

**Rapporteur's  
Final Assessment Report  
for paediatric studies submitted in accordance  
with Article 46 of Regulation (EC) No1901/2006, as  
amended**

**UK/W/010/pdWS/003**

**Strattera**

**Atomoxetine**

**Marketing Authorisation Holder: Eli Lilly and co.**

<b>Rapporteur:</b>	<b>UK</b>
<b>Start of the procedure:</b>	<b>Day 0 – Start procedure: 4<sup>th</sup> Jan 2011</b>
<b>Date of this report:</b>	<b>6<sup>th</sup> September 2009</b>
<b>Deadline for Rapporteur's pdAR(Day 70):</b>	<b>Preliminary PdPAR: 15<sup>th</sup> March 2011</b>
<b>Deadline for MS comments:</b>	<b>30<sup>th</sup> March 2011</b>
<b>Day 90</b>	<b>5<sup>th</sup> May 2011</b>
<b>Day 120</b>	<b>5<sup>th</sup> June 2011</b>

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Strattera
INN (or common name) of the active substance(s):	Atomoxetine hydrochloride
MAH:	Eli Lilly and co.
Currently approved Indication(s)	treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children aged 6 years and above and in adolescents in the United Kingdom on 27 May 2004.
Pharmaco-therapeutic group (ATC Code):	Centrally acting sympathomimetics (NO6B A09)
Pharmaceutical form(s) and strength(s):	5 mg, 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg capsules.

## EXECUTIVE SUMMARY

This is an assessment of data for atomoxetine, as part of the Article 46 EU work-sharing procedure. The UK is Rapporteur for this product; the initial assessment report (day 70) is due to be circulated to concerned Member States on 15 March 2011. On 13 September 2010, the MAH submitted 9 completed paediatric studies for atomoxetine, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use. A critical expert overview was also provided. The submitted studies are for the treatment of children and adolescents with ADHD and comorbid conditions including oppositional defiant disorder (ODD) and autism.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for atomoxetine and that there is no consequential regulatory action.

Strattera (atomoxetine) capsules were first authorized for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children aged 6 years and above and in adolescents in the United Kingdom on 27 May 2004. Subsequent Mutual Recognition Procedures (MRP) with the UK as Reference Member State (RMS) have resulted in atomoxetine being authorised in the majority of EU countries for use in children and adolescents as part of a comprehensive treatment programme. The Marketing Authorisation (MA) is currently undergoing renewal through the MRP with the UK as RMS.

In the UK, atomoxetine is a Black Triangle drug (a new drug under the MHRA intensive monitoring scheme). Since the original approval there have been several serious safety issues including psychiatric ones (eg suicidality, psychosis), leading to regulatory action.

### **Clinical data submitted**

Studies in ADHD provided useful data regarding the effect of atomoxetine on quality of life and neuropsychological outcomes. There were also data regarding the use of the drug in Asian patients. A double blind randomised control trial for the use of atomoxetine in ODD provided useful data; however similar to most studies, the design was poor as no behavioural methods had been used. With regard to the use of atomoxetine in autism and autistic spectrum disorders, useful short term data were provided, especially with regard to tolerability.

The submitted data were therefore insufficiently robust to warrant any changes in dosage or new indications. In addition, there were no significant safety findings in the submitted data; the ADRs detailed are already included in the SmPC.

None of the submitted studies provided any findings that require changes to the product information. Overall, in all of the studies, atomoxetine was well tolerated; there were few serious adverse events reported.

### **Recommendations**

**The assessor concludes that no changes to the product information or other regulatory action are required.**

## I. INTRODUCTION

This is an assessment of data for atomoxetine, as part of the Article 46 EU work-sharing procedure. The UK is Rapporteur for this product; the initial assessment report (day 70) is due to be circulated to concerned Member States on 15 March 2011. On 13 September 2010, the MAH submitted 9 completed paediatric studies for atomoxetine, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use. A critical expert overview was also provided. The submitted studies are for the treatment of children and adolescents with ADHD and comorbid conditions including oppositional defiant disorder (ODD) and autism.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for atomoxetine and that there is no consequential regulatory action.

### Regulatory History

This is the second Article 46 procedure for atomoxetine; the first was submitted and assessed in 2009; no subsequent SmPC changes were made.

Strattera (atomoxetine) capsules were first authorized for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children aged 6 years and above and in adolescents in the United Kingdom on 27 May 2004. Subsequent Mutual Recognition Procedures (MRP) with the UK as Reference Member State (RMS) have resulted in atomoxetine being authorised in the majority of EU countries for use in children and adolescents as part of a comprehensive treatment programme, with a notation in the Summary of Product Characteristics (SPC) that in some cases it might be appropriate to continue treatment into adulthood. Diagnosis should be made according to DSM-IV criteria or ICD-10 guidelines. The current UK Summary of Product Characteristics (SPC) for atomoxetine states that 'treatment must be initiated by or under the supervision of a physician with appropriate knowledge and experience in treating ADHD'. Atomoxetine can be administered as a single daily dose in the morning, with or without food, or as twice daily evenly divided doses if a satisfactory clinical response to a single daily dose is not achieved.

Over 5.5 million patients are estimated to have been treated with atomoxetine since the initial regulatory approval in the United States on 26 November 2002.

Eight dosage strengths (5 mg, 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, and 100 mg) have been approved, with the recent approval of 80 mg and 100mg on 05 June 2008 (in the UK). The Marketing Authorisation (MA) is currently undergoing renewal through the MRP with the UK as RMS. The double-blind phase of studies BZ-SD-LY15 (a) and BZ-MC-LYBX have already been submitted in the Strattera Wave 3 MRP submission; the safety data for these studies have therefore not been assessed as part of the Article 46 procedure.

Since the original approval the following safety issues have arisen :

- In 2005, an EMEA Article 31 referral procedure that reviewed suicidal and suicidal-related behaviours in children and adolescents treated with SSRIs and SNRIs including atomoxetine, resulted in the revision of the SPC to include a warning for hostility and emotional lability. A statement that atomoxetine is not indicated for the treatment of major depressive episodes and/or anxiety was also added. Also in 2006, clinical trial reported suicide-related events

was included in Section 4.8 as an uncommon event in children and adolescents (incidence  $\geq$  0.1% and  $<$ 1%); further revision of statements regarding suicidality has been made in 2008.

- In 2009, continued case reports of possible nervous-system and psychiatric adverse effects prompted a review of data from all sources, resulted in updated information on the risk of new-onset or worsening of serious psychiatric disorders, including psychotic reactions, hallucinations, mania, and agitation. Atomoxetine is associated with treatment-emergent psychotic or manic symptoms in children and adolescents without a history of such disorders.
- Other important safety issues associated with atomoxetine include seizures, hepatotoxicity and QT prolongation.

## **II. SCIENTIFIC DISCUSSION**

### **II.1 Information on the pharmaceutical formulation used in the studies**

Atomoxetine capsules were used in all of the clinical studies.

### **II.2 Clinical aspects**

#### **II.2.1. Introduction**

The MAH submitted 9 final study reports for the treatment of children and adolescents with ADHD and ADHD and comorbid conditions including oppositional defiant disorder (ODD) and autism.

#### **Attention-Deficit/Hyperactivity Disorder (ADHD)**

ADHD is a heterogeneous behavioural syndrome defined as a “persistent pattern of inattention or hyperactivity—impulsivity that is more frequently displayed and more severe than is typically observed in individuals at a comparable level of development.” It is the most commonly diagnosed psychiatric disorder in children, affecting about 3 to 5% of children globally with symptoms starting before seven years of age. ADHD is generally a chronic disorder with 30 to 50% of those individuals diagnosed in childhood continuing to have symptoms into adulthood. As they mature, adolescents and adults with ADHD are likely to develop coping mechanisms to compensate for their impairment. Though previously regarded as a childhood diagnosis, ADHD can continue throughout adulthood. Four percent of American adults are estimated to live with ADHD. ADHD is diagnosed twice as frequently in boys as in girls, though studies suggest this discrepancy may be due to subjective bias. Common comorbid conditions include oppositional defiant disorder (ODD), conduct disorder, learning difficulties, depression, substance misuse and epilepsy.

The updated National Institute for Health and Clinical Excellence (NICE) Guidelines for ADHD (September 2008) recommend that the diagnosis should only be made by a specialist psychiatrist, paediatrician or other healthcare professional with training and expertise in the diagnosis of ADHD.

For a diagnosis of ADHD, symptoms of hyperactivity/impulsivity and/or inattention should:

- meet the diagnostic criteria in DSM-IV or ICD-10 (hyperkinetic disorder) **and**
- be associated with at least moderate psychological, social and/or educational or occupational impairment based on interview and/or direct observation in multiple settings, **and**
- be pervasive, occurring in two or more important settings including social, familial, educational and/or occupational settings.

ADHD management usually involves some combination of medications, behaviour modifications, lifestyle changes, or counselling. The NICE guideline recommends that in school-age children and young people with severe ADHD, drug treatment should be offered as the first-line treatment. Parents should also be offered a group-based parent-training/education programme. Drug treatment for children and young people with ADHD should always form part of a comprehensive treatment plan that includes psychological, behavioural and educational advice and interventions. Methylphenidate is usually the first line drug of choice. Others include: dexamphetamine, atomoxetine, tricyclic antidepressants and clonidine.

The NICE guideline recommends that atomoxetine (or methylphenidate) should be the first-line choices for medication treatment of school-age children and young people with severe ADHD when tics, Tourette's syndrome, anxiety disorder, stimulant misuse or risk of stimulant diversion are present. It also recommends that atomoxetine should be used if methylphenidate has been tried and has been ineffective at the maximum tolerated dose, or the child or young person is intolerant to low or moderate doses of methylphenidate.

### **Oppositional defiant disorder (ODD)**

Oppositional defiant disorder (ODD) is a recurrent pattern of negativistic, defiant, disobedient, and hostile behaviour toward authority figures that persists for at least 6 months. Behaviours included in the definition include the following: losing one's temper; arguing with adults; actively defying requests; refusing to follow rules; deliberately annoying other people; blaming others for one's own mistakes or misbehaviour; and being touchy, easily annoyed or angered, resentful, spiteful, or vindictive. The base prevalence rates for oppositional defiant disorder (ODD) range from 1-16%, but most surveys estimate it to be 6-10% in surveys of nonclinical, non-referred samples of parents' reports. Before puberty, the condition is more common in boys; after puberty, it is almost exclusively identified in boys, and whether the criteria are applicable to girls has been discussed. The disorder usually manifests by age 8 years. ODD and other conduct problems are common reasons for referrals to outpatient and inpatient mental health settings for children, accounting for at least half of all referrals.

The diagnosis of ODD is complicated by relatively high rates of comorbid, disruptive, behaviour disorders. Some symptoms of ADHD) and conduct disorder overlap. Researchers have postulated that, in some children, ODD may be the developmental precursor of conduct disorder. Comorbidity of ODD with ADHD has been reported to occur in 50-65% of affected children. The presence of ODD together with ADHD is a serious clinical problem. Children with ADHD combined with ODD tend to have more severe ADHD symptoms, peer problems, and family distress compared with children with ADHD alone. However, few rigorous, adequately designed studies of pharmacologic treatments for ODD have been reported, although data from recent preliminary studies suggest that medications may be of benefit.

In some children, ODD commonly occurs in conjunction with anxiety disorders and depressive disorders. Cross-sectional surveys have revealed the comorbidity of ODD with an affective disorder in about 35% of cases, with rates of comorbidity increasing with patient age. High rates of comorbidity are also found among ODDs, learning disorders, and academic difficulties. Given

these findings, children with significant oppositional and defiant behaviours often require multidisciplinary assessment and may need components of mental health care, case management, and educational intervention to improve.

## **Autism**

Autism is a neurodevelopmental disorder characterized by impaired social interaction and communication, and by restricted and repetitive behaviour. These signs all begin before a child is three years old., but often long before this<sup>1</sup> There is currently no effective treatment for autism; children are usually managed with behavioural therapy, speech and language therapy and educational methods. Particularly in the United States, psychocative drugs are used to treat some of the difficult autistic symptoms. Many autistic children have associated ADHD and may be treated with stimulants or atomoxetine; however, there are very limited data available regarding this.

## **Pharmacological properties**

Unlike all other currently approved medicinal products to treat ADHD, atomoxetine is not a stimulant. It is a potent, selective and highly specific inhibitor of the presynaptic norepinephrine transporter (NET). It has minimal affinity for either the serotonin or dopamine transporters, or for other neurotransmitter receptors. Specific inhibition of the NET is believed to be the mechanism for the efficacy of atomoxetine in ADHD. Following oral administration of atomoxetine it is rapidly and almost completely absorbed resulting in maximal plasma concentrations after 1 to 2 hours. Metabolism is rapid and primarily by aromatic ring hydroxylation, aliphatic oxidation and N-demethylation to phase I metabolites (4-hydroxyatomoxetine, desmethlyatomoxetine and 2-hydroxymethyl-atomoxetine). CYP2D6 is the major enzyme involved in the aromatic hydroxylation to the major metabolite 4-hydroxyatomoxetine, which undergoes further metabolism resulting in the formation of the primary ultimate metabolite of atomoxetine, 4-hydroxyatomoxetine-O-glucuronide. This conjugated metabolite is subsequently eliminated in the urine and the mean elimination half life is about 3.6 hours in extensive metabolisers and 21 hours in poor metabolisers. Atomoxetine does not cause clinically significant inhibition or induction of CYP1A2, CYP3A, CYP2D6 or CYP2C9.

The pharmacokinetics of atomoxetine are linear over the range of doses studied. In the paediatric population pharmacokinetic analysis, body weight had a significant effect on atomoxetine pharmacokinetics and therefore a weight-based dose regimen is authorised.

### **II.2.2 . Submitted clinical studies**

These are listed below:

#### **Studies in ADHD Alone**

**Study B4Z-EW-LYDY: A Randomized, Controlled, Open-Label Study of the Long-Term Impact on Functioning using Atomoxetine Hydrochloride Compared to Other Early Standard Care in the Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in Treatment-Naïve Children and Adolescents**

**Study B4Z-SB-LYDV: A Randomized, Double Blind Comparison of the Effects of Atomoxetine versus Placebo on Neuropsychological Outcomes across the Day in Children with Attention-Deficit/ Hyperactivity Disorder (ADHD) by Use of a Computer**

**Based Continuous Performance Test (cb CPT).Studies in AD Studies in ADHD Asian Patients**

**Study B4Z-CR-S018: Evaluation of Academic Performance in Asian Children Aged 8 to 11 Years with Attention-Deficit/Hyperactivity Disorder Treated with Atomoxetine Hydrochloride.(Available as poster and manuscript only).**

**Study B4Z-JE-LYDA: A Long-Term Extension, Open-Label, Study of Atomoxetine Hydrochloride in Child Outpatients with Attention Deficit/Hyperactivity Disorder.**

#### **ADHD with Comorbid Conditions**

**Study B4Z-IT-LYDS:An Open-Label Study of the Efficacy of Atomoxetine Hydrochloride on Quality of Life of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder with or without comorbid conditions**

**Study B4Z-SB-LYDW: A Randomised, Double-Blind Comparison of Atomoxetine versus Placebo in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder and Comorbid Oppositional Defiant Disorder.**

**Study B4Z-UT-LYEL: An Open Label Pilot Study of Atomoxetine Hydrochloride in Adolescents with Attention Deficit/Hyperactivity Disorder and Comorbid Cannabis.**

**Study B4Z-UT-S003: An Open-Label Pilot Study of Atomoxetine for Attention-Deficit and Hyperactive/Impulse Behaviour Problems in Children and Adolescents with Autism Spectrum Disorders.**

**Study B4Z-UT-S017(b): A randomized, double-blind comparison of atomoxetine hydrochloride and placebo for symptoms of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents with autism spectrum disorder**

The above studies are detailed below:

#### **Studies in ADHD Alone**

**II.2.2 .1 Study B4Z-EW-LYDY- A Randomized, Controlled, Open-Label Study of the Long-Term Impact on Functioning using Atomoxetine Hydrochloride Compared to Other Early Standard Care in the Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in Treatment-Naïve Children and Adolescents**

This was a randomised open-label outpatient study in approximately 400 pharmacologically naïve children with ADHD (aged 6-17 years)

**The primary objective** of the study was to test the hypothesis that atomoxetine given for 6 months is superior to other early standard therapy (OEST) in improving quality of life, as measured by the achievement domain of the Child Health and Illness Profile – Child Edition, Parent Report Form (CHIP-CE PRF). An optional open-label long-term extension phase of an additional 6 months was available.

In the OEST group, 98.5% received pharmacotherapy and 3 patients received psychoeducation only. The majority of patients were taking monotherapy long-acting methylphenidate (MPH) osmotic-release oral system (OROS) (53.6% of these patients) or short-acting MPH (39.1%).

**The primary efficacy variable** was the change after 6 months of treatment in the achievement domain of the CHIP-CE parent form. The CHIP-CE is a parent rated assessment of a child's health status and level of functioning. It is a comprehensive measure of a child's functioning and examines 5 domains and 13 domains.

Baseline CHIP-CE achievement domain mean T-scores were about 1 SD below the normative range of 40 to 60 for both treatment groups, showing a substantial impairment in that domain in this ADHD treatment naïve patient population.

**Secondary efficacy variables** included the ADHDRS-IV-Parent:Inv score and the Clinical Global Impression-Severity-ADHD (CGI-ADHD-S) . The ADHD Rating Scale-IV is a validated instrument that includes 18 items, both used for diagnosing ADHD in children and adolescents and for assessing treatment response.

## Results

The primary efficacy analysis showed no superiority of atomoxetine over OEST treatment in the CHIP-CE PRF achievement domain after 6 months of treatment. In both treatment groups a statistically significant and clinically relevant improvement, in mean T-scores was seen.

In both treatment groups, the ADHD-RS-IV Parent:Inv mean scores had statistically significantly improved at the 4 and 6 months endpoint compared to baseline. The difference between treatment groups was statistically significant in favour of the OEST group for the ADHD-RS total score and the ADHD-RS inattentive subscore, but not the ADHD-RS hyperactive/impulsive subscore. According to CGI-ADHD-S, patients were on average "markedly/severely ill" at baseline. In both treatment groups, the mean CGI-ADHD-S score improved to "mildly/moderately ill" at Months 4 and 6. No statistically significant differences in improvement between treatment groups were seen with the CGI-ADHD-S.

With regard to safety, mean scores in all secondary efficacy parameters were maintained between Month 6 and 12 in both treatment groups. No statistically significant differences in overall Treatment Emergent Adverse Events (TEAE) rates, serious TEAEs, or discontinuations due to TEAEs were found between treatment groups during the 6 month controlled period.

### Assessor's comments:

**The above study provides useful data regarding the long term effect of atomoxetine on quality of life outcomes.**

## II.2.2.2 Study B4Z-SB-LYDV: A Randomized, Double Blind Comparison of the Effects of Atomoxetine versus Placebo on Neuropsychological Outcomes across the Day in Children with Attention-Deficit/ Hyperactivity Disorder (ADHD) by Use of a Computer Based Continuous Performance Test (cb CPT).

This 8-week, randomized, double-blind, multicenter placebo-controlled study in children aged 6 to 12 years had the primary objective to test the hypothesis that atomoxetine 1.2mg/kg is

superior to placebo in the treatment of ADHD, as measured by neuropsychological outcomes assessed via standard variables of a computer based Continuous Performance Test (cb CPT).

The secondary objectives were to compare atomoxetine treatment versus placebo in children with ADHD with respect to reduction of ADHD symptoms as measured by standard rating scales.

This study was a randomized, double-blind, multicenter Phase 4, two-arm placebo-controlled, parallel group comparison in day-patients, inpatients and outpatients (specialized clinical practices) who meet DSM-IV diagnostic criteria for ADHD. Following a 3- to 28-day screening and washout period (Study Period I), eligible patients were randomly assigned to receive 8 weeks of double blind treatment (Study Period II) with either atomoxetine or placebo. Patients received a lead in dose of 0.5 mg/kg per day for 1 week, followed by 7 weeks on the standard target dose of 1.2 mg/kg per day. Visits took place at week 1, 2, 4, 6 and 8 after randomization.

The computer based Continuous Performance Test (cb CPT; Qbtech AB, Gruvgatan 6, S-421-30 Göteborg, Sweden) involves rapid presentation a grey circle (target), or a grey circle with a cross (non-target), appearing on the screen at a pace of one per two seconds (0.5 Hz), and visible for 100 milliseconds. The response profile, the kind and number of errors and the patterns of movement indicate type and level of attention deficit, impulsivity and hyperactivity. The cb CPT was scheduled in the morning (7:00 - 9:00 a.m., prior to study medication intake), around noon (12:00 a.m. - 3:00 p.m.), and in the late afternoon/early evening (5:00 - 7.00 p.m.) at every visit.

## Results

Atomoxetine was superior compared to placebo in reducing symptom severity of ADHD as measured by the q-scores of the cb CPT for all primary variables. ADHD symptom severity as measured by the ADHD-RS-IV:Parent:Inv and CGI-S-ADHD scale was also reduced to a greater degree in the atomoxetine group compared to the placebo group; the observed difference in reduction was statistically significant. The highest effect size was seen for the ADHD-RS-IV:Parent:Inv hyperactivity-impulsivity subscore). No or small correlations were seen at baseline between the cb CPT q-scores and the scores of the questionnaires. No correlations to moderate correlations were seen for changes from baseline to the last observed value (LOCF).

The tolerability profile observed during the study did not differ from previous studies of atomoxetine. No clinically relevant changes in physical parameters (blood pressure, heart rate, weight) was observed.

### Assessor's comments:

**The above double blind study provides useful data regarding the effect of atomoxetine on neuropsychological outcomes. However, it is disappointing that no psychological treatments were used; these should be routine clinical practice.**

## Studies undertaken in Asian patients with ADHD

### II.2.2.3 Study B4Z-CR-S018

The primary objective of this 24 week, open-label study in treatment naive patients aged 8 to 11 years from China, Taiwan and Korea with ADHD, receiving atomoxetine up to 1.4 mg/kg/day,

was to determine whether atomoxetine improved the symptoms of ADHD, as measured by the ADHDRS-IV-Parent:Inv total score and improved school grades as measured by School Grade Average (SGA) scores .

### **Methods:**

This multi-centre, open-label study enrolled patients from China, Taiwan and Korea meeting DSM-IV-TR criteria for ADHD. Patients, aged 8 through 11, naïve to ADHD medications and meeting a symptomatic severity threshold of 1.5 standard deviations above the age and gender norm for the ADHDRS-IV-Parent:Inv total score, were eligible. Screening was followed by open-label atomoxetine treatment for up to 24 weeks. Patients received atomoxetine at a dose of 0.5 mg/kg for 7 days, followed by 1.2 mg/kg for 7 days and then an adjustable dose in the range 0.8 to 1.4 mg/kg for the remainder of the study. During this period, administration of other psychoactive agents was not permitted. Data collection included patient characteristics, ADHDRS-IV-Parent:Inv, academic outcome as measured by School Grade Average (SGA), CGI (improvement and severity), CPRS-R:S and adverse events. The SGA, a simple composite average score from 0 to 100 for Language, Mathematics and Science classes (obtained from school reports of these individual grades), was obtained for two time-points (based on assessment date, rather than school report dissemination): no more than 8 weeks prior to medication initiation (baseline) and 16 to 24 weeks thereafter (endpoint). Given an expected completion rate of 70%, a sample size of 250 enrolled patients was intended to provide 90% power to detect a correlation of 0.25 between the change in ADHD symptoms and the change in SGA, given a two-sided significance level  $\alpha=0.05$ .

### **Results:**

A total of 228 enrolled and evaluable patients from 261 screened, were included from China (n=82), Taiwan (n=76) and Korea (n=70). The majority were male (85.1%), baseline mean (SD) age was 9.6 (0.96) years. 2.2%, 36.0% and 61.8% of patients were diagnosed as ADHD hyperactive, inattentive and combined type, respectively. Mean baseline ADHDRS-IV-Parent:Inv total score was 35.3 (7.09) and SGA 73.9 (15.82). 77.2% of patients completed the study. Statistically significant ( $p<.001$ ) mean (SD) baseline to endpoint improvement in ADHDRS-IV-Parent:Inv and SGA scores (-18.8 [9.27] and 4.7 [10.68], respectively), were observed. No linear correlation between change in total ADHDRS-Parent:Inv score and SGA (-0.083,  $p=.293$ ) was observed nor for any of the individual grades of Language (-0.086,  $p=.276$ ), Mathematics (-0.126,  $p=.110$ ) or Science (-0.058,  $p=.464$ ). 5.0% of patients discontinued due to a treatment-emergent adverse event.

The adverse event profile was similar to that seen in other atomoxetine studies, with the majority of adverse of events being mild to moderate and not leading to study discontinuation.

#### **Assessor's comments:**

**The above study provides useful short term data regarding the use of atomoxetine in Asian children.**

#### **II.2.2.4 Study B4Z-JE-LYDA**

The primary objective of this open-labelled long-term study was assessment of safety and tolerability of atomoxetine in Japanese children and adolescents with ADHD who completed Study LYBC (previously assessed in 2009), as measured by safety assessments collected during the course of the study.

The results from this study showed that daily doses of atomoxetine between 0.5-1.8 mg/kg/day were safe and tolerable for periods up to 3 years or more in Japanese children and adolescents with ADHD.

There were no deaths in the study and 6 SAEs were reported in 6 patients. A causal relationship with atomoxetine could not be ruled out for 3 SAEs (abnormal hepatic function, schizophrenia, thyroiditis). All other SAEs were judged by investigators to be unrelated to atomoxetine. No notable patterns were found for the AEs, the discontinuations or the analysis of laboratory analytes. Three suicide related events were reported: one suicide attempt and two reports of suicide ideation; however, no relationship was identified between these 3 AEs and the dose/time of atomoxetine administration.

Patient mean weight percentiles decreased from baseline during the first 6 months on atomoxetine therapy, but then remained stable until month 27 when a slow recovery became apparent. After 36 months this tendency became more pronounced, and mean weight percentiles reached and then exceeded baseline during months 39 through 45. During the last few months (46-51 months) mean weight percentiles were below baseline; however the number of patients on therapy decreased to less than 14 patients after month 45, with only 2 patients still on therapy by the end of the study. During the first 24 months on therapy there was a steady decrease from baseline in mean height percentiles, however percentile values appeared to stabilize with longer exposure to atomoxetine (24-42 months), and at 42 months there was a return to baseline. As seen with weight, mean height percentiles also appeared to drop toward the end of the study as the number of patients on therapy decreased. Interpretation of these late study results (> 45 months) for mean weight and height percentiles were difficult due to the comparatively small number of patients and the large SD values.

Statistically significant ( $p < 0.001$ ), but not clinically significant, increases were seen in mean heart rate (pulse) and blood pressure (systolic and diastolic) during all treatment time periods. The changes in mean heart rate were not unexpected given atomoxetine's noradrenergic mechanism of action. Analysis of ECG data showed that even though both the Fridericia and Data Driven corrections detected statistically significant QTc prolongation for all treatment periods after 12 months, the actual changes were small (5.36-13.19 msec).

A maximum QTc interval >450 msec (Data Driven) was observed for 1 patient during the 1-2 year treatment period, however there were no clinically significant changes and it was not considered by the investigator to be an adverse event. Increases from baseline  $\geq 60$  msec, but with the QTc intervals <450 msec (Fridericia and Data Driven), were observed for another 2 patients, however no clinically significant changes were associated with either event and they were not considered by investigators to be an adverse events.

**Assessor's comments:**

**The above open label study provides useful data particularly with regard to the longer term tolerability of atomoxetine in Asian patients.**

**Studies in ADHD and other co-morbid conditions**

**II.2.2 .5 Study B4Z-IT-LYDS: An Open-Label Study of the Efficacy of Atomoxetine Hydrochloride on Quality of Life of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder with or without comorbid conditions.**

This was a phase IIIb, multicenter, open-label trial in paediatric patients, aged 6 years to 15 years with ADHD with or without comorbidities.

**The primary objective of the study** was to describe the efficacy of atomoxetine, given in an open-label manner, at flexible dosage (up to 1.2 mg/kg/day, once daily) for 12 weeks in improving psychosocial functioning of ADHD children and adolescents, in the presence of comorbid conditions. The effect on emotional and social well being of the child and the family was evaluated by the mean change of the score of the domains “Achievement” of the parent-rated Child Health and Illness Profile – Child Edition (CHIP-CE).

**The secondary objectives included** whether the effect of atomoxetine in improving (parent-rated) ADHD core symptoms was influenced by the presence of comorbid conditions and other objectives.

The study consists of 3 study periods: Study Period I, which is a screening assessment/evaluation period (of minimum 3 days) to ensure eligibility for the study; Study Period II, which is a 12-week period of open-label treatment with atomoxetine. At the start of study period II, patients were assigned to one of the following groups accordingly with the diagnosis: Group 1, pure ADHD; Group 2, ADHD plus internalizing disorders (anxiety and/or mood disorders); Group 3, ADHD plus externalizing disorder (ODD, Oppositional Defiant Disorder); Study Period III, which was an optional, open-label, long-term extension phase for patients who complete study period II. Subjects started treatment with atomoxetine the day after Visit 2. Patients started on a dose of approximately 0.5 mg/kg/day (range 0.5-0.8 mg/kg/day) and increased to the target dose of 1.2 mg/kg/day (at day 8, range 1.0-1.4 mg/kg/day) that they continued to take for the 12 weeks of the acute treatment (Study Period II).

**The Primary efficacy variable** was the Child Health and Illness Profile – Child Edition (CHIP-CE).

**Secondary variables included the following:** Swanson, Nolan and Pelham Rating Scale revised (SNAP-IV, Clinical Global Impression – ADHD – severity (CGI-ADHD-S).

## Results

Treatment with atomoxetine given for 12 weeks was associated with statistically significant improvements in the achievement domain and in academic performance subdomain (as measured by the CHIP-CE) in patients with pure ADHD or with ODD, while improvements in relations with peers were observed in patients with anxiety or mood disorders comorbidities.

Patients with ADHD and ODD significantly improved in all the other aspects of quality of life measured with the other CHIP-CE domains, while significant improvements in patients with pure ADHD were observed only in Risk Avoidance and in patients with ADHD and anxiety/mood disorders were observed only in the comfort and the risk avoidance domain.

General clinical condition, as measured by CGI-ADHD-S, significantly improved from baseline to Day 84 in all groups, without differences between them. Significant improvements were also observed in all patient’s groups, in all other subscales of SNAP-IV, at the end of study period II.

The analysis of the effects of atomoxetine on problems behaviours in the school setting, showed improvements in all subscales in patients with pure ADHD or with externalizing disorders, while improvements only in the ADHD index were observed for the patients with ADHD and internalizing disorders.

With regard to safety, the adverse events and vital signs documented were in line with the known safety profile of atomoxetine.

**Assessor's comments:**

The above open label study provides useful data regarding the effect of atomoxetine on ADHD and co-morbid conditions. However, again it is disappointing that no psychological treatments were used; these should be routine clinical practice.

**II.2.2 .6 Study B4Z-SB-LYDW: A Randomised, Double-Blind Comparison of Atomoxetine versus Placebo in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder and Comorbid Oppositional Defiant Disorder (ODD).**

This was a three-arm, randomized, double-blind, placebo-controlled Phase 4 multicenter study to compare the efficacy and safety of ATX vs. placebo in 180 children and adolescents aged 6 through 17 years with ADHD and comorbid ODD who were treated as outpatients in Germany.

**The Primary Objective** was to test the hypothesis that atomoxetine (ATX), given once daily for approximately 9 weeks (target dose of 1.2 mg/kg per day), using either fast or slow titration, was superior to placebo in the outpatient treatment of oppositional defiant disorder (ODD) symptoms in children and adolescents with ADHD and comorbid ODD. ODD symptoms reduction was measured primarily using the investigator-rated ODD subscale of the Swanson, Nolan and Pelham Rating Scale-Revised (SNAP-IV ODD).

**The Secondary Objective** was to compare ATX using fast and slow titration versus placebo in children and adolescents with ADHD and comorbid ODD with respect to reduction of ODD, conduct disorder (CD) and ADHD symptoms, changes in the child's health-related quality of life and safety.

**The Primary Efficacy Variable** was the investigator-rated ODD subscale of SNAP-IV. The SNAP-IV is a 26-item scale that includes 1 item for each of the 18 symptoms contained in the DSM-IV diagnosis of ADHD and 1 item for each of the 8 symptoms contained in the DSM-IV diagnosis of ODD. Each item is scored on 0 to 3 scale (0 = "Not at All", 1 = "Just a Little", 2 = "Pretty Much", 3 = "Very Much").

**Secondary measures** were the investigator-rated ADHD subscales of SNAP-IV scale, parent-rated scales for ADHD and ODD/CD and quality of life (KINDL) and family burden (FaBel) questionnaires.

After an initial 3- to 28-day screening and washout phase, patients were randomly assigned to 9 weeks of double-blind treatment with ATX using fast titration, ATX using slow titration, or placebo. The 2-week up-titration period was succeeded by a 7-week treatment period at the target dose. Randomization was stratified by patient age at Visit 1 (age < 12 years or = 12 years).

**Results**

**Primary Efficacy Outcome - SNAP-IV ODD:** The primary repeated measures analysis (MMRM) showed that 9-week treatment with ATX once daily, using either fast or slow titration up to a target dose of 1.2 mg/kg per day, was significantly superior to placebo in reducing ODD symptoms as measured by the SNAP-IV ODD subscale score ( $\Delta$  LS mean at Week 9, ATX pooled minus placebo [95% CI]: -3.2 [-5.0 to -1.5], effect size: -0.693,  $p < 0.001$ ).

Looking at the ATX slow and fast titration groups separately , each individual group had significantly reduced ODD symptoms as well (MMRM analysis,  $p < 0.001$  and  $p = 0.003$  vs. placebo), whereas the direct comparison of ATX fast vs. slow titration group did not reveal a significant difference ( $p = 0.669$ ).

**Secondary Efficacy Outcomes:** All investigator-rated efficacy outcome parameters had statistically significantly improved in the ATX pooled group compared with placebo at Week 9, that is all SNAP-IV ADHD subscale scores, all ADDB-Inv severity and impairment scores, scores reflecting intensity and frequency of Individual Target Behaviours (ITB-Inv), and all CGI-severity ratings. Parent ratings of the patients' overall health-related quality of life, as assessed by the KINDL total score (co-primary outcome), had significantly improved after 9 weeks of ATX treatment when compared with placebo. There was no significant treatment effect of ATX regarding changes in family burden, as assessed by the parent-rated FaBel questionnaire total score,

With regard to safety, overall, once daily ATX treatment was well tolerated and no new safety signals were detected in this study. Most frequent treatment-related adverse events observed ( $\geq 10\%$ ) were fatigue, nausea, headache, vomiting, upper abdominal pain, and anorexia.

Overall rates of treatment-related adverse events (ATX fast 70.0%, ATX slow 57.4%, placebo 30.5%) and discontinuations due to adverse events (ATX fast N=6, ATX slow N=2, placebo N=1) were lower with the slower titrate group.

### Conclusions

In summary, 9-week treatment with ATX once daily (target dose 1.2 mg/kg per day) significantly reduced symptoms of both ODD/CD and ADHD and improved measures of health-related quality of life in children and adolescents with ADHD and when compared to placebo. Slow up-titration of ATX may be better tolerated than fast up-titration while showing similar efficacy.

#### Assessor's comments:

**The above double blind study provides some evidence of efficacy for the use of atomoxetine in co-morbid ODD. However, the data are of limited validity, since behavioural methods were not used.**

### Studies in autistic spectrum disorder and autism

#### II.2.2 .7 Study B4Z-UT-S003

The primary objective of this 10 week, open label, single centre study was to test the hypothesis that atomoxetine titrated to a maximum dose of 1.8 mg/kg/day (once daily) was effective in reducing the symptoms of ADHD in 12 patients aged 6 to 17 years with a diagnosis of autism spectrum disorder (ASD) and ADHD. These patients also had to meet DSM-IV-TR criteria A to D for ADHD. Patients could also continue onto a 20-week open-label extension phase during which all patients received atomoxetine.

**The Primary efficacy variable** was the reduction in the ADHD-RS-IV scales relative to baseline.

### Results

Atomoxetine significantly reduced symptoms of ADHD, as measured by the ADHD-RS-IV rating scale (44% change-  $p=0.003$ ) and the CGI scale. The most common reported AEs were anorexia, irritability and sleep problems. Mean heart rate statistically significantly increased from baseline to endpoint; ECGs revealed PR, QRS and QTC intervals were all unchanged.

### **II.2.2 .8 Study B4Z-UT-S017(b)**

**The primary objective** of this 8 week double blind controlled study was to test the hypothesis that atomoxetine given at a dose up to 1.2 mg/kg/day (once daily) was superior to placebo in treating ADHD in 100 in- and outpatients aged 6 to 17 years with a diagnosis of autism spectrum disorder (ASD). These patients also had to meet DSM-IV-TR criteria A to D for ADHD.

**The secondary objectives** were:

To assess the efficacy of acute treatment with up to 1.2 mg/kg/day atomoxetine versus placebo for 8 weeks on symptoms of ADHD as measured by Clinical Global Impression-ADHD-Improvement scale (CGI-ADHD-I) and the Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R:S).

To assess the efficacy of maintenance treatment with atomoxetine during open-label follow-up on symptoms of ADHD as measured by the ADHD rating scale-IV-parent version: investigator scored, CGI-ADHD-I and the CTRS-R:S.

Other secondary objectives included measuring the effect of atomoxetine on behaviour and sleep patterns.

#### **Design**

Study period I was a screening and wash-out period and was a minimum of 3 and a maximum of 28 days. Study period II (visits 2–6) was the 8-week, double-blind, placebo-controlled phase. Patients were randomised at visit 2 to either atomoxetine or placebo. Doses of atomoxetine and placebo were increased in a step-wise fashion from 0.5 mg/kg/day to 1.2 mg/kg/day. Study period III (visits 6–11) was the 20-week open-label extension phase during which all patients received atomoxetine.

**The primary efficacy measure** was the change from baseline in the total score of the ADHDRS-IV-Parent.

**The secondary outcome measures** included the following instruments for measurement of efficacy: CGI-ADHD-I, CTRS-R:S, the sleep outcomes scale, ABC, CSBQ, ANT, GHQ, and NOSI.

#### **Bioanalytical**

Patients' drug metabolic status was characterized as being either an extensive metabolizer, intermediate, or a poor metabolizer by ascertaining their cytochrome P450 2D6 (CYP2D6) genotype.

#### **Results**

The baseline ADHDRS-IV-Parent total score for the atomoxetine group was (SD) 40.7 (7.47) and for placebo it was 38.6 (8.43). At the end of the double-blind treatment phase (visit 6), the mean ADHDRS-IV-Parent total score was lower in the atomoxetine group compared with the

placebo (atomoxetine [SD] = 32.3 [10.97] and placebo 37.3 [9.57]). In addition, the change from baseline was greater for the atomoxetine group (atomoxetine [SD] = -8.2 [8.77] and placebo - 1.2 [7.25]). The results of the MMRM analysis showed that after 8 weeks, ADHD-RS improved significantly more in the atomoxetine than in the placebo group (MMRM adjusted mean [95% CI] for atomoxetine was 31.6 [29.2 to 33.9] and for placebo was 38.3 [36.0 to 40.6]). The LOCF ANCOVA analysis also showed consistent results where the atomoxetine group had a lower estimated least squares (LS) mean compared with placebo (31.2 versus 38.3) at the end of double blind period. The difference between LS means was -7. 95% confidence interval (CI) - 10.3, -3.7. This difference was statistically significant ( $p < 0.001$ ). In addition, atomoxetine was superior to placebo in the treatment of symptoms of ADHD as assessed by a number of secondary objectives.

There was no significant effect of CYP2D6 genotype (extensive and intermediate versus slow metabolizers) on the primary endpoint. Further improvements in ADHDRS-IV-Parent occurred in the extension phase in both groups of patients: those who had been treated with atomoxetine and those who had received placebo during the double-blind phase.

During this study, atomoxetine was well tolerated and the profile of reported AEs was similar to ADHD without ASD. No SAEs were reported during the double-blind phase. One patient discontinued atomoxetine treatment owing to an AE, which was fatigue and was related to study treatment. The two SAEs reported during the open-label phase were not related to study treatment.

**Assessor's comments:**

**The above studies provide useful efficacy and tolerability data regarding the use of atomoxetine in children with autism and autistic spectrum disorders. The use of other methods, including behavioural ones was not detailed.**

## **II.2.2 .9 Study B4Z-UT-LYEL**

The primary objective of this open label pilot study was to test the hypothesis that atomoxetine given at a dose up to 1.2 mg/kg/day (once daily) for 12 weeks reduced symptoms of ADHD versus baseline in outpatients aged 13 to 17 years with a diagnosis of ADHD and comorbid cannabis abuse.

The study was terminated early due to recruitment difficulties with only 7 patients entered and no conclusions could be drawn with regard to the study objective. No unexpected AEs or SAEs were reported.

## **III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION**

### **Overall conclusion**

The submitted studies provide useful data regarding the use of atomoxetine for ADHD and other co-morbid conditions: oppositional defiant disorder and autism. Some of the study designs were disappointing as they did not include the use of non-drug methods in the treatment of ADHD, which are part of a comprehensive treatment plan. The data were therefore insufficiently robust to warrant any changes in dosage or new indications. In addition, there were no significant safety findings in the submitted data; the ADRs detailed are already included in the SmPC.

## **Recommendation**

No changes to the product information or other regulatory action are recommended.

No further action required.

## **IV. ADDITIONAL CLARIFICATIONS REQUESTED**

Not applicable.

## **V. MEMBER STATES COMMENTS**

One comment was received from the Netherlands as follows:

Further clarification was requested regarding whether the ADRs assessed were included in the SmPC .

***Assessor's comment: This has been clarified in section III of the AR. Issue resolved***

## **VI. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION**

There are no outstanding issues regarding this procedure. No further regulatory action is required.