials assessed the efficacy of treatment according to scales developed from the DSM-IV diagnostic criteria[1]. A summary of the study design and results from each trial used in the indirect comparison is presented in Appendix 1. A Bayesian network meta-analysis model was used to take into account both direct and indirect evidence.

Results from the indirect analysis are presented in Table 1. The 95% credible interval of atomoxetine versus placebo and Concerta® XL versus placebo were found to

overlap for both the fixed effects and random effects models. The company conclude that atomoxetine had a similar efficacy to Concerta® XL, as the credible interval for the indirect analysis included zero[1].

**Table 1. Results of treatment effect (fixed and random effects models): standardised mean difference**[1]

| | Standardised mean difference (95% CI) | |
|---|---|---|
| **Treatment** | **Fixed effects** | **Random effects** |
| Atomoxetine versus placebo | 0.46 (0.37, 0.55) | 0.46 (0.36, 0.56) |
| Concerta® XL versus placebo | 0.51 (0.41, 0.62) | 0.51 (0.40, 0.63) |
| Atomoxetine versus Concerta® XL | −0.05 (−0.17, 0.07) | −0.05 (−0.18, 0.08) |
| CI: credibility interval | | |

### 3.3 Comparative safety

The Medicines and Healthcare products Regulatory Agency (MHRA) state that trials involving atomoxetine in adults showed no unexpected or significantly different findings compared to the established safety profile of atomoxetine in children[5]. In total, 926 and 765 patients were exposed to atomoxetine in the short- and long-term studies respectively. They note that adverse events (AEs) observed during the short- or long-term treatment trials were within acceptable safety and tolerability, and no evidence of serious safety concerns emerged[5]. In both the short- and long-term studies submitted to the MHRA, AEs occurred more frequently in patients receiving atomoxetine compared to placebo. Common AEs reported in ≥ 5% patients receiving atomoxetine included nausea, dry mouth, decreased appetite, and insomnia[5]. During the short-term trials, discontinuation due to AEs was reported in 8.9% of patients receiving atomoxetine and in 4.0% of patients receiving placebo; during the long-term studies, discontinuation due to AEs was reported in 17.9% of patients receiving atomoxetine and in 6.3% of patients receiving placebo[1,5]. The MHRA stated that cardiovascular related safety is widely recognised and has been reported across all current ADHD medications. Atomoxetine was not associated with AEs on cardiac repolarisation (QT interval); mean changes to blood pressure and pulse were modest and consistent with increased noradrenergic activity when compared with placebo-treated patients[5].

Safety results from the indirect analysis focused on the number of discontinuations due to AEs or any reason; the company conclude that no evidence of difference was demonstrated between atomoxetine and Concerta® XL[1,10].

### 3.4 AWTTC critique

- Atomoxetine represents the only licensed medication for the initiation of treatment in adults with ADHD[2]. NICE CG72 states that pharmacological treatment should be used first line for adults with ADHD with either moderate or severe levels of impairment. Methylphenidate is positioned as first-line treatment; however, if methylphenidate is ineffective or unacceptable, atomoxetine or dexamfetamine may then be tried. Currently there are no formulations of methylphenidate or dexamfetamine licensed for the initiation of ADHD treatment in adults[11–13].
- The company consider Concerta® XL as the most appropriate comparator. The rationale includes the first-line positioning of methylphenidate in NICE CG72; the company report Concerta® XL is the most commonly prescribed ADHD medication and is the only formulation licensed for the continuation of treatment in adults[1]. In their submission, the company did not provide any information on alternative comparators.
- As no head-to-head studies in the ADHD adult population exist to compare the relative efficacy and safety of atomoxetine with Concerta® XL, the company submission included an indirect analysis[1]. While a common approach to the lack of

direct head-to-head data, an indirect analysis has inherent limitations. In relation to the indication under consideration, studies included differed with regards to inclusion/exclusion criteria, baseline characteristics, disease severity, dose/dose titration and efficacy measurements. The company conducted sensitivity analyses for each of the base case results in order to account for any differences between the trials. The results of the sensitivity analyses supported the finding that there was no evidence of difference in efficacy and safety between the two treatments[1]. However, due to differences in methodology and patient population (see Appendix 1), the findings of the indirect comparison should be interpreted with caution.

- The indirect analysis included in the company submission compared the efficacy and safety of atomoxetine and Concerta® XL for up to 12 weeks, as no long-term studies with Concerta® XL were identified in a systematic review[1]. However, the efficacy and safety of atomoxetine has been demonstrated in the LYDO trial for up to two years[9], and via additional post marketing experience[1].
- Unlike methylphenidate and dexamfetamine, atomoxetine is not a controlled drug[14]; therefore, there would be no requirement for special controls on prescribing, storage, supply and associated administration[1]. In addition, the MHRA suggest that atomoxetine treatment is associated with a lower risk of abuse and misuse in comparison to stimulants such as Concerta® XL[5]. NICE CG72 states that where there may be a concern about the potential for drug misuse and diversion, then atomoxetine may be considered as a first-line treatment for ADHD in adults[4].

## 4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

### 4.1 Cost-effectiveness evidence

#### 4.1.1 Context

The company submitted a cost minimisation analysis (CMA) comparing atomoxetine 80 mg or 100 mg per day to Concerta® XL 72 mg per day, an extended release formulation. The company submission reported Concerta® XL as the most commonly used first treatment (55% of prescriptions) for adult patients with ADHD[1].

The submission considers a 72 mg per day dose of Concerta® XL, reflecting the average daily dose required to achieve a response in clinical trials[15–17]. The range was 68 to 81 mg per day. The first prescribable dose of Concerta® XL in this range is 72 mg (2 x 36 mg tablets). The company sought the opinion of nine UK specialists, who indicated that around 20% of patients taking Concerta® XL may require addition of an immediate release formulation of methylphenidate to provide adequate control of ADHD symptoms[1]. The analysis considers the recommended maintenance doses of atomoxetine (80 or 100 mg/day doses). Drug Tariff Prices (July 2013 edition) for Concerta® XL and atomoxetine are used. A controlled drugs' dispensing fee of £15 annually (£1.28 per item[18]) is applied to Concerta® XL.

There are no direct comparative trials to compare the efficacy and safety of atomoxetine and Concerta® XL. The CMA assumes therapeutic equivalence based on results of an indirect analysis that compared treatments with respect to:

- Efficacy measured as change in disease severity from baseline; and
- Safety measured as the odds ratios of discontinued treatment due to adverse events and discontinuation for any reason.

Analysis included trials of up to 12 weeks duration; comparable efficacy and safety is assumed beyond 12 weeks for both treatments despite the lack of longer-term data for Concerta® XL.

Medicine costs for a one year period are considered in the CMA; other costs associated with treatment initiation, titration, monitoring and management of AEs are

assumed to be the same for patients taking atomoxetine or Concerta® XL. An NHS Wales costing perspective is used.

### 4.1.2 Results

Table 2 presents the base case results.

**Table 2. Results of base case analysis per patient**

| | Concerta® XL 72 mg once-daily | Atomoxetine 80/100 mg once-daily | Difference |
|---|---|---|---|
| Pack costs | 36 mg x 30 tabs (£42.45) | 80 mg x 28 caps (£83.28)<br>100 mg x 28 caps (£83.28) | |
| Acquisition costs (yearly) | £1,034 | £1,086 | £52 |
| Acquisition costs (yearly) + controlled drug dispensing fee | £1,049 | £1,086 | £37 |

Two sensitivity analyses are provided in Table 3. The first uses the maximum licensed dose for Concerta® XL of 54 mg per day. This increases annual cost of atomoxetine relative to Concerta® XL (including dispensing fee) from £37 to £174. The second assumes a dose of 90 mg per day of Concerta® XL. With this scenario atomoxetine is less costly by £358 (including dispensing fee).

**Table 3. Results of the sensitivity analysis per patient**

| | Concerta® XL 54 mg once-daily | Atomoxetine 80/100 mg once-daily | Difference |
|---|---|---|---|
| Pack costs | 27 mg x 30 tabs (£36.81) | 80 mg x 28 caps (£83.28)<br>100 mg x 28 caps (£83.28) | |
| Acquisition costs (yearly) | £896 | £1,086 | £190 |
| Acquisition costs (yearly) + controlled drug dispensing fee | £912 | £1,086 | £174 |
| | **Concerta® XL 90 mg once-daily** | **Atomoxetine 80/100 mg once-daily** | **Difference** |
| Pack costs | 36 mg x 30 tabs (£42.45)<br>18 mg x 30 tabs (£31.19) | 80 mg x 28 caps (£83.28)<br>100 mg x 28 caps (£83.28) | |
| Acquisition costs (yearly) | £1,413 | £1,086 | −£327 |
| Acquisition costs (yearly) + controlled drug dispensing fee | £1,444 | £1,086 | −£358 |

The company concluded atomoxetine and Concerta® XL are expected to be of comparable costs at the doses required to achieve a satisfactory clinical response.

### 4.1.3 AWTTC critique

The CMA presented by the company is only appropriate if the company has demonstrated atomoxetine is therapeutically equivalent to the relevant comparator. The company notes that there are key differences between atomoxetine and Concerta® XL. These include:

- Atomoxetine is the only licensed medication for initiation of treatment in adults.
- Methylphenidate is a stimulant medication and a controlled drug; atomoxetine is neither a stimulant nor a controlled drug. AEs are different with each.
- Concerta® XL and atomoxetine are both administered once daily; however, 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[2,11,12].

The indirect analysis has measured equivalence in respect of tolerance to the medicines, not safety. The CMA does not enable sensitivity analysis of safety and efficacy parameters.

Strengths of the economic evidence include:

- In the absence of direct comparative data, the company has undertaken a systematic review of relevant clinical trials and conducted a meta-analysis with sensitivity analysis to compare atomoxetine and Concerta® XL.
- The CMA uses appropriate drug unit costs.

Weaknesses of the economic evidence include:

- Use of CMA despite the differences in efficacy, patient populations, duration of benefit and side effects.
- AE profiles are assumed to be comparable based on the respective Summary of Product Characteristics (SPCs).
- No other comparators are used in the CMA. Valid comparators may include other methylphenidate preparations and dexamfetamine.
- The company has not considered the potential for higher medicine costs with atomoxetine if patients take the daily dose as two evenly divided doses. Similarly, there is the possibility of higher medicine costs with Concerta® XL if 20% of patients on that medicine require the addition of an immediate release formulation of methylphenidate to provide adequate cover of ADHD symptoms.
- Comparable efficacy beyond 12 weeks for both treatments is assumed despite the absence of data on Concerta® XL.

### 4.2 Review of published evidence on cost-effectiveness

A literature search conducted by AWTTC identified two relevant evaluations. The first was published by NICE (2008)[4]. In the absence of finding relevant cost-effectiveness studies, NICE commissioned an economic model with comparators including methylphenidate and atomoxetine. This concluded that medication in adults with ADHD is cost-effective[4]. A comparison of annual costs of medicines concluded atomoxetine 80 mg (£1,548) is more expensive than modified release methylphenidate 72 mg (£972). The guideline notes the clinical evidence indicates that methylphenidate is likely to be more effective than atomoxetine in adults with ADHD, and consequently methylphenidate is possibly dominant over atomoxetine. However, the guideline added other factors need assessing, such as discontinuation rates, adverse effects and adherence which may affect the relative cost effectiveness of methylphenidate and atomoxetine[4]. Subsequently, the annual cost for 80 mg has fallen from £1,548 to £1,086.

A health technology assessment conducted in Germany in 2009, evaluated pharmaceutical therapies for ADHD in adults; this assessment concluded that more economic studies are required to inform on the cost-effectiveness of therapies[19].

## 5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

### 5.1 Budget impact evidence

#### 5.1.1 Context and methods

Budget impact estimations are based on treatment of newly referred patients annually. An incidence rate of 17.5 adult patients per 100,000 adult population[20] is applied to Welsh census data[21] to derive an incidence rate of 416 patients per year. The company assumed availability of a licensed treatment (atomoxetine) will increase the rate of referral (relative to year one) by 5% in year two and 10% in year three, with no further increase in referral rates in years four and five. All patients who are referred are assumed to receive medication.

The company assumes that the comparator displaced by atomoxetine (80/100 mg/day) would be Concerta® XL (72 mg/day). The budget impact analysis compares the cost of current treatment assuming atomoxetine's market share is stable at 8% of new patients. This is assumed to increase to 25% at year three. As therapeutic equivalence of atomoxetine and Concerta® XL (72 mg/day) is assumed, only medicine costs are considered. No other resource use or costs are included in the analysis.

### 5.1.2 Results

The company-reported numbers of patients referred and their treatment currently and post receipt of the licensed indication, together with the cost implications over a five year period, are summarised in Table 4.

**Table 4. Company-reported costs associated with use of atomoxetine for treatment of ADHD with future and current treatment practice**

| | Year 1 (2013) | Year 2 (2014) | Year 3 (2015) | Year 4 (2016) | Year 5 (2017) |
|---|---|---|---|---|---|
| Future number of referrals | 416 | 437 | 458 | 458 | 458 |
| Proportion receiving atomoxetine | 15% | 20% | 25% | 25% | 25% |
| – Number | 62 | 87 | 115 | 115 | 115 |
| – Cost | £67,789 | £94,948 | £124,388 | £124,388 | £124,388 |
| Proportion receiving Concerta® XL | 48% | 43% | 38% | 38% | 38% |
| – Number | 200 | 188 | 174 | 174 | 174 |
| – Cost | £206,401 | £194,235 | £179,898 | £179,898 | £179,898 |
| TOTAL | £274,190 | £289,183 | £304,286 | £304,286 | £304,286 |
| **Current treatment** | £272,655 | £272,655 | £272,655 | £272,655 | £272,655 |
| **Difference between 'future' and 'current' treatment practice** | **£1,535** | **£16,527** | **£31,631** | **£31,631** | **£31,631** |

### 5.1.3 Scenario analyses

Two sensitivity analyses are conducted. Assuming a daily dose of 54 mg of Concerta® XL is displaced by atomoxetine 80/100 mg/day increases the budget impact in year three onwards to £39,152; assuming a daily dose of 90 mg of Concerta® XL reduces the cost increase to £10,836. In year one, there is no assumed increase in market share; the saving of £9,523 arises because atomoxetine is less costly than Concerta® XL 90 mg.

**Table 5. Company-reported sensitivity analysis use of atomoxetine for the treatment of ADHD**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Base case (Concerta® XL daily dose 72 mg) | **£1,535** | **£16,527** | **£31,631** | **£31,631** | **£31,631** |
| **Sensitivity Analyses** | | | | | |
| Cost of Concerta® XL daily dose 54 mg (2 x 27 mg tabs) | £5,534 | £22,143 | £39,152 | £39,152 | £39,152 |
| Cost of Concerta® XL daily dose 90 mg (2 x 36 mg tabs + 1 x 18 mg tabs) | -£9,523 | £1,000 | £10,836 | £10,836 | £10,836 |

### 5.1.4 AWTTC critique

- The CMA is only valid if atomoxetine and Concerta® XL are therapeutically equivalent. This has not been demonstrated, particularly for AEs.

- The company has used an accepted source to estimate incidence rates. However, it was derived by seeking consensus opinion from the NICE topic-specific advisory group on ADHD and thus subject to uncertainty. This is not tested in the sensitivity analysis.
- The analysis considers only Concerta® XL as an alternative to atomoxetine but other medicines could be relevant comparators.
- Medicine prices used are consistent with those in the economic evaluation.

### 5.2 Comparative unit costs

**Table 6. Examples of acquisition cost of atomoxetine and other treatments for management of ADHD in adults**

| Treatment* | Example dose* | Example cost per patient per year*** |
|---|---|---|
| Atomoxetine (Strattera®)10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg hard capsules | 40–100 mg once-daily | £814–£1,086 |
| Methylphenidate (Concerta® XL) 18 mg, 27 mg and 36 mg prolonged release tablets | 18–108 mg once-daily | £379–£1,549 |
| Methylphenidate (Equasym XL®) 10 mg, 20 mg and 30 mg modified release hard capsules | 10–100 mg once-daily | £304–£1,582 |
| Methylphenidate (Medikinet XL®) 5 mg, 10 mg, 20 mg, 30 mg and 40 mg modified release hard capsules | 10–100 mg once-daily | £292–£1,756 |
| Methylphenidate hydrochloride (non-proprietary) 5 mg, 10 mg and 20 mg tablets | 10–100 mg daily (in 2–3 divided doses) | £73.73–£665 |
| Dexamfetamine sulfate (non-proprietary) 5 mg tablets | 10–60 mg daily (in 2–3 divided doses) | £493–£2,956 |
| * Doses based on British National Formulary (BNF) September 2013[14]<br>**Not all regimens may be licensed specifically for the indication under consideration. See relevant SPCs for full licensed indications and dosing details[2,11–13,22–25]<br>***Costs are based on MIMS September 2013[26]<br>This table does not imply therapeutic equivalence of drugs or the stated doses. | | |

## 6.0 ADDITIONAL INFORMATION

### 6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, atomoxetine (Strattera®) may be appropriate for prescribing within NHS Wales for the indication under consideration with a shared care agreement.

The company do not anticipate that atomoxetine (Strattera®) will be supplied by a home healthcare provider.

### 6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

### 6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

### 6.4 Evidence search

**Date of evidence search:** 3 September 2013 and 5 September 2013

**Date range of evidence search:** No date limits were applied to database searches.

## GLOSSARY

**Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)**
The DSM-IV-TR criteria for ADHD require that an individual (at any age) must display at least six symptoms of inattention or at least six symptoms of hyperactivity/Impulsivity, or both. Three distinct ADHD subtypes are recognised: the inattentive, the hyperactive-impulsive, and combined subtypes. The subtypes must have interfered with at least two spheres of his or her functioning and must have been present before the age of seven years old[5].

**Conners' Adult ADHD rating scale – investigator short version (CAARS-Inv:SV)**
CAARS-Inv:SV is a 30-item scale containing three subscales: Inattention, Hyperactivity-Impulsivity, and the ADHD index. The 18-item Total ADHD symptoms score is the sum of the Inattention and Hyperactivity-Impulsivity subscales. Each of the 18 items is linked to one of the 18 symptoms used to diagnose ADHD as defined by the DSM-IV. Each item is rated on a scale of 0 (never or not at all) to 3 (very often).

**AISRS (Adult ADHD Investigator Symptoms Rating Scale)**
AISRS is an 18-item scale that captures the 18 DSM-IV symptoms of ADHD. The 18 items have been modified to reflect age-appropriate behaviours in adults with ADHD versus children. Nine items related to inattention alternate with 9 items related to hyperactivity/impulsivity. Each item is scored on the following scale: 0 (none), 1 (mild), 2 (moderate), 3 (severe). The maximum score is 54[5].

**Clinical Global Impression Scale (CGI-S, CGI-I)**
The CGI scale is a standardised assessment measure that permits a global evaluation of a subject's severity of illness (CGI-S) and improvement (CGI-I) over time and is completed by the investigator. The CGI-S is performed to rate the severity of a subject's condition using a 7-point scale ranging from 1 (normal, not at all ill) to 7 (amongst the most extremely ill). The assessment is made based on the clinician's overall experience with a particular illness or set of symptoms, and as such, considers both the severity of symptoms and consequent effect on functioning[5].

**Adult ADHD Quality of Life (AAQoL)**
The AAQoL is a 29-item patient-reported outcome measure used to examine the disease specific function impairments relevant to adults with ADHD. The domains included in the AAQoL are work functioning, family relationships, social functioning, activities of daily living (that is, driving, managing finances), and psychological adaptation (that is, life satisfaction, self-esteem), and are evaluated using subscales called Life productivity, Psychological Health, Life Outlook, and Relationships[5].

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## Appendix 1. Additional clinical information

### Table 1A. Atomoxetine trials used in the indirect analysis[1,10,17,27–34]

| Study | Study design | Main inclusion criteria | Treatment groups | Endpoint | Endpoint results |
|---|---|---|---|---|---|
| LYAA | Randomised, double-blind, placebo-controlled trial. Ten weeks in duration; based in USA | Patients who maintained the initial severity criteria required for study entry were randomised to receive atomoxetine or placebo for a 10-week period | Atomoxetine (n = 134) (Starting dose of 60 mg daily titrated to 120 mg to achieve response)<br><br>Placebo (n = 133) | CAARS total score change from baseline | Change from baseline<br>Atomoxetine: −9.50<br>Placebo: −6.0 |
| LYAO | Randomised, double-blind, placebo-controlled trial. Ten weeks in duration; based in USA | Patients who maintained the initial severity criteria required for study entry were randomised to receive atomoxetine or placebo for a 10-week period | Atomoxetine (n = 124) (Starting dose of 60 mg daily titrated to 120 mg to achieve response)<br><br>Placebo (n = 124) | CAARS total score change from baseline | Change from baseline<br>Atomoxetine: −10.5<br>Placebo: −6.7 |
| LYBY | Randomised, multicentre trial. Twelve weeks in duration; based in USA and Canada | Adults ≥ 18 years of age meeting DSM-IV-TR criteria for ADHD. Patients also met DSM-IV-TR criteria for alcohol use disorders (abuse or dependence) | Atomoxetine (n = 72) (25–100 mg daily)<br><br>Placebo (n = 75) | AISRS total score change from baseline | Change from baseline<br>Atomoxetine: −13.63<br>Placebo: −8.31 |
| LYDZ | Randomised, double-blind, placebo-controlled trial. Twelve weeks in duration; based in USA | Young adults (18–30 years old) who met DSM-IV-TR criteria for ADHD as determined by a clinical interview and assessed by the Adult ADHD Clinician Diagnostic Scale version 1.2. All participants also must have had a CGI-S score of 4 (moderate symptoms) or greater to be eligible for study participation | Atomoxetine (n = 192) (Starting dose of 40 mg daily titrated to 100 mg to achieve response)<br><br>Placebo (n = 199) | CAARS total score change from baseline | Change from baseline<br>Atomoxetine: −13.6<br>Placebo: −9.3 |

**Table 1A. Continued. Atomoxetine trials used in the indirect analysis**[1,10,17,27–34]

| Study | Study design | Main inclusion criteria | Treatment groups | Endpoint | Endpoint results |
|---|---|---|---|---|---|
| LYEE | Randomised, multicentre, double-blind, placebo-controlled study. Ten weeks in duration; based in Japan | Aged ≥18 years. Diagnosis of current & childhood ADHD (DSM criteria). At least moderate symptom severity (≥ 20 CAARS-Inv:SV 18-Item total ADHD symptom score or the AISRS score and ≥ 4 on the CGI-ADHD-S scale) | Atomoxetine (n = 191) (Starting dose of 40 mg daily titrated to 120 mg to achieve response)<br><br>Placebo (n = 195) | CAARS total score change from baseline | Change from baseline<br>Atomoxetine: −14.3<br>Placebo: −8.8 |
| McRae-Clarke, 2010 | Randomised, placebo-controlled trial. Twelve weeks in duration; based in USA | Adults aged 18–65 years of age who met DSM-IV criteria for marijuana dependence. Participants also had to meet DSM-IV criteria for ADHD with the exception of the criterion that the age of onset of symptoms had to be prior to seven years of age | Atomoxetine (n = 19) (Starting dose of 25 mg day titrated to 100 mg day to achieve response)<br><br>Placebo (n = 19) | CAARS total score change from baseline | Change from baseline:<br>Atomoxetine: −15.05<br>Placebo: −11.05 |
| Sutherland, 2012 | Randomised, placebo-controlled trial. Eight weeks in duration; based in USA | Adults aged 18–60 years of age who met DSM-IV criteria for ADHD | Atomoxetine (n = 97) (Starting dose of 40 mg titrated to 100 mg day to achieve response)<br><br>Placebo (n = 47) | AISRS total score change from baseline | Change from baseline<br>Atomoxetine: −17.30<br>Placebo: −14.50 |
| Weisler, 2012 | Randomised, double-blind, placebo- and active-controlled, parallel-group, multicentre study. Six weeks in duration; based in USA | Adults aged 18–55 years with an established diagnosis of ADHD | Atomoxetine (n = 73) (80 mg)<br><br>Placebo (n = 73) | ADHD-RS-IV total score change from baseline | Change from baseline<br>Atomoxetine: −15.30<br>Placebo: −8.80 |

**Table 1B. Concerta® XL trials used in the indirect analysis**[10,15,16,35–38]

| Study | Study design | Main inclusion criteria | Treatment groups | Endpoint | Endpoint results |
|---|---|---|---|---|---|
| Adler, 2009c | Randomised, placebo-controlled, parallel group study. Seven weeks in duration; based in USA | Adults aged 18–65 years with an established diagnosis of ADHD | Concerta® XL (n = 110) (Starting dose of 36 mg daily titrated to 108 mg daily to achieve response)<br><br>Placebo (n = 116) | AISRS total score change from baseline | Change from baseline<br>Concerta® XL: −10.6<br>Placebo: −6.8 |
| Biederman, 2006 | Randomised, placebo-controlled, parallel group study. Six weeks in duration; based in USA | Adults aged 18–60 years with an established diagnosis of ADHD. Patients receiving stable doses of non–monoamine oxidase inhibitor antidepressants or benzodiazepines for more than three months were eligible for this study | Concerta® XL (n = 67) (Starting dose of 36 mg day titrated to a maximum of 1.3 mg/kg to achieve response)<br><br>Placebo (n = 74) | AISRS total score change from baseline | Change from baseline<br>Concerta® XL: −18.9<br>Placebo: −12.9 |
| Biederman, 2010 | Randomised, double-blind, placebo-controlled, parallel study design. Six weeks in duration; based in USA | Adults aged 18–60 years with full diagnostic criteria of ADHD based on DSM-IV with childhood-onset and persistent symptoms based on clinical assessment and confirmed by structured diagnostic interview and an AISRS score of 24 or higher | Concerta® XL (n = 109) (Starting dose of 36 mg day titrated to a maximum of 1.3 mg/kg to achieve response)<br><br>Placebo (n = 114) | AISRS total score change from baseline | Change from baseline<br>Concerta® XL: −15.1<br>Placebo: −9.2 |
| Medori, 2008 | Randomised, double-blind, placebo controlled trial. Five weeks in duration; based in Europe | Adults aged18–65 years with full diagnostic criteria of ADHD, ADHD symptomatology from childhood to adulthood with some symptoms present before age seven years | Concerta® XL (n = 95) (Fixed doses of 18 mg, 36 mg or 72 mg day)<br><br>Placebo (n = 99) | CAARS:Inv total score change from baseline | Change from baseline<br>Concerta® XL: −13.7<br>Placebo: −7.6 |

**Table 1B. Continued. Concerta® XL trials used in the indirect analysis**[10,15,16,35–38]

| Study | Study design | Main inclusion criteria | Treatment groups | Primary endpoint | Endpoint results |
|---|---|---|---|---|---|
| Weisler, 2012 | Randomised, double-blind, placebo- and active-controlled, parallel-group, multicentre study. Six weeks in duration; based in USA | Adults aged 18–55 years with an established diagnosis of ADHD | Concerta® XL<br>(n = 68)<br>(54 mg)<br><br>Placebo (n = 73) | ADHD-RS-IV total score change from baseline | Change from baseline<br>Concerta® XL: −15.7<br>Placebo: −8.8 |
| Winhusen, 2010 | Randomised, double-blind, placebo-controlled trial. 11 weeks in duration; based in USA | Aged 18–55 years who met DSM-IV criteria for ADHD and who have an interest in quitting smoking | Concerta® XL<br>(n = 127)<br>(Starting dose of 18 mg day titrated to 72 mg day to achieve response)<br><br>Placebo (n = 128) | ADHD-RS total score change from baseline | Change from baseline<br>Concerta® XL: −18.3<br>Placebo: −11.8 |
| Konstenius, 2010 | Randomised, double-blind, placebo-controlled, parallel-group trial. 12 weeks in duration; based in Sweden | Patients who met the DSM-IV criteria for amphetamine dependence during the last 12-month period | Concerta® XL<br>(n = 12)<br>(Starting dose of 18 mg day titrated to 72 mg day to achieve response)<br><br>Placebo (n = 12) | CAARS:SV total score change from baseline | Change from baseline<br>Concerta® XL: −19.1<br>Placebo: −8.5 |

ADHD: attention-deficit/hyperactivity disorder; AISRS: Adult ADHD Investigator Symptoms Rating Scale; CAARS:SV: Conner's Adult ADHD rating scale – short version; CGI: Clinical Global Impression Scale; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; OROS: osmotic-release oral system