MHRA

Medicines and Healthcare products Regulatory Agency

Safeguarding public health

**PRELIMINARY ASSESSMENT REPORT**

# STRATTERA (atomoxetine) – Risk Benefit Assessment

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|---|---|
| Invented name of the pharmaceutical products in the Member State | Strattera |
| Name(s) of the active substance(s) (INN) | atomoxetine |
| Pharmacotherapeutic classification (ATC Code) | centrally acting sympathomimetics (N06BA9) |

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|---|---|
| Reference No for Mutual Recognition Procedure | UK/H/0686/01-06/II/001 |

| | |
|---|---|
| Reference Member State | UK |

| | |
|---|---|
| Date of this Report | 9 December 2005 |
| Name, telephone and telefax number of contact point in Member State for discussion of issues raised. | [redacted]<br>Telephone: [redacted]<br>Telefax:: [redacted] |

# 1.0 THE ISSUE

On 15 September 2005 the MHRA was informed by the Marketing Authorisation Holder for Strattera (Eli Lilly) of an analysis of double blind, randomised, placebo-controlled clinical trial data for atomoxetine which has identified a statistically significant increased risk of suicidal thoughts with atomoxetine compared to placebo in children with Attention Deficit/Hyperactivity Disorder (ADHD).

Strattera (atomoxetine hydrochloride) is authorised through the Mutual Recognition Procedure with the UK as Reference Member State. On discussion with CMS (Germany, the Netherlands and Norway) and subsequently with the Pharmacovigilance Working Party, it was agreed that these new data warranted a full risk:benefit evaluation of atomoxetine in its licensed indications, particularly in light of previous concerns about its safety profile including serious hepatic reactions and seizures. In the interim warnings about the risk of suicidal behaviour with atomoxetine were added via an Urgent Safety Restriction (USR) procedure to allow timely communication of the risk to health professionals and patients.

This paper considers the available data on the efficacy and safety of atomoxetine and considers what implications these may have for the currently licensed indication and product information.

# 2.0 BACKGROUND

## 2.1 Atomoxetine hydrochloride (Strattera)

### 2.1.1 Regulatory History

Strattera, the active constituent of which is atomoxetine hydrochloride, has been authorised in the USA since 26 November 2002 for the treatment of ADHD in children over the age of 6 years, adolescents and adults.

It was licensed in the UK on 27 May 2004 and subsequently through the Mutual Recognition Procedure (MRP) on 27 October with the UK as Reference Member State (RMS). Marketing Authorisation applications were completed on 26 September 2005 in a further 22 CMSs under a second-wave MRP.

Strattera is authorised in the EU for the treatment of ADHD in children 6 years and older and in adolescents as part of a comprehensive treatment programme. Diagnosis should be made according to DSM-IV criteria or ICD-10 guidelines. The current EU Summary of Product Chatacteristics (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.

In January 2005, following reports of severe liver injury associated with the use of atomoxetine, the SPC and PIL were updated via an expedited variation procedure to warn of the rare risk of liver injury with the advice to stop treatment immediately if liver injury is suspected. This advice was communicated in the UK via a Dear Doctor Letter from the CSM Chairman on 3 February 2005 and also within Europe by a company Dear Doctor letter.

Atomoxetine was included in the recent EU Article 31 referral of paediatric use of antidepressants. Following review of the data submitted by Lilly on 22 February 2005, the EU Committee on Medicinal Products for Human Use (CHMP) concluded that there was no signal of an increased risk of suicide related behaviour in the atomoxetine studies however there was an increased risk of hostility and emotional lability. This was based on a combined analysis of 6 trials which identified 1 report of suicidal behaviour in the atomoxetine group and 0 reports in the placebo group.

Atomoxetine was originally studied in more than 1200 adults with Major Depressive Disorder (MDD) and in one urinary incontinence (UI) trial during the late 1980s and early 1990s. The efficacy of atomoxetine in these trials was not demonstrated to be superior to placebo and therefore product development in these indications was abandoned. The current SPC includes the statement 'Strattera is not indicated for the treatment of major-depressive episodes and/or anxiety, as the results of clinical trials that were conducted in adults did not show any effect compared to placebo and therefore were negative'.

On 15 September 2005 the MHRA was informed by the MAH of two new analyses of double blind, randomised, placebo-controlled clinical trial data for atomoxetine which had identified a statistically significant increased risk of suicidal behaviour with atomoxetine compared to placebo in children with ADHD. The full report is attached at Annex 1.

### 2.1.2 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 the following weight-based dose regimen is authorised in the paediatric population:

*In children/adolescents whose body weight is up to 70 kg*
Initiated at a total daily dose of approximately 0.5mg/kg. This dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance dose is approximately 1.2mg/kg/day (depending on the patient's weight and available dosage strengths).

*In children and adolescents whose body weight is over 70 kg*
Initiated at a total daily dose of 40mg. This dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance dose is 80mg and the maximum recommended total daily dose is 100mg.

## 2.2 Attention Deficit - Hyperactivity Disorder (ADHD)

### 2.2.1 Epidemiology

ADHD is the most common and most studied neurobehavioural disorder of childhood. ADHD is defined by 'core' signs of inattention, hyperactivity, impulsiveness and is commonly co-morbid with disorders such as oppositional defiant and conduct disorders, learning disorders, anxiety, depression, tic disorders and Tourette's syndrome. Prevalence rates across different cultures and countries are between 2% and 5% of children. It is estimated that boys are between three and five times more likely to have ADHD than girls. However, this may be biased due to the greater prevalence of behavioural and conduct problems in boys, leading to a higher referral rate. The diagnostic criteria for ADHD in DSM-IV and ICD-10 are similar with differences relating primarily to symptom severity and pervasiveness.

ADHD is commonly noticed at the age of 5 years, often when the disruptive behaviour becomes apparent in the classroom situation. It is thought that ADHD has a significant genetic component. For example, a family with one child with ADHD has a 30-40% chance that another sibling will have the disorder and a 45% or greater chance that at least one parent has the disorder. Concordance for ADHD in monozygotic twins is approximately 90%.

Other research has suggested that in a small percentage of cases ADHD may be linked to injury during development to specific regions of the brain, for example premature delivery with associated minor brain bleeding or accidental head injury after birth, could all cause ADHD-like symptoms. ADHD has not been associated with purely social

factors such as family stress or excessive TV watching although these can exacerbate a pre-existing condition.

Treatment needs to be individualised and involves psychological, educational and social measures as well as pharmacological interventions. Psychostimulants are generally considered the first line of drug treatment for the core symptoms of confirmed ADHD. The psychostimulants available in the UK for the treatment of ADHD are methylphenidate, and dexamphetamine.

The UK National Institute for Health and Clinical Excellence (NICE) is the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health. NICE is currently developing a guideline on ADHD with the remit to "prepare a guideline for the NHS in England and Wales on the effectiveness of methylphenidate and other pharmacological and psychological interventions in combination or separately for the treatment of Attention Deficit Hyperactivity Disorder". This guideline will apply to children, young people and adults.

### 2.2.2 The benefits of treating ADHD

Children with severe ADHD can develop poor self-esteem, emotional and social problems, the consequences of which can be serious for themselves, their family and for society. ADHD can also have a severe effect on a child's education.

The signs of ADHD may persist into adolescence and adulthood, and may be associated with continuing emotional and social problems, unemployment, criminality and substance misuse.

Current treatments for ADHD include a range of social, psychological and behavioural interventions, dietary interventions (in cases where particular foods can be linked with onset of hyperactivity), and drug treatment (e.g. methylphenidate, dexamphetamine, atomoxetine).

However, there remains some controversy surrounding the 'medicalisation' of 'naughty behaviour' and thus with drug treatment of ADHD.

## 3.0 DATA CONSIDERED

The following data are considered in this risk:benefit assessment:

- Pre-clinical data
- Clinical data
  - Clinical trial data (MRP assessment report and MAH meta-analyses)
  - Post-marketing data: studies, usage data, spontaneous ADR reports, PSUR data
  - Published literature
- Observational data

Some of these data have previously been assessed as part of the current second-wave Mutual Recognition Procedure (UK/H/686/01-06/E01) (e.g. preclinical studies, clinical efficacy studies). Therefore this assessment report on the balance of risks and benefits of Strattera in ADHD will provide an overview of the data previously considered in the MRP. For more detailed discussions of the data, the repeat use MRP assessment report (dated 8th June 2005) is attached at Annex 2. Readers will be referred to the appropriate sections of Annex 2 where relevant. New and previously un-assessed data will be considered in greater depth in this assessment report.

## 4.0 USAGE DATA

The MAH estimates that the post marketing patient exposures for atomoxetine from 26 November 2002 through 26 August 2005 is estimated to be 3,429,000 patients worldwide.

Table 1 lists the demographics of the patients in the United States market, which accounts for more than 95% of the total patient exposure for atomoxetine worldwide.

**Table 1. Demographics of United States Patient Exposure to Atomoxetine**

| Age Grouping | TOTAL | MALE | FEMALE |
|---|---|---|---|
| 0-5 | 2.2% | 71.5% | 28.5% |
| 6-12 | 42.1% | 71.4% | 28.6% |
| 13-17 | 22.3% | 71.1% | 28.9% |
| 18-64 | 32.7% | 50.8% | 49.2% |
| 65+ | 0.6% | 45.1% | 54.9% |
| n/a | 0.1% | 58.2% | 41.8% |
| **Total** | **100%** | **64.5%** | **35.5%** |

Table 2 below lists the EU usage of atomoxetine by country.

**Table 2. EU Usage Data estimates from MAH**

| Country | Patients |
|---|---|
| UK | 14,100 – 14,600 |
| Germany | 10,130 |
| Netherlands | 1,300 |
| Norway | 2,500 – 2,900 |

**Assessor's comments:** The algorithm used by the MAH to estimate the number of patients exposed to atomoxetine is likely to result in an overestimate. This is due to the relatively low estimate of daily dose used (40mg), the difficulty in identifying how many patients have shared care between hospital specialist and community physician and the use of the latest monthly sales figures to estimate usage in the previous months.

The data used to estimate UK patient numbers were based on the number of kilograms

dispensed in hospital and retail pharmacies in the UK in July 2005. This represents a maximum usage level for atomoxetine and therefore will over-estimate the number of patients exposed since launch. This over-estimate will be further compounded by the underestimate of the daily dose which Lilly now estimate to be about 47mg and the potential for 'double counting' of patients who start therapy in hospital and are then continued in primary care.

The MAH comments that patients in the UK are almost exclusively treated and prescribed in secondary care. However, part of the pharmacovigilance plan involves a prescription event monitoring study which is based exclusively in primary care.

# 5.0 BENEFIT EVALUATION

## 5.1 Data assessed in the repeat use Mututal Recognition Procedure (MRP) Assessment Report

The clinical efficacy of atomoxetine is discussed in detail in the repeat use assessment report for the second-wave Mutual Recognition Procedure (Annex 2).

Table 3 below provides a summary of the controlled studies designed to assess the efficacy of atomoxetine (numbers enrolled into each treatment group in brackets).

**Table 3. Controlled studies designed to assess the efficacy of atomoxetine.**
***Short Term Controlled Studies***

| Trial | Treatment Groups | Description |
|---|---|---|
| ***Paediatric*** | | |
| **HFBD** | ATX (65) Vs. PBO (62) Vs. MPH (20, for study design validation purposes) | Exploratory 9 week, randomised, double-blind, placebo-controlled study in children/adolescents dosed twice daily, assessed primarily in the home setting. |
| **HFBK** | ATX (64) Vs. PBO (62) Vs. MPH (18, for study design validation purposes) | Exploratory 9 week, randomised, double-blind, placebo-controlled study in children/adolescents dosed twice daily, assessed primarily in the home setting. |
| **LYAC** | 0.5 (44), 1.2 (84), 1.8 (85) mg/kg/day ATX Vs. PBO (84) | Dose finding study. 8 week randomised, double-blind, placebo-controlled dose-response study (twice daily dosing) in children/adolescents, assessed primarily in the home setting. |
| **LYAT** | ATX (85) Vs. PBO (86) | 6 week phase III randomised, double-blind, placebo-controlled study in children /adolescents dosed once daily. Home setting. |
| **LYBG** | ATX (133) Vs. PBO (64) | 8 week phase III randomised, double-blind, placebo-controlled study in children/ |

| | | |
|---|---|---|
| | | adolescents dosed once daily. Home setting. |
| **LYAW** | ATX (101) Vs. PBO (52) | 7 week phase III randomised, double-blind, placebo-controlled study in children/ adolescents dosed once daily. School setting. |
| **LYAS** | ATX (76) Vs. PBO (72) | 18 week, double-blind, placebo-controlled study to assess non-inferiority between atomoxetine and placebo in tic severity in patients with ADHD and comorbid tic disorder. |
| **LYBI** | ATX Vs. PBO Vs. Concerta | Short-term, randomised, double-blind, study in paediatric patients with ADHD comparing atomoxetine with placebo control and slow release methylphenidate (Concerta). |
| ***Adults*** | | |
| **LYAA** | ATX (141) Vs. PBO (139) | 10 week, randomised, double-blind, placebo-controlled study in adults. |
| **LYAO** | ATX (129) Vs. PBO (127) | 10 week, randomised, double-blind, placebo-controlled study in adults. |

***Long Term Placebo Controlled Studies (Paediatrics only)***

| Trial | Treatment Groups | Description |
|---|---|---|
| **LYAF** | ATX (292) Vs. PBO (124) | Placebo-controlled, long-term relapse prevention discontinuation study (following a 10 week open label atomoxetine period) in children and adolescents. |
| **HFBE** | ATX (59) Vs. PBO (20) | Placebo-controlled, long-term relapse prevention discontinuation study (following a 10 week open label atomoxetine period) in children and adolescents. |

Abbreviations: ATX = atomoxetine; PBO = placebo; MPH = methylphenidate

A further seven open-label studies were submitted in support of the MRP. Studies HFBF, LYAI and LYAR are open-label extension studies for eligible patients who had participated in a previous acute atomoxetine study.

### 5.1.1 Short-term efficacy studies

*Twice Daily Dosing (Paediatrics)*

Three pivotal trials evaluated the acute efficacy of twice daily dosing. These were the (only) dose-finding study LYAC (ATX 0.5, 1.2, 1.8mg/kg/day and placebo) and studies HFBD and HFBK. Studies HFBD and HFBK were identical to each other in design and included three treatment groups - flexible ATX, placebo and MPH (Annex 2).

The results of the dose-finding study LYAC, showed that atomoxetine 1.2 and 1.8 mg/kg/day were both clinically and statistically significantly superior to placebo in the

primary efficacy analysis, on both the inattention and hyperactivity-impulsivity subscales, and on a number of the secondary endpoints including responder analyses.

However, 0.5mg/kg/day atomoxetine was not statistically significantly superior to placebo. In addition, there was no evidence of any additional benefit from increasing the dose from 1.2 to 1.8mg/kg/day. Study LYAC shows evidence of a dose-response with the steep part of the curve at around 0.5mg/kg/day and the response plateau after 1.2mg/kg/day.

Questions regarding the dosing and posology were raised at the time of the initial MRP assessment and were resolved at that time. The current SPC for Strattera clearly states that for children and adolescents up to 70kg in body weight, Strattera should be initiated at a total daily dose of approximately 0.5mg/kg. The initial dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance dose is approximately 1.2mg/kg/day (depending on the patient's weight and available dosage strengths of atomoxetine) and that no additional benefit has been demonstrated for doses higher than 1.2mg/kg/day.

The results of HFBD and HFBK confirm the statistically significant effect of atomoxetine relative to placebo in the primary efficacy endpoint and the responder analysis. Atomoxetine was found to be statistically significantly superior to placebo on some but not all of the secondary endpoints in HFBD and HFBK. There was no evidence of rebound effects following abrupt discontinuation of study medication in these studies.

*Once Daily Dosing (paediatrics)*

Studies LYAT, LYBG and LYAW were short-term once-daily dosing trials. None of these studies were dose finding studies. Studies LYBG (0.8-1.8mg/kg/day ATX) and LYAW are of particular interest since LYBG assessed both morning and evening efficacy and LYAW assessed the efficacy of atomoxetine in the school setting. Further details and discussion of these studies can be found in Annex 2.

In all three studies atomoxetine was shown to be clinically and statistically superior to placebo in the primary endpoint, ADHD symptoms on the ADHDRS-IV-Parent:Inv Total score (ADHDRS-IV-Teacher:Inv Total score for LYAW) and also on the Inattention and Hyperactivity-Impulsivity subscales.

In study LYBG, atomoxetine was statistically significantly superior to placebo on evening and morning ADHD symptoms.

The results of study LYAW indicate that the acute efficacy of a once-daily dose of atomoxetine appears to be transferable to the school setting.

*Combined results of Short term Paediatric Efficacy Studies*

The six short-term studies (LYAC, HFBK, HFBD, LYAT, LYBG, and LYAW) were pooled for an overall assessment of short-term efficacy of atomoxetine. The results of the pooled analysis confirm the effects observed in the individual studies.

### 5.1.2 Long-term efficacy studies

The long-term efficacy of atomoxetine in children and adolescents with ADHD was evaluated in two placebo-controlled long-term relapse prevention discontinuation studies (LYAF and HFBE).

The results of study LYAF provide compelling evidence for efficacy of long-term treatment. After 1 year of atomoxetine treatment, patients continuing for a further 6 months with treatment rather that switching to placebo were statistically significantly less likely to relapse or experience partial symptom return as demonstrated by the 52-week relapse prevention data.

A low relapse rate on placebo (approx. 12%) was observed in the extension phase and this raised a further issue for consideration. As the majority of patients continuing on placebo did not experience a relapse in the 6 months following the second randomisation, it is credible that a number of patients might be able to discontinue treatment at some point. Appropriate information on the proportion of patients relapsing at 1 year (active and placebo) has been added to section 5.1 of the SPC and section 4.4 includes suitable advice on monitoring requirement for continued long term treatment.

HFBE is a second relapse prevention study. The primary efficacy endpoint showed no difference from placebo, thus HFBE is considered a failed study. The MAH stated that "because of a number of potentially confounding factors and problems with the study design that were not identified before implementation, the results of this study cannot be definitively interpreted with respect to the efficacy". Study HFBE was a Phase II exploratory study which was conducted prior to finalising the design of the larger Phase III study LYAF.

It was concluded that study LYAF provides clear evidence of efficacy of atomoxetine for medium to long term treatment and that this evidence is adequate despite the failure of study HFBE. The failure of this study is discussed further in Annex 2.

### 5.1.3 Subgroup Analyses from the Combined Paediatric Efficacy Data Set

Data from the acute placebo-controlled paediatric and adult studies and from the two open-label studies that included both poor CYP2D6 metabolisers (PMs) and extensive metabolisers (EMs) (Studies LYAB and LYBB) were combined for the purpose of subgroup analyses.

The following subgroup analyses were performed: ADHD subtypes, EM Vs PM, Dosing frequency, age<12 and ≥12, gender, race, previous stimulant exposure, and co-morbid Oppositional Defiant Disorder.

Statistically significant interactions on the effects of atomoxetine were identified for the different ADHD subtypes and between CYP2D6 extensive metaboliers and poor metabolisers (Annex 2).

The interaction identified for ADHD subtypes (Combined subtype Vs Hyperactive/Impulsive or Inattentive subtypes) is considered to be of little consequence since a beneficial effect was seen in all subgroups - only the magnitude of the treatment effect differed (statistically significant greater improvement seen in the Combined subtype).

A statistically significant greater mean improvement in ADHD symptoms was seen in the PM subgroup compared with the EM subgroup. However, as only 16 patients were included in this analysis this result should be interpreted with caution.

### 5.1.4 Clinical Studies in Special Populations (LYAS)

Study LYAS was an acute, double-blind, placebo-controlled study in patients with ADHD and co-morbid tic disorder (Tourette's Disorder or chronic motor tic disorder).

The results of the study demonstrated formal non-inferiority of atomoxetine compared with placebo in terms of tic severity. Atomoxetine was found to be statistically significantly superior to placebo when only the data from patients with Tourette's syndrome were analysed. This result should be interpreted with caution since it was a secondary analysis, however this result does contrast with stimulants which are contraindicated in Tourette's syndrome due to exacerbation of tics.

### 5.1.5 Active Comparator Phase III Study LYBI

Study LYBI is a three way acute treatment study with placebo and active comparators. Data from this study indicate that the efficacy of atomoxetine might be a little less than that of methylphenidate, however this was not considered to be a serious deficiency in the overall evidence of efficacy for atomoxetine (Annex 2).

Further active comparator data are available in the Phase II studies HFBD and HFBK. However, these studies were unable to provide any confirmatory evidence of relative efficacy with methylphenidate due to insufficient numbers of patients treated with methylphenidate.

## 5.2 Additional Data Submitted by the MAH (submitted 14 October 2005)

### 5.2.1 Comparative Efficacy

Since the MAA submission a total 5 studies (LYAU, LYAV, LYBI, LYBM, LYBR) have been completed in which comparative efficacy of atomoxetine with methylphenidate is studied. There is also an ongoing study (LYBU). The results of one of the completed studies (LYBI) were submitted as part of the responses to the MAA (February 2004). Due to the small number of patients included in the studies and their primary objectives very limited information on comparative efficacy can be obtained from studies LYAU, LYAV and LYBM.

**Study LYBR**

Comment on Efficacy Data from LYBR

This was a randomised, double-blind, multicentre (13) comparison of atomoxetine hydrochloride (Strattera, 0.8 mg/kg/day to 1.8 mg/kg/day) and methylphenidate hydrochloride (0.2 mg/kg/day to 0.6 mg/kg/day) in paediatric outpatients with DSM-IV ADHD.

Description of Trial Design

The trial aimed to demonstrate non-inferiority between the two active treatments on ADHD symptoms following a treatment period of 8 weeks. The trial also included a 5-33 day washout period prior to randomisation and a discontinuation phase following randomised treatment of approximately 1 week. Primary assessment was based on ADHD rating scale IV Parent version: Investigator Administered and Scored. Response was defined as at least a 40% reduction from baseline at endpoint. Secondary efficacy measures included the Conners' Parent Rating Scale Revised: Short-Form and the Clinical Global Impressions ADHD Severity Scale.

One-sided and two-sided exact 95% confidence intervals were generated for the primary hypothesis test comparing the proportion of responders on the primary endpoint. Non-inferiority was declared if the lower confidence limit of the one-sided interval was greater than -18%. In addition, treatment effects were evaluated using repeated measures analysis and totals / subtotals of efficacy rating scales, analysed by calculating the change from baseline to endpoint and ANCOVA (using LOCF). The primary analysis population comprised subjects having taken at least one dose of study medication, had both baseline and post-baseline score and had no more than one interval of non-compliance. Fourteen randomised patients were excluded from the primary population.

Subjects were required to be children of 6-16 years of age who met DSM-IV criteria for ADHD (any subtype) according to investigator assessment. Cut-off scores on ADHDRS-IV-Parent:Inv were required to be ≥25 for boys and ≥22 for girls (or >12 for a specific subtype) as well as CGI-ADHD-S score ≥4 at both Visit 1 and Visit 2. Subjects with history of bipolar I or II disorder, psychosis or pervasive developmental disorder, subjects

at serious suicidal risk, subjects with Tourette's (or family history thereof) or motor tics were excluded. It is noted that only 3 subjects classified as poor CYP2D6 metabolisers were included in the study.

A total of 330 patients were randomised to treatment, 164 to atomoxetine hydrochloride (AT) and 166 to methylphenidate hydrochloride (MT). Of these patients, 138 completed the trial on AT and 152 on MT. The differential rates of withdrawal were due to an excess of withdrawals due to adverse event on AT (18 vs 6, p=0.011). Patients were predominately male, Asian, without prior stimulant-exposure and with mean age of 9.65 years. Compliance was similar in both treatment groups throughout the study.

The primary efficacy endpoint compared the ADHDRS-IV-Parent:Inv Total Score in compliant subjects (a type of per-protocol population). Response rates of 77.4% for AT and 81.5% for methylphenidate give a 1-sided lower bound of -11.7 and a two-sided confidence interval for the difference between treatments of (-13.2, 4.9), p=0.405 from Fisher's exact test). Results in the 'All randomised patients population' are similar, AT=75.9%, MT=81.1%, two-sided 95% interval (-14.2, 3.9), p=0.282. Differences between treatments were similar regardless of age, ADHD subtype, gender and previous stimulant use.

Assessor's Comments on Trial Methodology

- The external validity of the trial should be considered.
    - A dose of 1.8mg/kg/day AT was permitted at discretion of investigator. This is not in line with the UK SmPC. The mean final prescribed daily dose (mg/kg) was 1.37 for AT (range 0.57 – 2.11) and 0.52 for methylphenidate. There was, previously, insufficient evidence of dose-response to conclude that the 1.8 mg/kg dose had a favourable risk; benefit profile. Nevertheless, the trial results may not be applicable to the UK, in particular if efficacy is increased at this dose,
    - The trial was conducted in China, Korea and Mexico. This raises concerns with regards trial conduct or 'type' of patient. As well as possible ethnic differences there are big cultural differences in the way ADHD is managed and we would need the company to review what is in the literature about such differences.
- The choice of delta is inadequately justified. The approach taken is to assess the historical differences observed between methylphenidate and placebo and to choose delta as a proportion of that difference. It is argued that excluding differences greater than delta would, therefore, indicate indirect superiority to placebo. This is a reasonable approach for a Phase III confirmatory trial aiming to establish absolute evidence of efficacy (though the variability of the estimated difference between methylphenidate and placebo should have been taken into account). However, it is not necessarily an appropriate basis on which to draw the conclusions on relative efficacy, in particular that the effects of the two treatments are 'similar' or 'non-inferior'. This requires that the confidence interval for the difference between the treatments exclude all differences of clinical importance. It is not clear that a lower confidence bound of the preferred two-sided 95% interval: -13.2% (-14.2 in the 'All randomised patients population') achieves this. Furthermore, a number of concerns

remain over the construction of this confidence interval. The differences between the treatments might be greater than portrayed. In particular:

  - The handling of patient withdrawals in the primary analysis is unclear. It would probably be appropriate to treat them as non-responders regardless of response whilst on treatment. This is of particular importance given the differential rate of withdrawal.
  - The construct of the primary analysis population is questioned. The rationale for including a 'per-protocol' type analysis population is that differences between treatments may be minimised in the 'All randomised patients population' because of the 'noise' introduced by protocol violators. It is not clear that sufficient exclusions were made such that any difference between treatments could be observed in the primary analysis population.

- The absence of placebo complicates the assessment of assay sensitivity. However, notwithstanding the above concerns, given that the efficacy exhibited by the two treatments is of similar magnitude to other studies of atomoxetine and methylphenidate in similar patient populations, this is likely of no concern.
- There are a number of concerns with the secondary analyses, including the use of LOCF, the pooling of centres and the absence of the stratification variable in the relevant statistical models (this is also relevant for the primary analysis).
- It is not clear why the SAP was completed 3 months after last patient completed the study. However, the major details of the statistical approach are included in the trial protocol, which is reported not to have been amended since prior to the commencement of the study.
- The trial report describes the number of Lilly personnel who were unblinded to treatment allocation prior to study completion as a 'minimum'. It is unclear to whom this pertains and how many personnel are covered by 'minimum'.
- There appears to be a treatment by country interaction with patients in Korea responding to methylphenidate more frequently than patients on atomoxetine. This is not of major concern.

Overall Conclusions on LYBR

Generally, the study appears to be of reasonable quality. However, it is not clear that a conclusion of non-inferiority is supported or, indeed, that the trial results are relevant to the UK use of Strattera. A number of questions remain outstanding and some re-analyses may be desirable. In particular, the dose of Strattera used is higher than that licensed in the UK and, whilst AT is clearly effective, it is questionable whether differences of -13 / -14% in response rate can be deemed clinically irrelevant.

**Assessor's Comments- Clinical Efficacy**

Evidence of efficacy of Strattera in children and adolescents with ADHD has been clearly established. The MAH has conducted a large number of trials which evaluated

once-daily and twice-daily dosing, long term efficacy (through randomised withdrawal designs) and tested atomoxetine in each relevant age group.

The validity of the study populations, diagnostic criteria, exclusion criteria, treatment regimens, primary efficacy measures, definition of response to treatment and secondary efficacy and quality of life measures are discussed in Annex 2. Sufficient evidence was provided by the MAH at the time of the MRP to adequately validate/justify the tools used in the studies.

Due to the small number of patients included in the studies and their primary objectives, very limited information on comparative efficacy can be obtained from studies LYAU, LYAV and LYBM. Study LYBR was multi-centre, randomised, double-blind study comparing the safety and efficacy of atomoxetine and methylphenidate in 330 children. Whilst this study has limitations and design/analysis issues that mean it is not completely applicable to the use of atomoxetine in the EU (patient population is predominantly Asian plus Mexico) which might not be directly comparable to a typical EU population. it does support what has been seen previously in that there is trend in favour of greater efficacy for methylphenidate. It is recommended that further large, well-designed studies are warranted to help clearly establish the comparative efficacy of atomoxetine to alternative treatment for ADHD.

Of note (in particular given the new signal of increased suicidal behaviour associated with the use of atomoxetine in children with ADHD), co-morbid conditions including depression and anxiety disorders (including generalised anxiety disorder, panic disorder, and social phobia) were not exclusion criteria in the paediatric studies and this was considered appropriate given that it is representative of the population likely to receive atomoxetine in clinical practice. However, the number of patients with co-morbid psychiatric disorders in the trials was relatively low. Patients who were considered to be at serious suicidal risk and those with current or a previous history of bipolar depression were excluded from the trials.

# 6.0 RISK EVALUATION

Section 6.0 of this risk:benefit assessment first considers safety data for atomoxetine (section 6.1) and secondly considers safety data for two other products authorised for the treatment of ADHD, methylphenidate and dexamphetamine (section 6.2).

Section 6.1 (atomoxetine) includes an overview of pre-clinical and clinical trial data for atomoxetine which was available at the time of authorisation, UK spontaneous adverse event reports, and data from the most recent PSUR for atomoxetine (covering the period 27 November 2004 – 26 May 2005). In addition, four key safety issues were identified suicidal thoughts/behviour and other psychiatric adverse events, hepatobiliary adverse events, seizures and cardiac adverse events (in particular QTc interval prolongation). Cumulative reviews of these four issues (inlcuding pre-clinical, clinical trial, spontaneous reporting data and observational data) have been assessed and an overview of the data is included in section 6.1.5 below. The full assessment of these issues can be found in Annex 4 (psychiatric disorders), Annex 6 (hepatobiliary disorders), Annex 7 (seizures) and Annex 8 (cardiac disorders).

Section 6.2 discusses the safety profiles of methylphenidate and dexamphetamine.

## 6.1 Overall Safety Profile of Atomoxetine

### 6.1.1 Pre-clinical data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenicity, or reproduction and development (see repeat use MRP assessment report, Annex 2).

### 6.1.2 Clinical Trial data

The repeat use MRP assessment report discusses the safety and tolerability data from clinical trials for atomoxetine in some detail (Annex 2). This section provides a brief overview of the main findings. Annex 9, the Summary of Product Characteristics for atomoxetine, also provides information on adverse events from clinical trials for the drug since Section 4.8 (Undesirable Effects) of the SPC is based upon the findings of both paediatric and adult clinical trials.

The safety of atomoxetine was evaluated in 15 paediatric clinical studies and 3 clinical studies in adults with a DSM-IV diagnosis of ADHD. A total of 3262 children and adolescents were exposed to at least one dose of atomoxetine (1704 for more than 6 months, 1236 more than 1 year, and 425 more than 2 years). A total of 478 adults were exposed to atomoxetine (236 for longer than 6 months, and 173 for more than a year). A total of 238 poor metaboliser paediatric patients (7.3% of the total – comparable to the number of PMs in the general population), and 30 adult poor metabolisers were studied.

These data are further supported by data from clinical pharmacology studies (>300 adults), 1 abuse-potential study, and 10 historical depression and urinary incontinence studies (>1200 adults).

Common treatment-emergent events seen in the paediatric population (acute efficacy studies) that were reported statistically significantly more frequently in atomoxetine treated (N=657) than in placebo-treated (N=408) patients were: Upper abdominal pain (18% Vs 12.5%), Decreased appetite (16.1% Vs 5.6%), Vomiting (11.4% Vs 5.6%), Somnolence (10.0% Vs 4.2%), Irritability (7.2% Vs 4.2%), Fatigue (6.5% Vs 3.4%), Dizziness (5.2% Vs 2.0%), Dyspepsia (4.7% Vs 1.2%), Decreased weight (2.4% Vs 0.0%), Anorexia (2.1% Vs 0.5%), Mood swings (2.1% Vs 0.5%), Early morning awakening (1.2% Vs 0%), and Mydriasis (1.2% Vs 0%). Subgroup analysis of age, sex and racial origin did not reveal any differences in tolerability and during long-term treatment, reporting rates for most adverse events declined. The pattern of adverse events was similar to acute treatment and there was no evidence of unexpected, late-occurring events.

In summary, the clinical trial data indicate common gastrointestinal and CNS effects in both children and adults. Vasovagal attacks and syncope were noted as a potential safety issue. Genitourinary effects were also apparent as well as effects on blood pressure and heart rate which are predictable from the known noradrenergic effects of atomoxetine. The effects on blood pressure and heart rate however, were noted to be less marked than those produced by methylphenidate. .

Other effects of atomoxetine noted during clinical trials were an initial modest weight loss. Atomoxetine was not associated with adverse effects on hepatic or other laboratory parameters or cardiac depolarisation (QT interval). No evidence of withdrawal reactions or abuse potential was observed.

It was concluded at the time of licensing from review of the clinical trial reports that psychiatric adverse events did not appear to occur more frequently in patients treated with atomoxetine compared with placebo and that a review of these events indicated that it was more likely related to the underlying disorder than atomoxetine. Depression and generalised anxiety however, were numerically more frequently reported in poor metabolisers and the SPC reflects this.

### 6.1.3 UK Spontaneous Reporting Data for Atomoxetine

Up to 3 October 2005 a total of 173 reports of 471 reactions have been received in the UK in association with atomoxetine. None of these reports had a fatal outcome. The majority of the reported reactions (76%) belong to the following five system organ classes (SOCs) - Psychiatric disorders, Gatrointestinal disorders, Nervous system disorders, General disorders, and Investigations.

Overall the most commonly reported reactions include nausea (n=29), vomiting (n=29), headache (n=24), aggression (n=23), dizziness (n=12), weight decreased (n=10).

*Psychiatric disorders*
The most commonly reported psychiatric disorders are listed in the table below.

| Reaction | Number of reports |
|---|---|
| Aggression | 23 |
| Anxiety | 8 |
| Tic | 8 |
| Suicidal ideation | 8 |
| Agitation | 7 |
| Depressed mood | 7 |
| Insomnia | 7 |
| Tearfulness | 6 |
| Mood swings | 6 |
| Depression | 5 |
| Irritability | 5 |
| Abnormal behaviour | 5 |

*Suicide attempts/ suicidal ideation*
A total of 8 reports of suicidal ideation and 2 reports of suicide attempt have been received. In addition there has been 1 report of suicidal depression and 1 report of intentional overdose.

Using the MedDRA Higher Level Term 'Suicidal and self-injurious behaviour', the combined Proportional reporting ratio (PRR) for the reports of suicidal ideation (n=8) and suicide attempt (n=2) was calculated. The PRR is a measure of the disproportionality of reports for a particular event for a drug of interest versus all other drugs in the database. A value less than 1.0 indicates that the proportion or number or events is less than expected based on all other reports in the database. A value greater of 1.0 indicates a greater than expected proportion or number of events. The UK PRR for the HLT 'Suicidal and self-injurious behaviour' is 10.98 with a chi-squared value of 80.67.

These cases are discussed in the MAH's cumulative review of suicidal behaviour in section 6.1.5.3 below and Annex 4.

*Overdose*
There has been 1 report of intentional overdose. This case is discussed in the MAH's review of suicidal behaviour in section 6.1.5.3 below and Annex 4.

*Gastrointestinal disorders*
A total of 80 reports of gastrointestinal disorders have been received. The most commonly reported reactions were: nausea (n=29), vomiting (n=29), abdominal pain (n=9), and upper abdominal pain (n=3). All of these reactions are recognised for atomoxetine and are listed in the product information.

*Nervous system disorders*

The most commonly reported reactions in this SOC are headache (n=24), dizziness (n=12), epilepsy/convulsions/simple partial seizures (n=6), somnolence (n= 5), and syncope (n=4). Headache, dizziness and somnolence are listed adverse effects of atomoxetine. Convulsions are discussed further in section 6.1.5.4 below and also in Annex 6.

*General disorders*
The most commonly reported reactions in this SOC are 'feeling abnormal' (n=8), fatigue (n=4), chest pain (n=4), malaise (n=3), influenza-like illness and condition aggravated (n=3). There is also one report of drug withdrawal syndrome. Fatigue and influenza-like illness are recognised reactions and are listed in the product information for atomoxetine.

*Investigations*
A total of 28 reports are included in the Investigations SOC. These are: weight decreased (n=10), heart rate increased (n=3), blood alkaline phosphatase increased (n=3), blood bilirubin increased (n=3), and liver function test abnormal (n=3). There were also reports of blood pressure increased (n=2), weight increased (n=2), aspartate aminotranferase increase (n=1) and urine analysis abnormal (n=1). Weight decreased, tachycardia, abnormal liver function tests and increased blood pressure are recognised adverse effects of atomoxetine.

The following suspected adverse reactions have not been commonly reported in the UK but are included to allow comparison with methylphenidate and dexamphetamine.

*Drug dependence/abuse*
There have been no cases of drug dependence or drug abuse. There has been one report of Drug withdrawal syndrome in which the patient experienced highly disturbed behaviour and suicidal thinking on withdrawal of atomoxetine and recovered within 2 hours of restarting. This patient had a history of depression/ suicidal behaviour and also of bi-polar disorder.

*Hepatic disorders*
A total of 5 reports of hepatic disorders have been received. These are 4 reports of jaundice, and 1 report of liver disorder. Liver injury associated with atomoxetine has previously been reviewed in detail which resulted in the addition of 'abnormal liver function tests', 'jaundice' and 'hepatitis' to the SPC in January 2005. An updated review of hepatic adverse events has been provided by the MAH in the most recent PSUR. The review of January 2005 is included in Annex 5. An overview of the updated cumulative review covering the period 26 November 2002 – 26 May 2005 is provided in Section 6.1.5.2 of this report below.

*Cardiac disorders*
A total of 13 reports of cardiac disorders have been received. The most commonly reported reactions in this SOC are tachycardia (n=6), palpitations (n=5), arrhythmia (n=1), and cyanosis (n=1). Tachycardia and palpitations are recognised reactions and are listed in the atomoxetine SPC.

*Blood and lymphatic disorders*

The reported reactions in this SOC include neutropenia (n=5), leukopenia (n=1), lymphopenia (n=1), and thrombocytopenia (n=1). These are not recognised adverse effects of atomoxetine. Blood and lymphatic disorders are discussed in the most recent Periodic Safety Update Report (PSUR) for atomoxetine covering the period 27 November 2004 – 26 May 2005, which is attached at Annex 3.

### 6.1.4 Data from the most recent Periodic Safety Update Report (covering the period 27 November 2004 – 26 May 2005)

This report provides an overview of the spontaneous adverse event reports, studies and literature reports from the most recent PSUR for atomoxetine (covering the period 27 November 2004 to 26 May 2005).

The key issues identified from the PSUR data which are most relevant to the risk:benefit assessment of atomoxetine are highlighted and discussed in this section. These issues are: suicidal behaviour, hepatotoxicity, seizures and cardiovascular adverse effects including QT interval prolongation, Raynaud's phenomenon, reports of lack of efficacy, reports of drug abuse, drug withdrawal reactions, adverse events reported with long term use (>12 months) and an analysis of reports according to special patient population groups. The remaining reported adverse events are discussed in the relevant system organ classes in the main overview of the PSUR in Annex 3 of this report.

**Overview of all reports received during the reporting period**
For the purpose of this PSUR, where reports of reactions affecting more than one system organ class (SOC) have been received, the MAH has assigned the report to the SOC of the most clinically significant serious reaction (primary reaction). The other reactions in the case report are listed in the SOC of the primary reaction so that cases only appear once in the line listing. In addition, a summary of all of the reported reactions for each SOC is provided in which each reaction is listed in its relevant SOC independently of other reactions that may have been reported in the case.

A total of 1020 reports were received worldwide during the period covered by the report (estimated patient exposure for the same period is 1,272,000 patients). Of these 1020 reports, 1012 were spontaneous reports (24 from Regulatory Authorities), 7 reports from clinical trials and 1 report from a post-marketing study.

There were 7 fatal cases: 2 Cardiac Disorders; 2 General Disorders and Administration Site Conditions; 1 Hepato-biliary Disorder; and 2 Psychiatric Disorders.

There were 187 serious cases reported during the period covered by the PSUR. The most frequently reported serious cases fell into the following SOCs: Cardiac Disorders (14), Gastrointestinal disorders (19), Hepato-biliary disorders (13), Investigations (21), Nervous System Disorders (38), Psychiatric Disorders (43).

Table 4 below summarises the number of cases in each System Organ Class (SOC) for the six month period covered by this PSUR and compares it to the six month period covered by the preceding PSUR.

## Table 4. Reported cases for atomoxetine

| System Organ Class | Current Period (27 Nov 2004 through 26 May 2005) | | | | | Previous Period (27 May 2004 through 26 Nov 2004) | |
|---|---|---|---|---|---|---|---|
| | Fatal Cases | Total Serious Cases | Non-Serious Cases | Total Cases Serious & Nonserious | Frequency (%) | Total Cases (Serious & Nonserious) | Frequency (%) |
| Blood and lymphatic system disorders | 0 | 2 | 1 | 3 | 0.3% | 2 | 0.2% |
| Cardiac disorders | 2 | 14 | 29 | 43 | 4.2% | 40 | 3.6% |
| Congenital and familial/genetic disorders | 0 | 0 | 1 | 1 | 0.1% | 3 | 0.3% |
| Ear and labyrinth disorders | 0 | 0 | 2 | 2 | 0.2% | 4 | 0.4% |
| Endocrine disorders | 0 | 0 | 0 | 0 | 0% | 0 | 0% |
| Eye disorders | 0 | 3 | 28 | 31 | 3.0% | 27 | 2.4% |
| Gastrointestinal disorders | 0 | 19 | 114 | 133 | 13.0% | 126 | 11.4% |
| General disorders and administration site conditions | 2 | 9 | 43 | 52 | 5.1% | 61 | 5.5% |
| Hepato-biliary disorders | 1 | 13 | 4 | 17 | 1.7% | 3 | 0.3% |
| Immune system disorders | 0 | 0 | 1 | 1 | 0.1% | 6 | 0.5% |
| Infections and infestations | 0 | 1 | 6 | 7 | 0.7% | 7 | 0.6% |
| Injury and poisoning | 0 | 2 | 13 | 15 | 1.5% | 15 | 1.4% |
| Investigations | 0 | 21 | 165 | 186 | 18.2% | 112 | 10.1% |
| Metabolism and nutrition disorders | 0 | 2 | 3 | 5 | 0.5% | 13 | 1.2% |
| Musculoskeletal, connective tissue and bone disorders | 0 | 3 | 7 | 10 | 1.0% | 9 | 0.8% |
| Neoplasms benign and malignant (including cysts and polyps) | 0 | 0 | 0 | 0 | 0% | 1 | 0.1% |
| Nervous system disorders | 0 | 38 | 88 | 126 | 12.4% | 139 | 12.6% |

(continued)

| System Organ Class | Current Period (27 Nov 2004 through 26 May 2005) | | | | | Previous Period (27 May 2004 through 26 Nov 2004) | |
|---|---|---|---|---|---|---|---|
| | Fatal Cases | Total Serious Cases | Non-Serious Cases | Total Cases Serious & Nonserious | Frequency (%) | Total Cases (Serious & Nonserious) | Frequency (%) |
| Pregnancy, puerperium and perinatal disorders | 0 | 0 | 0 | 0 | 0% | 0 | 0% |
| Psychiatric disorders | 2 | 43 | 156 | 199 | 19.5% | 274 | 24.8% |
| Renal and urinary disorders | 0 | 4 | 47 | 51 | 5.0% | 41 | 3.7% |
| Reproductive system and breast disorders | 0 | 1 | 46 | 47 | 4.6% | 60 | 5.4% |
| Respiratory, thoracic and mediastinal disorders | 0 | 1 | 5 | 6 | 0.6% | 24 | 2.2% |
| Skin and subcutaneous tissue disorders | 0 | 5 | 46 | 51 | 5.0% | 60 | 5.4% |
| Social circumstances | 0 | 0 | 0 | 0 | 0% | 0 | 0% |
| Surgical and medical procedures | 0 | 0 | 2 | 2 | 0.2% | 60 | 5.4% |
| Vascular disorders | 0 | 6 | 26 | 32 | 3.1% | 19 | 1.7% |
| **Total** | **7** | **187** | **833** | **1020** | **100%** | **1106** | **100%** |

***Fatal Cases***

The seven reported cases with a fatal outcome were:

[redacted] Cardiorespiratory arrest
Myocardial infarction
Death, drug level increased
Death
Hepatic failure, renal insufficiency, vomiting, prothrombin time prolonged
[redacted] Completed suicide
Completed suicide

These reports are discussed in more detail in the relevant System Organ Classes in the overview of the PSUR data in Annex 3. In addition the fatal cardiac disorders, hepatic disorders and suicide cases are included in the relevant cumulative reviews of these issues.

Case [redacted] (Death, Drug level increased) involved a [redacted] patient with unknown medical history. [redacted] received fluoxetine, celecoxib and sertraline concomitantly and had been receiving olanzapine for at least 6 years at the time that atomoxetine was started. Atomoxetine was started at 25mg daily, increasing to 40mg daily after one month. Eight months after starting atomoxetine the patient was found

dead in [redacted] home; [redacted] had been dead for 4 days. Although the correct amounts of medications were found in [redacted] containers, the patient had high blood levels of unspecified drugs. The physician attributed this to the drugs being released from the dead tissue into the body fluids and giving the appearance of an overdose ingestion prior to death. The police and the medical examiner suspected that the patient had committed suicide; however, the reporting psychiatrist did not agree. No information was provided regarding autopsy or toxicology.

Case [redacted] involved a [redacted] patient of unknown age and unknown medical history. [redacted] was concomitantly receiving topiramate. At the the time that the patient died the patient was receiving atomoxetine at an unspecified dose. No information was provided as to the cause of death and the autopsy results are awaited.

**Cardiac Disorders**

There were 43 case reports in which the primary reaction coded to the cardiac disorders SOC (14 serious, 27 non-serious). Two cases had a fatal outcome (cardio-respiratory arrest and myocardial infarction).

In total there have been 58 reactions categorised in this SOC. Of these 15 were serious (8 unlisted, 7 listed), and 43 were classed as non-serious (7 unlisted, 36 listed).

There have been 8 serious, unlisted reactions during the reporting period in this SOC. In only six of these cases, the *primary* reaction coded to cardiac disorders SOC. These cases were 'arrhythmia'; 'atrioventricular block first degree'; 'bundle branch block' and 'chest pain'; 'cardiomegaly'; 'extrasystoles'; and 'mitral valve prolapse'.

Of note, there are a cumulative total of 25 serious cases of QTc prolongation (13) and QT-prolonged (12) in the Investigations SOC. Questions were raised at the time of licensing of atomoxetine with regards to its QT interval prolonging potential and these issues were resolved at that time (see page 110, repeat MRP assessment report, Annex 2). Also clinical trial data showed no effect of atomoxetine on ECG recordings and atomoxetine did not significantly affect QTc in either CYP2D6 PMs or EMs. However, due to the number of spontaneous reports the MAH was requested to perform a cumulative review of all spontaneously reported cardiac disorders. A summary of the cumulative review covering the period 26 November 2002 – 26 November 2004 can be found in section 6.1.5.1 of this assessment report. A full assessment of this data can be found in Annex 8.

**Hepatobiliary Disorders**

During the period covered by PSUR 4 (27 November 2004 – 26 May 2005) there have been 17 case reports with a primary reaction which coded to the Hepatobiliary SOC (13 serious).

In total there have been 30 reactions categorised in this SOC (22 serious). Of the 22 serious reactions, 2 were considered unlisted. There was one fatal report.

Further hepatobiliary reactions were reported which were categorised in the investigations SOC. These were: alanine aminotransferase increased (n =48); aspartate aminotransferase increased (n=40); hepatic enzyme increased (n=29); blood bilirubin increased (n=18); and alkaline phosphatase increased (n=13).

Since the previous cumulative review of liver injury (January 2005; Annex 5) and the subsequent update of the SPC and healthcare professional communications, the MAH has observed an increase in the number of reports of hepatic adverse events for atomoxetine.

The MAH has performed an updated cumulative review of post-marketing spontaneous reports of liver toxicity associated with atomoxetine, a summary of which is provided in section 6.1.5.2 below. The full review of this data is attached in Annex 6.

**Investigations**
There have been 186 case reports where the primary reaction SOC coded to Investigations (21 serious, 165 non-serious).

There have been a total of 336 reactions categorised in the Investigations SOC during the period covered by PSUR 4. The most frequently reported reactions were: weight decreased (48); alanine aminotransferase increased (48); aspartate aminotransferase increased (40); hepatic enzyme increased (29); heart rate increased (21); blood bilirubin increased (18); alkaline phosphatase increased (13), weight increased (12), drug screen false positive (12). Weight decreased, abnormal liver enzymes, jaundice, tachycardia are listed adverse effects of atomoxetine in the EU SPC.

There have been 6 serious case reports with an unlisted primary reaction which coded to investigations. These are: blood sodium decreased (1); blood urine present (1); QTc interval prolonged (2); ECG T-wave inversion (1); weight increased (1).

Of note, there are a cumulative total of 25 serious cases of QTc prolongation (13) and QT-prolonged (12).

**Nervous System Disorders**
There have been 126 case reports in which the primary reaction coded to the Nervous System Disorder SOC (38 serious, 88 non-serious).

There have been a total of 281 reactions categorised in the nervous system disorders SOC. Of these, 77 were serious (66 unlisted, 11 listed) and 204 were non-serious (132 unlisted, 72 listed). The most frequently reported reactions were: dizziness (48); headache (46); somnolence (46); convulsion (20) (plus 3 petit mal epilepsy, 1 grand mal convulsion, 2 epilepsy, 1 partial seizures); disturbance in attention (13); psychomotor hyperactivity (13) and syncope (11). Dizziness, somnolence, headache and syncope are recognised adverse effects of atomoxetine and are listed in section 4.8 of the EU SPC.

There have been 36 serious cases with an unlisted reaction as a primary reaction in this SOC.

The serious case reports were (excluding convulsions – see below): cerebrovascular accident; extrapyramidal disorder; headache, Gilbert's syndrome, malaise, epistaxis and pyrexia; headache, dizziness and hot flush; hypotonic-hyporesponsive episode, lethargy, dizziness, coordination abnormal, feeling abnormal, tachycardia, hypertension, dizziness, cold sweat, livedo reticularis, and blood glucose increased; migraine and vomiting; myoclonus; loss of consciousness and memory impairment; syncope and blood glucose decreased; syncope, hallucination, fatigue and nausea; syncope, dizziness, heart rate increased, and blood pressure decreased; syncope, dizziness, heart rate increased and hypotension; syncope, palpitation, tachycardia and arrhythmia; and syncope. Orthostatic hypotension is a recognised adverse effect of atomoxetine.

There were a total of 21 serious case reports with the primary reaction of convulsion (16), epilepsy (1), grand mal convulsion (1), partial seizures (1) or petit mal epilepsy. The MAH has conducted a cumulative review of all reported cases of seizure (26 November 2002 – 26 November 2004) with an additional review of subsequent cases reported 27 November 2004 - 26 May 2005. An overview is provided in section 6.1.5.4 of this report below. The full assessment of the MAH review can be found at Annex 7.

Other reactions of note which warrant further assessment are: hypoaesthesia (6) /paraesthesia (4); speech disorder (1)/dysarthria (1) (plus two cumulative serious cases of each); movement disorders (dyskinesia, dystonia, extrapyramidal disorder); and tremor.

**Psychiatric disorders**

During the six-month period covered by this PSUR there were a total of 199 case reports (43 serious) in which the primary reported reaction coded to the 'Psychiatric disorders' SOC. Two of the case reports had a fatal outcome and both were reports of completed suicide involving young adults with previous psychiatric history (schizotypal personality disorder; depression and substance abuse).

In total there have been 430 reactions categorized in the "Psychiatric disorders" SOC during the period covered by this PSUR assessment and of these 77 were classified as serious. Due to the large number of psychiatric reactions reported (the majority of which are unlisted), in September 2005 the MHRA requested the MAH to perform a cumulative review of all psychiatric disorders reported for atomoxetine. The MAH is currently performing the review and it is anticipated that it will be available during the first quarter of 2006. In the mean time the MAH has provided a summary of the total number of psychiatric adverse events reported for atomoxetine since first launch. A discussion of these events together with a cumulative review of all spontaneous reports of suicidal behaviour reported for atomoxetine can be found in section 6.1.5.3 of this report below and also in Annex 4 of this report.

**Vascular Disorders**
There have been 32 case reports in which the primary reported reaction coded to the Vascular Disorders SOC (6 serious, 26 non-serious).

A total of 57 reactions were reported during this six month period which coded to the Vascular Disorders SOC. Eleven of these reports were serious (5 unlisted, 6 listed) and 46 were classified as non-serious (17 unlisted, 29 listed). The most frequently reported reactions were: hypertension (18); peripheral coldness (6); hot flush (6); pallor (6); Raynaud's phenomenon (4); hypotension (4); orthostatic hypotension (4); and flushing (4). Increase in blood pressure is mentioned in section 4.8 of the SPC for atomoxetine (children and adults) and peripheral coldness is listed in section 4.8 of the atomoxetine SPC in the adult clinical trial section.

In total there have been 3 serious reports with an unlisted reaction which coded to the Vascular Disorders SOC. These were: 'malignant hypertension'; 'Raynaud's Phenomenon', 'difficulty in walking', 'dysmennorhoea' and 'fatigue'; and a case of 'vasoconstriction' with 'abdominal pain', 'dizziness', 'disturbance in attention', 'dissociation' and 'fatigue'.

*Raynaud's phenomenon*
The MAH has conducted a cumulative review of spontaneous adverse reports of Raynaud's phenomenon for the period 26 November 2002 – 26 May 2005. Further details of the review can be found in Annex 3. A summary is provided below.

The MAH atomoxetine safety database was searched for consumer and healthcare professional reports using the following MedDRA preferred terms:*Raynaud's phenomenon, skin discolouration, peripheral coldness, livedo reticularis, nail discolouration, peripheral vascular disorder, poor peripheral circulation, and cyanosis.*

A total of 142 case reports (of 154 adverse events) were retrieved using the search. Eighty (56%) of the reports were consumer reports and the rest were from healthcare professionals. Four of the 154 adverse events were considered serious. The following table provides an overview of the cases.

**Table 5**

| MedDRA Preferred Term | No. of Events | No. Serious Events |
|---|---|---|
| Raynaud's phenomenon | 16 | 1 |
| Peripheral Vascular disorder | 1 | 0 |
| Peripheral coldness | 58 | 0 |
| Poor peripheral circulation | 8 | 1 |
| Skin discoloration | 57 | 1 |
| Nail discoloration | 1 | 0 |
| Livedo reticularis | 1 | 0 |
| Cyanosis | 12 | 1 |
| **Total Events** | **154** | **4** |

Following review of the cases, the MAH concludes that atomoxetine has the potential to exacerbate pre-existing Raynaud's phenomenon with 7 cases that described a worsening of symptoms. The MAH also state that whilst these 'cases are not compelling that atomoxetine causes the development of peripheral vascular instability and/or Raynaud's phenomenon in a patient without risk factors, the known pharmacology of atomoxetine makes it plausible that atomoxetine may be associated with the symptoms of Raynaud's phenomenon.

Raynaud's phenomenon should be added to section 4.8 of the SPC for atomoxetine.

**Summary of Case Reports with Syncope or Loss of Consciousness**
There have been a total of 14 cases (16 adverse reactions) of syncope (10 serious, 1 non-serious) or loss of consciousness (5 serious) reported during the period covered by PSUR4 (see Nervous System Disorder SOC).

Orthostatic hypotension was suggested as the possible cause of syncope by the reported in 4 cases. Orthostatic hypotension is a recognised adverse effect of atomoxetine and is listed in the SPC.

The possible causes of syncope/loss of consciousness in other reported cases are: tachycardia (listed), palpitation and unspecified arrhythmia in a patient who was also taking amphetamine/dexamphetamine; diarrhoea, vomiting and abdominal pain were reported in another case of syncope; low blood sugar was reported in the seventh case (teenager did not have breakfast); and there were 3 cases in which no specified causes could be identified.

The MAH proposes to continue to monitor cases of syncope and loss of consciousness.

**Drug Abuse and Drug Withdrawal Syndrome**
Cases which reported intentional, persistent, or sporadic, excessive use of atomoxetine inconsistent with the recommended use were coded as drug abuse. This section also looks at cases of addiction, dependence, and discontinuation/withdrawal symptoms associated with the use of atomoxetine.

During the six month period covered by PSUR 4, a total of 6 reports were received which coded to 'drug withdrawal syndrome' (4) and 'drug screen positive' (2). There were no reports of drug abuse.

No pattern in the symptoms of withdrawal can be detected from the small number of reports although the majority were psychiatric in nature. In two cases the patient recovered upon restarting atomoxetine. The outcome was unknown in one case and the reaction was continuing despite restarting atomoxetine in the remaining case. The MAH should continue to closely monitor reports of withdrawal reaction given that similar drugs are known to cause such events.

The two non-serious cases of 'drug screen positive' involved patients who had tested positive for amphetamines in a drug screen. No further information was available regarding these cases.

**Efficacy Related Information**

During the reporting period of PSUR 4 (27 November 2004 – 26 May 2005), there have been 64 spontaneous reports of lack of efficacy (including the terms 'drug ineffective', 'drug effect decreased' and 'therapeutic response decreased'). The MAH calculate a reporting frequency of 0.005%. All of the case reports were classified as non-serious. This is a decrease compared with the previous PSUR reporting period in which a reporting frequency of 0.015% was calculated for reports of lack of efficacy.

The dose of atomoxetine was provided in 46 of these reports and is summarised as follows: average daily dose (in 44 reports) was 57.5mg, the median dose was 40mg, with a range of 18mg to 180 mg daily. The remaining two reports reported the atomoxetine dose as 1.2mg/kg and 1.4mg/kg daily.

A total of 156 events were described in the 64 case reports of lack of efficacy. The most frequently reported event (except drug ineffective) was prescribed overdose (12). The MAH states that reports of prescribed overdose would typically be expected in lack of efficacy cases due to dose titration for a therapeutic effect.

Other frequently reported events in the 64 reports of lack of efficacy included abnormal behaviour (6), fatigue (5), abdominal pain upper (3), anxiety (3), disturbance in attention (3), headache (3), and irritability (3).

Twenty-five of the 64 case reports only contained the event 'drug ineffective' with no other reported events. Six reports contained 'drug ineffective' with 'prescribed overdose' with no other reported events. Thirty-three reports contained one or more non-serious adverse events.

The MAH concludes that the reports of lack of efficacy do not raise any safety concerns or identify any therapeutic or quality issues with atomoxetine.

**Experience with Overdose, Deliberate or Accidental, and Its Treatment**

The MAH conducted a search of their safety database for cases of overdose. An overdose of atomoxetine is considered to be a daily dose greater than 1.8mg/kg (for children and adolescents up to 70kg), or a daily dose greater than 120mg, which ever is less. This is in accordance with the Company Core Data Sheet (CCDS) dosing guidelines.

**Assessor's comments:**

The SPC states that for children under 70kg in weight "no additional benefit has been demonstrated for doses higher than 1.2mg.kg.day. The safety of single doses over 1.8mg/kg/day and total daily doses above 1.8mg/kg have not been systematically

evaluated". For children/adolescents over 70kg in body weight the maximum recommended daily dose is 100mg. The MAH uses the CCDS definition of 'overdose' which are slightly higher doses than those recommended in the SPC.

During the reporting period, 116 cases of overdose were identified. Thirty-nine of these reports were received from a poison control centre and were published within a journal (see published literature section).

Of the 116 reports, 17 were categorised as serious. There were two cases with a fatal outcome. Two cases (including one of the fatal cases) were excluded from the analysis since upon review they were not considered to be atomoxetine overdoses. The first excluded case was the fatal case in which raised blood levels of the patients medications were found post mortem. It was unclear in this case as to whether the patient had taken an overdose. The second excluded case was a case of complex partial seizures which was initially considered to involve an overdose of atomoxetine, however on review the daily dose for this patient was 1.18mg/kg.

The total number of cases analysed was 114 (1 fatal possible overdose of atomoxetine and other medications). Among the 114 cases, 67 cases of chronic overdose (including 62 cases of prescribed overdose) and 47 acute overdoses were identified.

Of the 67 cases of chronic overdose, 25 exceeded the CCDS recommended daily maximum dose and 42 did not exceed the CCDS recommended daily dose but were categorised as overdose since the reported doses exceeded the US Prescribing Information maximum recommended daily dose (1.4mg/kg or 100mg in children up to 70kg bodyweight, whichever is less; 100mg in children and adolescents over 70kg and adults). A total of 37 reports did not contain any adverse events and/or were coded to drug effect decreased/drug ineffective or were reported with disease exacerbations (irritability, psychomotor activity, abnormal behaviour, impulsive behaviour, disturbance in attention) and atomoxetine was being titrated upward. A significant number of the other case reports contained adverse events which are considered listed (e.g. heart rate increased, tachycardia, weight decreased, dizziness, urticaria). Of note there were six cases that contained changes in liver function tests and three reports that involved seizure activity. These are included in the review of heaptobiliary disorders and seizure events at Annex 6 and Annex 7 of this report.

Of the 47 cases of acute overdose, 38 cases were provided in the publication 'Atomoxetine ingestions in children: A Report for Poison Centres' (Henderson). The article indicated that atomoxetine induced extreme irritability, aggression, mania or hypomania in 33% off 153 children with ADHD. Based on this publication, the US FDA requested the MAH to provide a cumulative review of psychiatric adverse events reported for atomoxetine. This review is anticipated in the first quarter of 2006.

Of the remaining nine cases of acute overdose 5 were considered to be accidental and 4 were determined to be intentional overdoses. The patients were asymptomatic in 2 of the five cases of accidental overdose. Seizures were reported in a 1–year old with a history of petit mal epilepsy and heart rate increased was noted in another patient. In the final

case of accidental overdose no symptoms were provided but it is unclear from the MAH report whether the patient was actually asymptomatic.

Three of the four cases of intentional overdose involved mixed overdoses and one involved overdose of atomoxetine alone. Three of the four cases also reported suicide attempt/suicide complete. The four cases of intentional overdose are discussed in the review of suicidal behaviour in section 6.1.5.3 below and considered in detail at Annex 4.

**Assessor's comments:**
The MAH have started to code cases of intentional overdose to the MedDRA preferred term 'Intentional misuse'. This seems completely inappropriate given that the MedDRA lower level term 'Intentional overdose' codes to the MedDRA preferred term 'non-accidental overdose'.

The MAH concluded that there is no new clinically significant information regarding atomoxetine in overdose during the reporting period. However the MAH has updated the company core data sheet (CCDS) regarding seizure in overdose during the period covered by the PSUR. Section 4.9 (Overdose) of the EU SPC should be updated to include seizure in line with the changes to the CCDS.

**Experience in Paediatric, Adolescent, Adult and Elderly Patients**
Table 6 below provides an overview of the number of case of adverse events this period by age group.

**Table 6**

| Age Groups | Age Range | PSUR 04 This reporting period | | PSUR 03 Previous Reporting Period | |
|---|---|---|---|---|---|
| | | Number of Cases | Percentage | Number of Cases | Percentage |
| **Paediatric** | 1 to 12 years | 395 | 38.7 | 424 | 40.8 |
| **Adolescent** | 13 to 17 years | 198 | 19.4 | 172 | 16.6 |
| **Adult** | 18 to 64 years | 200 | 19.6 | 211 | 20.3 |
| **Elderly** | 65 years and older | 5 | 0.5 | 3 | 0.3 |
| **Unknown** | Unknown | 222 | 21.8 | 228 | 22.0 |
| **Total** | | 1020 | 100 | 1038 | 100 |

The most frequently reported reactions and SOCs in these four age groups are provided in table 7 below.

**Table 7**

| Age Groups | Top 5 System Organ Classes | Count (%) | Top 5 Reactions | Count (%) |
|---|---|---|---|---|
| Paediatric 1-12 years | Psychiatric disorders | 226 (25.2) | Vomiting | 41 (4.6) |
| | Gastrointestinal disorders | 163 (18.2) | Nausea | 34 (3.8) |
| | Nervous system disorders | 114 (12.7) | Aggression | 26 (2.9) |
| | Investigations | 110 (12.3) | Somnolence | 24 (2.7) |
| | General disorders and administration site conditions | 64 (7.1) | Abdominal Pain | 23 (2.6) |
| | | | Weight decreased | 23 (2.6) |
| | ***Total Reactions*** | **895 (100)** | | **895 (100)** |
| | | | | |
| Adolescent 13-17 years | Investigations | 102 (23.2) | Nausea | 19 (4.3) |
| | Gastrointestinal disorders | 64 (14.6) | Alanine aminotransferase increased | 16 (3.6) |
| | Nervous system disorders | 54 (12.3) | Aspartate aminotransferase increased | 15 (3.4) |
| | Psychiatric disorders | 53 (12.0) | Blood bilirubin increased | 13 (3) |
| | General disorders and administration site conditions | 38 (8.7) | Vomiting | 13 (3) |
| | | | Weight decreased | 13 (3) |
| | ***Total Reactions*** | **439 (100)** | | **439 (100)** |
| | | | | |
| Adults 16-64 years | Investigations | 76 (17.0) | Alanine aminotransferase increased | 18 (4.0) |
| | Psychiatric disorders | 71 (15.9) | Aspartate aminotransferase increased | 13 (2.9) |
| | Nervous system disorders | 56 (12.6) | Nausea | 13 (2.9) |
| | General disorders and administration site conditions | 45 (10.0) | Ejaculation disorder | 11 (2.5) |
| | Gastrointestinal disorders | 42 (9.4) | Fatigue | 11 (2.5) |
| | ***Total Reactions*** | **446 (100)** | | **446 (100)** |
| | | | | |
| Elderly 65 years and older | Psychiatric disorders | 2 (25) | Insomnia | 1 (12.5) |
| | Gastrointestinal disorders | 2 (25) | Malignant hypertension | 1 (12.5) |
| | Cardiac disorders | 1 (12.5) | Myocardial infarction | 1 (12.5) |
| | Immune system disorders | 1 (12.5) | Nausea | 1 (12.5) |
| | Vascular disorder | 1 (12.5) | Nervousness | 1 (12.5) |
| | Renal and urinary disorders | 1 (12.5) | Season allergy | 1 (12.5) |
| | | | Stomach discomfort | 1 (12.5) |
| | | | Urinary retention | 1 (12.5) |
| | ***Total Reactions*** | **8 (100)** | | **8 (100)** |

Atomoxetine is authorised in the EU for the treatment of ADHD in children 6 years and older and adolescents however the adverse event data is from worldwide and atomoxetine is authorised for the treatment of ADHD in adults in the US. During the reporting period, the majority of the cases concerned patients aged 6-12 years (380 reports). Fifteen reports concerned children aged 5 years and under and 5 reports concerned patients aged 65 years and over.

The same five SOCs are included in the 'Top five SOCs' for each age group, although they occur in a different order of frequency. In the paediatric group, vomiting, nausea, somnolence, abdominal pain, and weight decreased were the most frequently reported reactions. These are recognised adverse effects of atomoxetine and are listed in section 4.8 of the EU SPC accordingly. Aggression has recently been added to section 4.4 of the SPC.

The top five reported reactions in both the adolescent and adult groups are recognised reactions and are listed accordingly in section 4.8 of the EU SPC for atomoxetine.

There are too few cases in the elderly group to allow an adequate comparison with other age groups.

**Studies**

*Newly Analysed Company Sponsored Safety Studies*

During the period covered by this PSUR, one company-sponsored study has been reviewed and completed. This was the Medical Claims based study of seizures in an ADHD population. A summary of the results of this study is provided in Annex 7 (cumulative review of seizure events).

*Targeted New Safety Studies Planned, Initiated or Continuing During the Reporting Period*

There has been one completed epidemiologic study, five targeted ongoing safety studies and one ongoing epidemiological study during the reporting period. These are summarised in Table 6 of Annex 3.

Of note is the 'Atomoxetine and Cardiovascular and Cerebrovascular Outcomes in Adults' study which is a retrospective cohort study using a proprietary insurance-claims database study (1 January 2003 – 31 December 2004). The aim is to study the incidence of selected cardiovascular and cerebrovascular outcomes among adult patients who initiate therapy with atomoxetine. The incidence for each outcome among atomoxetine initiators will be compared to the incidence in a cohort of similar patients who initiate stimulants and an age-and gender-matched general population cohort. The interim report of this study is discussed in section 6.1.5.1 below and is considered in more detail in Annex 8.

*Published Safety Studies*

There were 3 publications, all of which presented data from studies conducted by the MAH, during the period of PSUR 4. These were:

- interim analysis of ongoing, open-label study of adults with ADHD
- analysis of changes in symptoms and adverse events after discontinuation of atomoxetine. The MAH state that it was concluded that 'atomoxetine may be discontinued without risk for symptom rebound or discontinuation-emergent adverse effects. Tapering of dose is not necessary when atomoxetine is discontinued'.

- Presentation of clinical pharmacokinetics of atomoxetine. The study concluded that atomoxetine administration does not inhibit or induce the clearance of other drugs metabolised by CYP enzymes. The MAH states that in EMs, selective and potent CYP2D6 inhibitors reduce atomoxetine clearance; however, administration of CYP inhibitors to PMs has no effect on the steady-state plasma concentrations of atomoxetine.

**Published Literature**
Seven articles were published during the period covered by the PSUR. Four of these contained case reports of adverse reactions associated with the use of atomoxetine and these have been included in the MAHs safety database and presented either in this PSUR or in previous PSURs.

One publication (Henderson) indicated that atomoxetine induced extreme irritability, aggression, mania or hypomania in 33% of 153 children with ADHD. Section 4.4 of the EU SPC for atomoxetine was updated to include aggression, hostility and emotional lability. These events should be added to section 4.8 of the SPC also.

**Assessor's comments on the PSUR data:**
During the overview of the PSUR data further reported reactions were identified which require further assessment. These are: blood dyscrasias; cerebrovascular accident; serious skin disorders including erythema multiforme and Stevens Johnson Syndrome; urinary tract haemorrhage; testicular pain, testicular disorder and testicular atrophy; parasthesia/hypoaesthesia; speech disorder/dysarthria; dyskinesia, dystonia, extrapyramidal disorders and tremor; myalgia and arthralgia. Those adverse events which could potentially impact on the overall risk benefit balance of atomoxetine if, upon review they were considered to be causally related, are cerebrovacular accident and serious skin reactions. The MAH will be requested to provide further details regarding these cases and an assessment of the data will be provided in an addendum report prior to the January 2006 meeting of PhVWP.

## 6.1.5 Reviews of Cardiac Disorders, Hepato-biliary Disorders, Psychiatric Disorders, and Seizures.

Section 6.1.5 provides an overview of the data for the four key safety issues identified for atomoxetine - cardiac disorders, hepatobiliary disorders, psychiatric disorders and seizures. The data is considered in more detail in Annex 4 (psychiatric disorders), Annex 5 & 6 (hepato-biliary disorders), Annex 7 (seizures) and Annex 8 (cardiac disorders.

### 6.1.5.1 Cardiac Disorders
This section considers the pre-clinical and clinical trial data considered during the second-wave MRP, and a cumulative review of spontaneous reporting data to 30 September 2005. It also considers the interim report of the 'Atomoxetine Cardiovascular and Cerebrovascular Outcome Study in Adults' and the November issue of the WHO

drug safety bulletin SIGNAL which contains an article regarding serious cardiac effects of atomoxetine.

***Preclinical Data***

*In Vitro Studies*

Atomoxetine, DM-ATX and 4'-OH-ATX blocked cloned human $I_{Kr}$ (hERG) channel (cloned from human embryonic kidney 293 cells) with $IC_{50}$ of 0.869μM (222ng/ml), 5.71μM (1379ng/ml) and 20μM (5437ng/ml), respectively (Figure 2, below). Atomoxetine inhibited human cardiac $I_{Na}$ ($IC_{50}$ =36.1μM) and $I_{Ca2+}$ channels ($IC_{50}$ = 1.93μM). The effect on $I_{Na}$ was rate and voltage dependent, suggesting that as experimental conditions approach more physiologic levels, blockade is increased.

*In Vivo Studies*

Cardiovascular effects of ATX in three dog studies (single oral doses in conscious adult dogs, repeated daily oral doses in conscious young dogs and iv infusion in anaesthetised dogs) were investigated. Single oral administration of ATX (0, 4, 8 or 16mg/kg) to telemetered adult mongrel dogs caused no treatment-related effects on heart rate or blood pressure.

ECGs and heart rates were also assessed in telemetered young (8-9weeks of age) beagle dogs, administered ATX (0, 4, 8 or 16 mg/kg/day) orally for 1-month, as part of the sub-chronic toxicity study. No ECG abnormalities attributable to atomoxetine were observed at *ca* 1h post-dose (*ca* $C_{max}$ for ATX).

In anaesthetised dogs cardiovascular effects of ATX (iv infusion, 0.2mg/kg/min for 50min; cumulative doses of 0, 2, 4, 6, 8 or 10mg/kg) were compared to those of amitriptyline. ATX had no effect on blood pressure, peripheral resistance, cardiac output or stroke work index. ATX slightly increased heart rate (cumulative dose ≥2mg/kg) and increased QTc (corrected using Bazett formula) and P-R intervals at cumulative doses ≥6mg/kg and 8mg/kg, respectively.

***Assessor's comments***

*Atomoxetine and 4'-OH-ATX have high affinity and selectivity for norepinephrine transporter (NET) over serotonin & dopamine transporters. 4'-OH-ATX is as active as ATX as an NET inhibitor and may contribute to the pharmacological activity of parent drug. DM-ATX, however, is 20-times less active than ATX as an NET inhibitor. Inhibition of NET by ATX, appears to be stereospecific, S(+)-enantiomer being 10-fold less potent. In general, ATX and its two phase I metabolites (4'-OH-ATX and DM-ATX) had relatively low affinity for other receptors and ion channels. Atomoxetine is a potent and moderately long-lasting inhibitor of NET in vivo.*

*Atomoxetine, DM-ATX and 4'-OH-ATX inhibited $I_{Kr}$ (hERG) channel [$IC_{50}$ 0.869μM, 5.71μM and 20μM, respectively]. Atomoxetine and DM-ATX are highly bound to human plasma proteins. At therapeutic levels of ATX, as much as a 23.6% and 12.4% $I_{Kr}$ block (Figure 2) is anticipated in CYP2D6 PM and EM subjects, respectively. Plasma $C_{max}$ for unbound ATX after a dose of 1.4mg/kg/d were 0.021μM (CYP2D6 EM) and 0.103μM*

*(CYP2D6 PM). Therefore $IC_{50}$ of ATX in hERG assay is 42.7-fold and 8.4-fold plasma Cmax for unbound ATX in CYP2D6 EM and PM subjects, respectively. Based on MHRA's assessment of the Company's response to question 8, it is concluded that although hERG K+ channel inhibition predicted for ATX would indicate concern, there were no effects in dogs consistent with this observation. In addition, ATX caused significant inhibition of both human cardiac $I_{Na}$ and $I_{Ca2+}$ channels. Furthermore, inhibition of human cardiac hERG for the DM-ATX and 4'-OH-ATX metabolites at unbound Cmax in PM subjects is negligible (<2%) and is well below the threshold of hERG blockade considered to be predictive for prolongation of QT interval. Finally, this level of hERG inhibition provides >30-fold margin of exposure in PM subjects for the major metabolites. Therefore, there is no substantial clinical risk associated with ATX and its primary metabolites at the recommended clinical doses.*

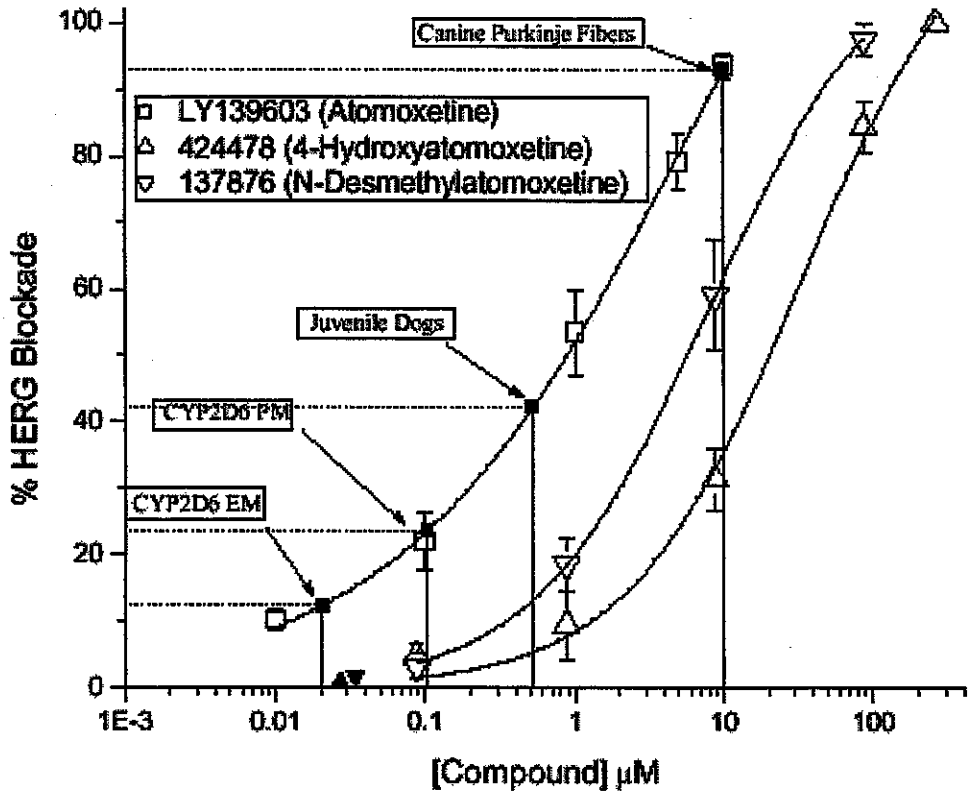



*Figure 2. Concentration-response relationship for block of hERG current by ATX and its two principal non-conjugated metabolites.*
*Plasma Cmax for unbound ATX in poor metabolisers (PM) and extensive metabolisers (EM) are shown superimposed on the ATX curve with the associated predicted hERG blockade. In addition, plasma Cmax for unbound ATX from juvenile dog toxicity study and concentrations tested in dog Purkinje fibres are plotted. Plasma Cmax for unbound metabolites DM-ATX and 4'-OH-ATX are shown on individual metabolite curves (solid triangles)*

*Plasma $C_{max}$ for unbound DM-ATX measured in humans were 34nM in CYP2D6 PMs and 0.6nM in CYP2D6 EMs. Plasma $C_{max}$ for unbound 4'-OH-ATX measured in humans were 3nM in CYP2D6 PMs and 27nM in CYP2D6 EMs. Therefore predicted $I_{kr}$ block by DM-ATX (0.1% and 2% in CYP2D6 EMs and CYP2D6 PMs, respectively) or 4'-OH-ATX (0.6% and 0.1% in CYP2D6 EMs and CYP2D6 PMs, respectively) is negligible (Figure 2). In addition, the $IC_{50}$ of 4'-OH-ATX and DM-ATX in hERG assay are more than 168-fold their corresponding unbound plasma Cmax in CYP2D6 EM and PM subjects.*

*In anaesthetised dogs, ATX increased heart rate and QTc (corrected by Bazett formula which overcorrects at high heart rates) interval. However, in conscious adult and young dogs, single and repeated oral doses of ATX, respectively, had no effects on ECG or heart rate at doses up to 16mg/kg/day. At 16mg/kg/day, plasma Cmax for unbound ATX in adult or young dogs was up to 25-fold and 5-fold higher than predicted Cmax after twice daily doses of 0.9mg/kg to CYP2D6 EM and CYP2D6 PM subjects, respectively.*

*High concentration tested in dog Purkinje fibres would be expected to block hERG by 93% in humans (Figure 2). This degree of $I_{kr}$ blockade would be expected to lengthen, not shorten, cardiac APD. Atomoxetine shortened APD by ca 21% in dog Purkinje fibres. The absence of a prolongation of APD in Purkinje fibres is reassuring. In addition, ATX caused significant inhibition of both human cardiac $I_{Na}$ and $I_{Ca2+}$ channels and therefore has an effect at the $Na^+$ and $Ca^{2+}$ channels co-incident with effect on hERG channel and appears to be a mixed ion channel blocker. Compounds that demonstrate this relationship have not been associated with clinical effects on QT and/or pro-arrhythmia.*

*In view of the potential of DM-ATX to accumulate in CYP2D6 PM subjects, its potential to prolong QT interval was questioned during the National UK application (see Company's response to Question 8 in Annex 2). This issue and the QT prolongation potential of ATX were adequately addressed during the National application.*

***Clinical Trial Data***

Atomoxetine increases noradrenergic tone and is known to affect the cardiovascular response to orthostatic change. In the acute efficacy studies there were just 2 reports of syncope (both in the active atomoxetine group) and no vasovagal attacks. However the data in poor CYP2D6 metabolisers raise the possibility of drug exposure related cardiovascular adverse effects. It is plausible that cardiovascular adverse events might be caused by the chronotropic and blood pressure effects of atomoxetine disrupting baroreceptor mediated homeostatic processes during postural change.

The detailed reports show that most episodes of syncope and all of the vasovagal attacks were considered non serious and did not result in study discontinuation. Syncope was recorded as a serious adverse event for 2 patients, both of whom were extensive metabolisers, and as the reason for discontinuation for 1 poor metaboliser patient in study LYBG.

An analysis of the cardiovascular adverse events and haemodynamic changes seen in healthy adults (Phase I studies) wsa presented. In healthy individuals atomoxetine had modest effects on blood pressure (mean increases of 2-3 mm Hg for both systolic and diastolic). However a few subjects demonstrated an exaggerated haemodynamic response resulting in orthostatic hypotension and/or syncope within 12 hours of dosing. There was a clear dose response relationship with cardiovascular effects seen mostly at doses of 40mg and above. There was no clear excess incidence in poor metabolisers, presumably because Cmax is only slightly elevated in this group.

It is likely that atomoxetine can contribute to orthostatic dizziness and syncope in some individuals, as reflected in the SPC. However the pattern of reporting does not at present indicate any substantial risk in either extensive or poor metabolisers. At the time of licensing it was recommended that this should be kept under review in post-marketing surveillance.

Atomoxetine consistently induced a modest sinus tachycardia at therapeutic doses. It is normally asymptomatic and well tolerated. Atomoxetine may also be associated with short-lived orthostatic sinus tachycardia and mild hypotension in both paediatric and adult populations, sometimes producing transient dizziness and possibly very occasionally syncope.

Atomoxetine consistently produced a small increase in diastolic and systolic blood pressures. Very few adverse events were reported in the clinical trials that relate to hypertension and long-term monitoring does not demonstrate any progressive tendency to the development of hypertension.

Effects on blood pressure and heart rate due to increased noradrenergic activity were of an acceptable magnitude and less marked than the changes produced by methylphenidate, which is licensed for ADHD. At the time of licensing, in paediatric patients the cardiovascular effects of atomoxetine were not considered to give cause for particular concern. However it was noted that there might be a potential safety issue in older adults with age related vascular disease and it was recommended that this should be the subject of close scrutiny in post-marketing surveillance.

ECG data were collected at baseline and during all studies, and were assessed in a blinded manner. No effect of atomoxetine on the ECG was seen. In particular atomoxetine did not significantly affect QTc in either CYP2D6 poor or extensive metabolisers and no dose or plasma concentration relationship to QTc was observed.

**Assessor's comments:**
Assessment of clinical trial data at the time of licensing demonstrates that atomoxetine has effects on heart rate and blood pressure and may contribute to orthostatic dizziness and syncope in some individuals. The SPC for atomoxetine reflects these findings. Post marketing surveillance of cardiovascular adverse effects of atomoxetine in adult patients was recommended and a summary of the interim report of the 'Cardiovascular and cerebrovascular Outcome Study in Adults' can be found below. No effect of atomoxetine

on the ECG was seen and no significant effects were seen on QTc interval either in CYP2D6 poor or extensive metabolisers.

***Spontaneous reporting data***

The MAH has submitted a review of spontaneous reports of cardiac disorders for the period 26 November 2002 – 26 November 2004 together with an addendum report which provided a line-listing of spontaneous reports of cardiac disorders for the period 27 November 2004 – 30 September 2005. These data are considered in detail in Annex 8 but the key points are summarised below.

The effects of atomoxetine on heart rate are apparent in the review of the spontaneous reporting data in which the majority of reported cardiac disorders were tachycardia, heart rate increased and palpitations. In total there were 717 reactions of tachycardia and heart rate increased reported for atomoxetine during the period 26 November 2002 – 30 September 2005. Cases of palpitations were not discussed by the MAH in the first review of cardiac disorders. A total of 49 cases of palpitations were reported during the period 27 November 2004 – 30 September 2005. The MedDRA preferred term 'palpitations' codes to the cardiac disorders SOC and therefore should have been included in the MAHs first review covering the period 26 November 2002 – 26 November 2004. The MAH will be requested to comment on this omission and this information will be assessed in an addendum report which will be circulated prior to January PhVWP.

Reports with a fatal outcome

During the period 26 November 2002 – 30 September 2005 there were a total of 11 case reports of cardiac disorders with a fatal outcome. These fatal cases involved 5 children and adolescents and 6 adults. Confounding factors or alternative causes of the events leading to death were present in the majority of the reports however, in two of the fatal cases in children there were no obvious confounding factors. Attributing any causality to atomoxetine in these two deaths however is very difficult given that both patients appeared asymptomatic until immediately prior to death, the lack of detail regarding time to onset, and the fact that both autopsies failed to reveal a cause of death. The eleven fatal cases are described in further detail in sections 4.7 and 5.1 of Annex 8. Of note the MAH did not include reports of sudden death in their review of cardiac disorders. In light of the two sudden and unexplained deaths in children, the MAH has been requested to perform a search of their post marketing safety database for reports of sudden death/sudden unexplained death which may potentially be indicative of fatal arrhythmias. An assessment of these cases will be provided in an addendum to this report prior to discussion at the January meeting of PhVWP.

QT/QTc interval prolongation

After reports of tachycardia, heart rate increased and palpitations, the most frequently reported cardiac disorders were QT/QTc interval prolongation – 33 cases were reported during the period 26 November 2002 – 30 September 2005. A total of 27 cases were reported during the period covered by the first cumulative review (26 November 2002 – 26 November 2004). In those cases where actual QTc values were provided, 5 cases

involved medically significant QTc interval prolongation (QTc>500msec or QTc change >60msec from baseline). However three of these reports were considered to be clearly or possibly confounded by the MAH. The confounding factors cited were: a history of hypokalaemia and concomitant potassium; a prior history of borderline QTc interval prolongation and a family history of cardiac disorders; and in the final case the possible confounders were listed as starting bupropion at the same time (although bupropion is not recognised to cause QTc interval prolongation at therapeutic doses) and sulfamethoxazole/trimethoprim and other unspecified antibiotics. The remaining two cases of medically significant QTc prolongation occurred following overdoses, one of which was a mixed overdose, the other involved an overdose of atomoxetine alone.

Both cases of overdose were excluded from further discussion by the MAH with the explanation that they do not represent the pharmacological actions of atomoxetine at therapeutic doses. However, the fact that these cases occurred as a result of an overdose of overdose of atomoxetine does not rule out a causal association with the drug. The case of overdose of atomoxetine alone may be indicative of a dose response and may warrant updating of the overdose section of the SPC. Two of the 'non-medically significant' cases may also indicate a dose response effect of atomoxetine on QT interval prolongation. In these two reports the MAH states that the events of QT interval prolongation occurred whilst the patients were receiving a prescribed daily dose of atomoxetine that exceeded the maximum recommended dose. These events were categorised as overdose cases by the MAH and were not considered to represent the properties of the drug at therapeutic doses and thus were not considered further. In both cases there was a positive dechallenge of atomoxetine and no possible risk or confounding factors are discussed/provided by the MAH. These cases would therefore seem to add some support to the possibility of QT interval prolongation at higher doses/overdoses of atomoxetine.

The MAH evaluated the 27 cases for risk or confounding factors. There were 2 cases in which the QTc interval prolongation was identified about 2 weeks after atomoxetine was discontinued. A further 4 cases were considered to have clear confounding/risk factors (prior history of QTc prolongation (2 cases, 1 case was considered medically significant and is discussed above), possible hypokalaemia (1 case, considered medically significant and discussed above), and pre-existing cardiac disorder (1 case)). Eleven cases (including 1 medically significant case of QTc prolongation discussed above) were considered by the MAH to be possibly confounded due to concomitant medication. However, QTc interval prolongation is not listed as a recognised adverse effect at therapeutic doses of the medication listed in 7 of these cases. There were four cases in which the relationship between atomoxetine and the reported events was considered to be 'indeterminate' due to lack of information available, however in two of these cases a positive dechallenge of atomoxetine was observed.

Two of the cases considered to be confounded by concomitant medication (bupropion and fluoxetine) were in male who children experienced borderline QTc prolongation (446msec and 462msec) less than 2 months after starting atomoxetine 25mg. Both continued on treatment and the events continued. These reports were from the same reporter who also reported 2 further similar cases involving young male patients who developed QTc intervals of 448 and 445msec less than 2 months after starting

atomoxetine 25mg. Neither concomitant medication (fluoxetine, bupropion) considered by the MAH to be confounders is recognised to cause QTc prolongation at therapeutic doses. These two cases are interesting given the WHO drug safety bulletin article considered below and discussed detail in section 7 of Annex 8. which discusses the possibility that pharmacokinetic and/or pharmacodynamic interactions between atomoxetine and inhibitors and substrates of CYP2D6 such as bupropion and fluoxetine may be responsible for QT interval prolongation in a case series of nine spontaneous case reports in the WHO database in patients taking SSRIs and atomoxetine (see below).

A further two cases of 'Electrocardiogram QT interval prolonged' and four cases of 'Electrocardiogram QTc interval prolonged' were reported during the period 27 November 2004 – 30 September 2005. Whilst the lack of detail with regard to QTc values makes these reports difficult to assess, in three of these cases a causal relationship with atomoxetine cannot be ruled out. The MAH should make every effort to follow up these reports in order that a full assessment can take place.

Arrhythmias and other ECG abnormalities

The review of the data concerning arrhythmias (supraventricular arrhythmias, ventricular arrhythmias and unclassified arrhythmias) did not establish a causal relationship between arrhythmias and atomoxetine. However the MAH should continue to closely monitor cases of atrial fibrillation, cardiac flutter and ventricular tachycardia. In addition, the MAH did not provide any details regarding the non-serious cases of 'arrhythmia unclassified' which prevented causality assessment in these cases. The MAH should be requested to provide a review of the case details for the 40 non-serious cases of unclassified arrhythmias reported for atomoxetine.

At present there is not enough evidence to suggest a causal relationship between atomoxetine and other ECG abnormalities, cardiac conduction disorders (including AV block or bundle branch block), or other cardiac disorders (including cardiac valve disorders, myocardial disorders and myocardial infarction). The MAH should continue to closely monitor such events.

The MAH review of cardiac disorders was limited to MedDRA preferred terms in the Cardiac Disorders System Organ Class (SOC) and the Higher level Group Term (HLGT) 'Cardiac and Vascular Investigations' in the Investigations SOC. Given the link between atomoxetine and peripheral ischaemia, the MAH will be requested to provide a line listing of all cases of adverse events relating to central ischaemia and an addendum report assessing the MAH response will be provided prior to the January 2006 meeting of PhVWP.

**Assessor's comments:**

The spontaneous reporting data suggest that atomoxetine may be associated with prolongation of QTc interval in cases of overdose. There are a further two cases in which prolongation of the QTc interval was observed at therapeutic doses and in which no other alternative causes could be identified. In addition there are at least 7 other cases in which (despite concomitant medication) the role of atomoxetine can not be excluded. Furthermore, in eighteen of the cases in which atomoxetine was discontinued, 15 of the patients recovered after drug withdrawal and the outcome was unknown in the remaining

three cases.

An addendum report which will assess the MAH responses to requests for further information will be provided before the January meeting of PhVWP. This report will consider the MAHs responses to a request for further information regarding omission of cases of palpitations from the first period of the cardiac review, reported cases of sudden death, review of the cases of QTc interval prolongation in which patients are receiving concomitant SSRIs, further details of the 40 cases of unclassified arrhythmias, and an overview of events related to central ischaemia.

***WHO data (article in November 2005 issue of the WHO drug safety bulleting 'SIGNAL')***

The November 2005 issue of the WHO drug safety bulletin 'SIGNAL' includes an article by Dr Emilio Sanz (Spain) which considers serious cardiac effects of atomoxetine.

According to the article, the WHO centre has received 26 cases of cardiac arrest (3), ventricular tachycardia (4), and "QT prolonged" (19) associated with the use of atomoxetine (2004;4; IC 1.64, IC025 0.63). The majority of these cases concerned children and young people under the age of 16 years (18 cases). Other side effects most frequently reported in these cases include tachycardia (10 cases), extrasystoles (4 cases), chest pain (5 cases) and atrial fibrillation (3 cases).

A more recent review of the WHO data has revealed an increase in the IC values from 1.64 (IC025 0.63) in 2004:4 to IC 2.10 (IC025 1.59) in 2005:2. As of 7 September 2005, there have been 38 cases of QT prolonged, seven cases of cardiac arrest and five cases of ventricular tachycardia. A re-calculation of IC values based on the sub-dataset of reports in children (as opposed to the whole database) is to be performed in the near future.

Nine patients were reportedly using at least one SSRI concomitantly. The article discusses the possible role of both pharmacokinetic and pharamcodynamic interactions between atomoxetine and SSRIs as 'co-adjuvant' reasons for a possible increase in the activity of atomoxetine. The interaction between atomoxetine and SSRIs is listed in the EU SPC for atomoxetine and states that "In CYP2D6 extensive metaboliser patients, selective inhibitors of CYP2D6 may increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in CYP2D6 poor metaboliser patients". The concomitant use of fluoxetine and venlafaxine (which are metabolised by CYP 2D6) have been reported in this case series (one case with fluoxetine, 3 cases with venlafaxine) and also three cases in which sertraline was used concomitantly.

The article states that from the available data it is not possible to determine whether it is the effect of atomoxetine or the SSRI alone, or a synergy between the two which is responsible for the observed QT interval prolongation. The article further discusses the possibility that the adrenergic stimulation caused by the increase in NA levels at the sympathetic synapses could also be linked to the arrhythmogenic effects of atomoxetine, because it is related to an increase in the magnitude of the $Ca^{2+}$ current, an increase in the

repolarizing $K^+$ and $Cl^-$ currents, increases the sinus rate and facilitates the passage through the AV node.

The author concludes that the current data suggests that cardiac effects associated with atomoxetine treatment should be carefully and specifically studied, and the prevalence of QT prolongation in treated patients is to be confirmed by other studies with special attention to the concomitant use of SSRIs. It is concluded that a warning should be added to the product information for atomoxetine.

**Assessor's comments:**
The WHO database contains a total of 38 cases of QT interval prolongation associated with the use of atomoxetine (cut off date 7 September 2005). In the review of spontaneous post-marketing reports, a total of 33 reports (27 + 6) were presented by the MAH for the period 26 November 2002 – 30 September 2005. The MAH should be requested to comment on the difference in number of reported cases of QT interval prolongation.

The article raises some interesting points and suggests that atomoxetine may cause QT interval prolongation in situations where steady-state plasma exposure to atomoxetine is increased, in particular in patients who are receiving concomitant medication (SSRIs) which inhibit CYP2D6.

***Observational data***
The interim report of the 'Atomoxetine Cardiovascular and Cerebrovascular Outcome Study in Adults' describes the identification of the two study cohorts; patients with a first dispensing of atomoxetine and patients with a first dispensing of stimulant ADHD medication. The matching algorithm using the propensity score is described and demographic details for both cohorts are presented both before and after matching.

Nearly one quarter of eligible atomoxetine patients were excluded from the study because no matched stimulant initiator could be found. A clear presentation of the difference in demographics, diagnoses and medications between the matched and unmatched initiators should be provided with diagnostic and therapy terms rather than codes to expand the information available from tables 4 to 6 (Appendix B of Annex 8). Future reports of the study will include the identification of cardiovascular and cerebrovascular claims events among the matched cohorts and comparators.

This interim report only contains information on the study cohorts and does not contain any results. Future reports will include the identification of cardiovascular and cerebrovascular claims events among the matched cohorts and comparators.

**Assessor's Overall comments (Cardiac Disorders):**
The cases of QT prolongation associated with atomoxetine and SSRIs in the WHO report and the spontaneously reported cases of QT prolongation associated with both intentional and prescribed overdose, together with the early pre-clinical concerns regarding concerns about QT interval prolongation in CYP2D6 poor metabolisers do not rule out the

possibility that at the very least, atomoxetine may cause QT interval prolongation in situations where steady-state plasma levels of atomoxetine are increased. The MAH should provide a summary of the cases of QT interval prolongation associated with atomoxetine and concomitant SSRIs with a view to strengthening the current warnings in the SPC about concomitant use of SSRIs.

### 6.1.5.2 Hepatobiliary Disorders

***Pre-clinical Data***

The preclinical studies of the metabolic and dispositional profile of atomoxetine did not suggest that treatment with atomoxetine was likely to be associated with hepatic injury. The pharmacokinetics of atomoxetine were shown to be generally predictable with no metabolic or dispositional characteristics of concern.

There was no major target-organ toxicity in studies of atomoxetine in adult mice (3 months duration), adult rats (3 & 12 month duration), adult dogs (3 & 12 month duration) or juvenile rats and dogs. Hepatic toxicity was not observed in rats given daily IV doses of up to 20mg/kg or in dogs given IV daily doses of up to 12mg/kg. Repeat-dose oral toxicity studies of atomoxetine in 10-day old rats given doses of up to 50mg/kg/day through adulthood (approx. 2.5 months duration) and in 8-week old dogs given atomoxetine up to 16mg/kg/day for one month showed no hepatotoxic effects.

Studies in adult male rats given dietary concentrations of ≥14mg/kg/day (equivalent) for 3 or 12 months showed changes in the liver including mottling and pallor of the liver, increased relative liver weights, hepatocellular vacuolation (vacuoles containing lipids) and increased serum transaminases. Similar findings were observed in male and female mice given dietary concentrations of 600mg/kg/day (equivalent) but not in mice given dietary concentrations of150mg/kg/day (equivalent), although these changes were not observed in juvenile animals or in dogs treted for 3 or 12 months. Furthermore, these changes were not due to the metabolic generation of reactive species. It was suggested that this vacuolation was due to exaggerated pharmacology (near toxic doses) since lipolysis is under adrenergic control, however no abnormal adipocyte pathology was observed.

In mice, rats and dogs, atomoxetine was found to be a weak inducer of hepatic microsomal enzymes. However, no inflammation or hepatic cellular necrosis was observed in rodents. Lack of enzyme induction in humans was confirmed.

**Assessor's comments:**
The metabolic and dispositional profile of atomoxetine suggests that it is unlikely to be associated with hepatic injury. The toxicology studies indicate mild effects on the liver at high doses.

***Clinical Trial Data***

Clinical pharmacology Studies

In 2001 the MAH performed an integrated assessment of liver injury biomarkers across all clinical pharmacology studies. This assessment has been included in previous reports to regulatory agencies. Table 8 below summarises the number of patients who developed an abnormal test result or a worsening of a pre-existing abnormal result:

**Table 8**

| Laboratory parameter | Subjects 1.5x above UL Normal Range (n) | Subjects>2 x Above UL Normal Range (n) |
|---|---|---|
| Alanine aminotransferase (ALT/SGPT) | 4 | 2 |
| Aspartate aminotransferase (AST/SGOT) | 7 | 1 |
| Alkaline phosphatase | 0 | 0 |
| Total bilirubin (TBILI) | 1 | 0 |
| Total subjects with HIGH | 12 | 3 |
| Total subjects with A Dose | 275 | . |

(abnormal threshold: 2 x ULN for AST and ALKPH and ALT, and 1.5 x ULN for TBILI)

Two healthy male subjects developed 2-fold elevations in ALT above ULN. Both were asymptomatic and recovered during further observation. One healthy male developed 2-fold elevation in AST above ULN. Again this patient was asymptomatic and he recovered. A further male patient developed a TBILI 1.5x (or greater) ULN (asymptomatic) although this patient's TBILI had increased prior to administration of atmoxetine (during administration of fluoxetine). His ALT, AST and ALKPH were normal throughout the study.

Cirrhotic patients given a single 20mg dose of atomoxetine (study of pharmacokinetic changes as a result of liver damage) did not show a worsening of their liver biomarkers. However this study involved a small number of patients and the patients received a single small dose.

**Assessor's comments:**
In clinical pharmacology studies no clinically significant events were reported and no patient experienced symptoms consistent with liver injury.

Clinical Trials

The data is derived from 27 clinical trials that were locked on or prior to 1 July 2004. The MAH employed a comprehensive search strategy in order to identify cases of interest. This included text strings for relevant preferred terms and laboratory test searches.

Hepatic Adverse event data

A search of the database identified a total of 135 possible cases of liver injury during clinical trials. Upon further review, the MAH considers that only 20 of these reports were possibly related to atomoxetine and therefore has only provided details for these 20 cases.

In 16 of the cases the patients were male, which the MAH state is similar to the sex distribution of patients in the ADHD population. The median time to onset in these cases was 362 days (range 16 -1058 days). In one half of these cases (10 out of 20) the increases were in the range of 1.5 to 3 x ULN. In a further six cases the elevations was of the order of ≤ 5 x ULN. Another patient experienced an increase in ALT of 13 x ULN but this was associated with gastrointestinal illness and paracetamol use. In two further cases, the increases in AST (33 x ULN in one case and 5.5 x ULn in another) and ALT (4 x ULN) can be explained by the patient's concurrent muscle injury. In the remaining case the elevation of ALKPH was present prior to starting atomoxetine treatment.

Treatment emergent changes in hepatic enzymes levels

The MAH has also provided data on elevations in hepatic enzymes levels that occurred during treatment from the studies in adult and paediatric populations. For these analyses a treatment emergent high value was defined as a change from a value of less than or equal to the ULN at baseline to a value greater than the ULN at any post baseline assessment. The significance of the overall differences was assessed using the Cochran-Mantel-Haenszel general association test stratified by study group.

Change from baseline to endpoint and baseline to maximum were also calculated for all hepatic enzymes (ALT, AST, ALKPH, TBILI and GGT) using a last observation carried forward (LOCF) approach. The mean change from baseline between treatments was assessed using analysis of variance (ANOVA).

Paediatric clinical trials

In the paediatric clinical trial population the percentage of patients who developed elevations of >3-5 x ULN in ALT (atomoxetine 1.0% (1/908) vs placebo 2.0% (1/540)) and >1.5 x ULN in TBILI (atomoxetine 0.3% (2/724) vs placebo 0 (0/436)) was similar to that in placebo-treated patients. Very few atomoxetine treated patients in these paediatric trials had an ALT >3 x ULN (0.3%, 11/3736), TBILI > 1.5 x ULN (0.8%, 25/3143) or ALKPH > 2 x ULN (0.1%, 2/3738).

Placebo treated patients compared with atomoxetine treated patients had statistically greater increases in mean change from baseline to maximum in ALT (atomoxetine -1.25 vs placebo 1.32, p=<0.001), AST (atomoxetine -0.63 vs placebo 0.69, p=<0.001), GGT (atomoxetine 0.04 vs placebo 0.40, p=0.009) and ALKPH (atomoxetine 0.09 vs placebo 11.84, p=<0.001).

Adult clinical trials

In the adult clinical trial population the percentage of patients who developed elevations of >1-3 x ULN in ALT (atomoxetine 0.4% (1/243) vs placebo 1.2% (3/241)) and TBILI (atomoxetine 0.5% (1/218) vs placebo 0 (0/225)) was similar to that in placebo-treated patients. Furthermore, no adult patients had an ALT >3 x ULN, TBILI > 1.5 x ULN or ALKPH > 2 x ULN.

Atomoxetine treated patients had significantly greater increases than placebo-treated patients in mean change from baseline to maximum for ALKPH (atomoxetine 4.75 vs placebo 0.90, p=<0.001). Whilst placebo treated patients had statistically greater

increases than atomoxetine treated patients in mean change from baseline to maximum in TBILI (atomoxetine 0.37 vs placebo 1.12, p=0.021).

Further details regarding the pre-clinical and clinical trial data relating to effects on the liver are provided in the repeat use MRP assessment report which is attached at Annex 2.

**Assessor's comments**: Whilst the available clinical trial data do not raise concerns about the risk of hepatic disorders in association with atomoxetine it is recognised that the patient population studied in clinical trials does not necessarily reflect the population which receive a product in routine clinical practice. Therefore these data do not provide reassurance that atomoxetine does not cause serious hepatic disorders in some individuals.

***Spontaneous Reporting Data***

Since the previous cumulative review of liver injury (January 2005; Annex 5) and the subsequent update of the SPC and healthcare professional communications, the MAH has observed an increase in the number of reports of hepatic adverse events for atomoxetine.

The MAH has performed an updated cumulative review of post-marketing spontaneous reports of liver toxicity associated with atomoxetine, a summary of which is provided below. The full review of this data is attached in Annex 6.

Between 26 November 2002 and 26 May 2005, a total of 19,245 spontaneous reports had been entered onto the MAH world-wide safety database. Potential reports of liver injury were identified via a comprehensive search strategy involving adverse event preferred terms, high level group terms and text string searches (as in the previous MAH review of October 2004 upon which the assessment in Annex 5 is based).

From launch to 26 May 2005 a total of 419 spontaneous reports of potential reports of liver disorders were identified. These reports were assessed and categorised by the MAH both diagnostically and etiologically. The etiological classification is outlined below (also Table 6). Diagnostic categorisation was also based upon an algorithm.

Class 0. Excluded: (1) the event was not liver related; or (2) none of the liver biomarker test results, ALT, AST, ALKPH or TBILI met diagnostic criteria; or (3) atomoxetine was administered after the event.

Class 1. Unlikely: (1) clear confounding/contributory factors present, such as chronic alcoholism, viral hepatitis, genetic disorders (Gilbert's syndrome), or other medical conditions; or (2) negative rechallenge of atomoxetine (e.g. liver biomarker test results remained normal even if atomoxetine was readministered).

Class 2. Possible: (1) confounding or contributory factors present, such as concomitant medications known to cause liver injury; or (2) positive dechallenge of atomoxetine, but no rechallenge information available.

Class 3. Probable: (1) No other confounding or contributory factors present; or (2) positive rechallenge of atomoxetine.

Class 4. Indeterminate: Insufficient information available for evaluation (e.g. no information on medical history of concomitant medication available).

**Table 9. Diagnostic Categorisation and Etiologic Classification of Spontaneous reports 26 November 2002 – 26 May 2005**

| **Diagnostic Categorisation of Liver Injury** | **Etiologic Classification** | | | | | **Total** | |
|---|---|---|---|---|---|---|---|
| | Class 1 (Unlikely) | Class 2 (Possible) | Class 3 (Probable) | Class 4 (Indeterminate) | Class 0 (Excluded) | | |
| Gilbert's Syndrome | 11 | N/A | N/A | N/A | N/A | 11 | **Total of Liver-Injury cases: N=175** |
| Hepatocellular | 17 | 33 | 0 | 7 | 1 | 58 | |
| Cholestatic | 0 | 5 | 0 | 3 | 0 | 7 | |
| Mixed Type | 2 | 2 | 1 | 0 | 0 | 5 | |
| Unknown Type | 12 | 15 | 0 | 65 | 2 | 94 | |
| Not Liver Injury | N/A | N/A | N/A | N/A | 244 | **Not Liver Injury N=244** | |
| **Total** | **42** | **55** | **1** | **74** | **Excluded: N=247** | **Total Cases Retrieved from database N=419** | |
| | **Total of Liver-Injury Cases in temporal association with atomoxetine: N=172** | | | | | | |

A total of 419 reports of possible hepatic adverse events were retrieved from the MAH atomoxetine safety database and upon review 247 reports were considered to be 'not cases of liver injury' (Class 0). Of the 172 reports which were considered to be cases of liver injury, 42 cases were considered to be unlikely related to atomoxetine due to other possible contributing/confounding factors (Class 1). In the remaining 130 cases an association with atomoxetine could not be completely ruled out (Class 2, 3 or 4) and these included one case in which the events were considered to be probably related to atomoxetine and 55 cases in which the events were considered to be possibly related to atomoxetine.

The patient age distribution in the 172 case reports ranged from 2 to 61 years. The following table provides further information on the patient age distribution in spontaneous reports of liver injury.

**Table 10. Patient age distribution of Spontaneous Cases of Liver Injury associated with atomoxetine**

| Age Group (Years) | Case classification | | | | Total (%) | Atomoxetine spontaneous cases | Atomoxetine patient exposure |
|---|---|---|---|---|---|---|---|
| | Class 1 (Unlikely) | Class 2 (Possible) | Class 3 (Probable) | Class 4 (Indeterminate) | | | |
| 0-12 | 11 | 16 | 0 | 22 | **49 (28.5%)** | **38%** | **44.7%** |
| 13-17 | 18 | 21 | 1 | 19 | **59 (34.3%)** | **15%** | **22.5%** |
| 18-64 | 10 | 18 | 0 | 19 | **47 (27.3%)** | **27%** | **32.2%** |
| *65 and older* | *0* | *0* | *0* | *0* | ***0*** | ***0%*** | ***0.6%*** |
| *Unknown* | *3* | *0* | *0* | *14* | ***17 (9.9%)*** | ***19%*** | ***0.1%*** |
| **Total** | **42** | **55** | **1** | **74** | **172 (100%)** | **100%** | **100%** |

The reporting rate of hepatic adverse events associated with atomoxetine has increased from 0.0021% (41 in 1,961,000 patients) to 0.0059% (172 in 2,902,000) since the previous review of the issue (January 2005) and subsequent communication with healthcare professionals. Hepatic injury associated with atomoxetine is still considered to be very rare (less than 0.01%). However, the reporting rates should be interpreted with caution since they are based on spontaneous reporting which is influenced by many factors including publicity and an unknown degree of under reporting.

In this updated 30 month cumulative review, there were four fatal cases, 3 of which were considered unlikely to be due to atomoxetine and were included in the previous type II variation assessment. The causes of death in the three previously assessed fatal cases were given as acute viral myocarditis ([redacted]); cardiomegaly, complications of alcoholism (hepatic cirrhosis), mitral valve degeneration and morbid obesity ([redacted]); and liver congestion consistent with dilated cardiomyopathy ([redacted]). The fourth case concerning a [redacted] was reported at the end of January 2005. At the time a complete assessment of this case was not possible due to lack of information. Follow up information concerning the case has been received and the relationship between the reported adverse events (hepatic failure, renal insufficiency, vomiting, prothrombin time prolonged) and atomoxetine in this case was considered to be 'Indeterminate' by the MAH, however a causal relationship can not be ruled out. This case ([redacted]) is discussed in further detail on page 317 in Annex 6.

Of the 172 reports of hepatic disorders, there were three cases in which a positive rechallenge of atomoxetine was observed, one of which was considered probably related and 2 were considered possibly related. The case which was considered probably related to atomoxetine was the case which triggered the first review of this issue in October 2004 and led to the subsequent amendment of the product information. The two 'possibly' related cases are new cases and involve a positive rechallenge of atomoxetine in patients with underlying liver disorders (exacerbation of underlying liver disorder). The MAH is inconsistent in their categorisation. A positive rechallenge should carry greater weight

than possible confounders and the 2 new cases should therefore be categorised as probably related to atomoxetine.

No obvious trend in time to onset was observed in the reported cases. There was also no obvious trend in the dose although this relationship is not easy to assess based on the data provided since the doses according to weight were not always provided and some of the cases occurred in adults and some occurred in children. The type of liver injury was predominantly hepatocellular (58 cases) where the information was available however the type of liver injury was unknown in 94 cases.

**Assessor's comments**
At the time of licensing in the UK, pre-clinical and clinical trial data for atomoxetine did not indicate any significant hepatotoxic effects.

The 30 month updated cumulative review of spontaneous reporting data for atomoxetine confirms the previous signal that atomoxetine is associated with liver injury and further confirms the very rare, idiosyncratic nature of the liver injury (no obvious trend in time to onset or dose) and the potentially severe nature of the events. The data suggest that the type of liver injury is predominantly hepatocellular in those reports where this information was available, however this information was unknown in 94/175 cases. The current product information for atomoxetine lists abnormal liver function tests, jaundice and hepatitis as very rare recognised adverse effects of the drug. Furthermore, the Special Warnings and Special precautions for Use section of the Summary of Product Characteristics for atomoxetine warns prescribers that atomoxetine is associated with severe liver injury and that treatment should be stopped and not restarted in patients who have laboratory evidence of liver injury. This updated cumulative review does not provide any further information which would allow better characterisation of hepatic reactions over and above what is already known (i.e potentially severe and idiosyncratic reaction), therefore no further updates to the product information are considered necessary.

The Pharmacovigilance Risk Management Plan for atomoxetine discusses potential methods of further evaluating the risk of hepatoxicity associated with atomoxetine post marketing. An assessment of the updated Pharmacovigilance Risk Management Plan will be circulated separately.

### 6.1.5.3 Psychiatric Disorders

***Clinical Trial Data***

At the time of licensing, the acute efficacy studies showed that decreased appetite, somnolence, irritability, fatigue, anorexia and mood swings were all reported more commonly in the active atomoxetine group (N=657) than in placebo (N=408). Mood swings were reported in 2.1% of atomoxetine treated patients compared with 0.5% in placebo treated patients. In addition data in poor CYP 2D6 extensive metabolisers (N=107) raise the possibility of drug exposure related depression and generalised anxiety

disorder. However the numbers of reports are too small (single figures) to indicate a causal link to atomoxetine, particularly since these conditions are seen more frequently in patients with ADHD than in the general population. Nevertheless they are listed in the SPC as possible uncommon undesirable effects.

There were a total of 39 serious cases of psychiatric adverse events reported in studies in children and adolescents. All except on of these reports (bipolar disorder "possibly related") were considered by the investigator to be unrelated to atomoxetine. There were 16 reported serious adverse events relating to depression, suicidal ideation or deliberate self-harm (8 reports) occurring during atomoxetine treatment and 10 relating to aggression or agitation. Most had a previous history of impulsive behaviour, self-harm and/or depression. There were no reported suicide attempts.

A review of individual cases of serious psychiatric AEs shows that in most cases strong risk factors unrelated to atomoxetine treatment were present at the time of study entry. Only 3 patients who developed serious adverse events relating to depression, suicidal ideation, or self-injury did not have either a history of depression or an evident psychosocial precipitant. The majority of episodes were reported at only one or two visits, which the MAH argued is inconsistent with an ongoing drug effect. Also, the timing of the onsets of most of these adverse events was not consistent with an acute medication related event. In the acute placebo controlled analysis there was no difference between atomoxetine and placebo for depression (0.8% versus 1.0%, p=0.739) but a non-statistically significant trend towards more reports of aggression or agitation in atomoxetine treated patients compared with placebo (1.8% versus 0.7%, p=0.185). At the time of licensing it was considered reasonable to conclude that there was no evidence that atomoxetine played a causal role in serious psychiatric adverse events although the possibility could not be discounted. Due to the primary and concomitant psychiatric morbidity in an ADHD population the reported frequencies of serious psychiatric adverse events were considered to be probably in line with expectations.

It should be noted that co-morbid conditions including depression and anxiety disorders (including generalised anxiety disorder, panic disorder, and social phobia) were not exclusion criteria in the paediatric studies and this was considered appropriate given that it is representative of the population likely to receive atomoxetine in clinical practice. However, the number of patients with co-morbid psychiatric disorders in the trials was relatively low. Patients who were considered to be at serious suicidal risk and those with current or a previous history of bipolar depression were excluded from the trials.

An analysis of placebo-controlled clinical trial data considered by the CHMP during the article 31 referral found an increased risk of aggression, hostility and emotional lability associated with atomoxetine.

Two new meta-analyses of atomoxetine clinical trial data identified a signal of suicidality associated with the use of atomoxetine. The European Assessment report dated 23 September 2005 is attached at Annex 1 for further details regarding the meta-analyses and assessment thereof.

These new analyses of clinical trial data (12 trials involving 1357 Strattera treated children/adolescents) showed an increase in the risk of suicidal thoughts/behaviour in Strattera treated individuals compared with those receiving placebo. Suicide related behaviours occurred at a frequency of approximately 4 in 1000 Strattera treated patients (6 out of 1357, one case of suicide attempt and five of suicidal ideation). There were no events in the placebo group (n=851). The age range of children experiencing these events was 7 to 12 years, however the number of adolescent patients included in the clinical trials was low. There were no completed suicides in these trials. The same signal is not observed in adults.

On 27 September 2005, an Urgent Safety Restriction was completed to include warnings about the risk of suicidal ideation in the SPC for Strattera.

**Assessor's comments:**
A meta-analyses of 12 clinical trials has identified an increased risk of suicidal thoughts/behaviour in children and adolescents treated with Strattera compared with those receiving placebo. The number of events reported in these trials was low and the absence of events in the placebo group is of some surprise. Patients with a history of bipolar disorder and those at serious risk of suicide were excluded in all of the trials included in the analyses.

The SPC for Strattera was updated to include warnings regarding the risk of suicidal behaviour via an urgent safety restriction on 27 September 2005. The SPC was also updated to include warnings about the increased risk of aggression, hostility and emotional lability on 27 September 2005.

***Spontaneous Reporting Data***
Upon the request of the MHRA (request date 23 September 2005), the MAH has submitted a cumulative summary of the total number of psychiatric adverse events reported for atomoxetine up to 22 September 2005. The most commonly reported psychiatric reactions (all reports or healthcare professionals (hcp) reports only) include insomnia, abnormal behaviour, aggression mood swings, irritability and agitation. Further information on these events can be found in Annex 4 of this paper

The MAH was also requested to provide a cumulative review of all cases of suicidal and self-injurious behaviour associated with atomoxetine. The first review submitted covered the period from 26 November 2002 until 22 September 2005. A second review of the cases received during the period 23 September 2005 – 25 October 2005 was subsequently submitted. These two reviews are considered in more detail in Annex 4 of this report. The data from the two reviews has been combined to provide an overall picture of the reported events and is summarised below.

Up to 25 October 2005, a total of 431 reports of suicidal and behaviour have been received (301 cases during the period 26 November 2002 – 22 September 2005, 130 cases during the period 23 September 2005 – 25 October 2005).

These reports include 20 classified as completed suicide, 63 classified as suicide attempt, 231 classified as suicidal ideation, 35 classified as self-injurious behaviour and 10 classified as self-injurious ideation.

In the cases where patient age was provided (369/431; 86%), the distribution ranged from 5 to 69 years and the majority of the suspected ADRs were in males (67%). In the cases where age is known, the majority of the completed suicides (95%) and the majority of suicide attempts (81%) occurred in adolescents or adults. There was one completed suicide in a [redacted] with a history of ADHD, oppositional defiance disorder (ODD) and possible bipolar disorder. Further details regarding the case (including the manner of suicide) are not available. The majority of reports of suicidal ideation (81%) and self-injurious behaviour (87%) occurred in children aged 12 years or below and adolescents.

The time to onset of the events ranged from 1 day to more than 2 years. In the reports where information on the time to onset is provided, just under two thirds (61%) of the events occurred within 2 months of starting treatment.

Where information is provided, there are confounding factors such as previous history, underlying illness or concomitant medication in the majority of reports of completed suicide (15 out of 15 cases), suicide attempt (45 out of 49 cases) and suicidal ideation (63 out of 92 cases). Based on these data, however, one cannot exclude the possibility that atomoxetine may have exacerbated the individuals underlying condition in these cases.

If the cumulative number of reports (26 November 2002 – 25 October 2005) of suicidal and self-injurious behaviour are considered in the context of exposure to date (3.5 million patients) then such reports have been reported rarely (<0.1%). The overall reporting rate has changed from "very rare" (<0.01%) for the first set of data covering the period 26 November 2002 – 22 September 2005) to "rare" (≥0.01% - <0.1%) for the total period covered by the two reviews (26 November 2002 – 25 October 2005). The increase in reporting rate observed during the period 23 September 2005 – 25 October 2005 is not unexpected following the healthcare communications/public advisories and press coverage concerning this issue during that time. The reporting rates should be interpreted with caution given that they are based upon spontaneous reporting data and thus are subject to the known biases/limitations including an unknown degree of under reporting.

Overall the MAH consider that these data do not suggest an association between treatment with atomoxetine and suicide-related or self-injurious behaviours. The arguments to support this are confounding by underlying illness and concomitant medication and the parallels between these spontaneous reports and what is seen in the general population in relation to the pattern and prevalence of suicidal behaviour. However, as stated above, the possibility that atomoxetine may have exacerbated the individual's underlying condition in these cases can not be completely excluded.

Following discussion at the October 2005 meeting of the CHMP Pharmacovigilance Working Party of the newly identified signal of a statistically significant increased risk of suicidal ideation with atomoxetine compared with placebo in children, the MAH was requested to provide a meta-analysis of suicide-related events in paediatric active-

comparator-controlled ADHD clinical trials. A discussion of this analysis is included in section 6.5.1.2 of this report.

**Assessor's comments:**
Whilst the spontaneous reporting data do not suggest an association between atomoxetine and suicide-related or self-injurious behaviours due to confounding by underlying psychiatric illness, the possibility that atomoxetine may have exacerbated underlying psychiatric conditions is these cases can not be completely excluded.

**Assessor's overall comments on psychiatric adverse events:**
Following analyses of clinical trial data, the SPC for atomoxetine has been updated to include warnings regarding the identified increased risk of suicidal thoughts/behaviour associated with atomoxetine and also with regards to an increased risk of aggression /hostility and emotional lability.

The review of spontaneous reporting data concerning suicide-related and self-injurious behaviour suggest that a significant number of reports had confounding factors such as previous history, underlying illness or concomitant medication. However, the possibility that atomoxetine may have exacerbated the individuals underlying condition in these cases cannot be excluded.

The overall spontaneous reporting rate of suicide-related events has increased from "very rare" (<0.01%) to "rare" (≥0.01% - <0.1%) following the healthcare professional communication concerning this newly identified risk.

The MAH cumulative review of reports of other psychiatric adverse events associated with atomoxetine is awaited in the first quarter of 2006.

### 6.1.5.4 Seizure

Following US approval in November 2002, spontaneous reports of seizure have been the most commonly reported serious adverse event for atomoxetine. Seizures are not currently listed in the SPC for atomoxetine, but were identified as a potential risk in the Pharmacovigilance Risk Management Plan for the drug.

The MAH has conducted a review of the available data for atomoxetine with respect to seizures (covering the periods 26 November 2002 – 26 November 2004 and 27 November 2004 - 26 May 2005). The MAH's review includes data from the atomoxetine clinical trial database, spontaneous post-marketing adverse event reports, and a Medical Claims Database study. A summary of the data is provided below and the full assessment can be found in Annex 7 of this report.

***Preclinical Data***

The very limited preclinical information provided do not suggest that atomoxetine is proconvulsive. No changes in pentylenetetrazol precipitated convulsions were observed

in mice and in a second model of seizure liability, higher currents were needed to elicit electroschock-induced convulsions compared to vehicle treated control mice, suggesting that atomoxetine might have anticonvulsant properties.

Seizures were observed in a number of toxicological studies but this observation was not considered relevant to doses used in the clinical setting.

Further details of preclinical data for atomoxetine are provided in the repeat use MRP assessment report (Annex 2).

**Assessor's comments:**
The pre-clinical data do not suggest that atomoxetine is proconvulsive.

***Clinical Trial Data***
The cut off date for adverse event text string searches in the clinical studies was 26 November 2004. Patients in all studies, including ongoing and completed Phase 2, 3, and 4 studies were included in the analyses. The analyses included 51 completed and 10 ongoing studies. Further details of these studies are provided in Annex 7.

A core set of exclusion criteria is used in all studies in the ADHD clinical trial databases. Patients with a history of seizure disorder (excluding febrile seizures) were excluded from the trials along with patients with uncontrolled hypertension, patients at serious risk for suicide and patients with ongoing alcohol or drug abuse.

The MAH performed a comprehensive search of the clinical trial database using 29 text strings to search for 63 possible seizure-related terms.

Reports unrelated to seizures were removed from the search results and the remaining cases were reviewed for diagnostic categorisation and etiological classification according to the following guidelines:

*Diagnostic Categorisation*

| | |
|---|---|
| Category 1. | Report of probable/possible generalised tonic-clonic seizure |
| Category 2. | Report of status epilepticus |
| Category 3. | Event reported as a seizure, but the seizure classification was indeterminate due to insufficient information in the report |
| Category 4. | Event reported as a seizure, but not considered a generalised tonic-clonic seizure based on the information provided in the report |
| Category 5. | Event was determined to **not** be a seizure based on the information provided in the report |

*Etiologic Classification*

| | |
|---|---|
| Class A. | Clear confounding or contributing factors (e.g. personal history of seizures, diagnosis of benign seizure disorder) |
| Class B. | Possible confounding or contributing factors (e.g. concomitant medication use, neurological conditions, family history of seizures) |

Class C. Indeterminate etiology with insufficient information available for evaluation

Class D. No apparent confounding or contributing factors, with sufficient information available to evaluate.

A total of 19 possible seizure events (15 patients) were identified.

Two of the reports of seizures occurred in patients who were not exposed to atomoxetine (exposed to other treatments) and these cases are not considered further in the review.

The remaining 17 events (13 patients) were categorised as follows.

| **Diagnostic categorisation of seizure** | **Etiological Classification** | | | | **Total cases** |
|---|---|---|---|---|---|
| | Class A (Clear confounding) | Class B (Possible confounding) | Class C (Indeterminate) | Class D (No confounding factors) | |
| Category 1 | 1 | 0 | 0 | 0 | **1** |
| Category 2 | 0 | 0 | 0 | 0 | **0** |
| Category 3 | 5 | 1 | 1 | 0 | **7** |
| Category 4 | 2 | 3 | 0 | 0 | **5** |
| **Total cases** | **8** | **4** | **1** | **0** | **13** |

The majority of the seizure-events reported in the atomoxetine clinical trial database were considered to be clearly confounded (8 out of 13 case reports). The reasons stated for this were: atomoxetine discontinued 2 days prior to onset and complicated perinatal period; subsequent diagnosis of Juvenile Myoclonic Epilepsy; head injury; hypoglycaemic seizure in a patient with type I diabetes; history of developmental delay and staring spells prior to atomoxetine with no events on continued therapy at higher doses; event associated with a vasovagal episode following phlebotomy; prior history of seizure; and a possible partial syncopal seizure which followed dental anaesthesia and blood loss.

*Clinical Trial Reports Related to Seizure (atomoxetine/placebo/methylphenidate)*

This analysis of the clinical trial reporting rate for seizure-related events is based on data from 31 locked clinical trials with an atomoxetine treatment arm in the indications of ADHD (including comorbid tic disorders, comorbid depression and comorbid anxiety disorders).

In the 31 clinical trials, 13 patients experienced at least one seizure-related event (12 children/adolescents and 1 adult).

Table 11 below provides the number of possible seizure adverse events by treatment and analysis group.

**Table 11**

| | | Atomoxetine | | Placebo | Methylphenidate | p-value* |
|---|---|---|---|---|---|---|
| | | n/N | Crude incidence | n/N | n/N | |
| **Paediatric Trials** | **Controlled Trials†** | 1/1614 | 0.06% | 0/849 | 0/523 | 1.000 |
| | **Overall§** | 12/5083 | 0.2% | N/A | N/A | N/A |
| **Adult Trials** | **Controlled Trials†** | 0/270 | N/A | 0/266 | N/A | N/A |
| | **Overall§** | 1/748 | N/A | N/A | N/A | N/A |

† Controlled trials - data from acute-treatment period of double-blind placebo controlled or comparator-controlled studies with atomoxetine.
§ Overall atomoxetine group – data from all phases of clinical trials regardless of indication with an atomoxetine treatment arm.
* p-value corresponds to exact Chi-squared test comparing incidence rates across three treatment groups.

The MAH calculate that clinical trial reporting rate for reports related to seizure in paediatric patients was 0.2% (12/5083) patients. For adults the reporting rate was calculated to be 0.1% (1/748).

The 1 case of seizure (classified "nontonic-clonic seizure"by the MAH) in the controlled-group phase occurred in study LYBR (comparative study with methylphenidate).

**Assessor's comments**: The clinical trial data do not provide strong evidence of a causal link of seizure events with atomoxetine. The MAH should be requested to clarify the case in which the confounding factor is listed as prior history of seizure disorder given the fact that according to the core exclusion criteria listed in the section above, patients with a prior history of seizure (excluding febrile seizures) were excluded from clinical trials.

***Spontaneous Reporting Data***
Using selected MedDRA preferred terms, a total of 507 events were identified from the spontaneous safety database (data lock 26 November 2004). The reports were then categorised and further details of categorisation and classification can be found in Annex 7. Of the 507 reports identified, 80 were grouped in Diagnostic Category 1 (probable/possible generalised tonic-clonic seizure), 4 in Category 2 (status epilepticus), 74 in Category 3 (seizure classification indeterminate due to insufficient information), and 25 in Category 4 (event not considered to be tonic-clonic seizure). A total of 324 case reports were grouped in diagnostic Category 5 (event was determined not to be a seizure based on the information provided in the report). The Category 5 reports are not discussed further in the MAH's report.

A review of spontaneous reporting data from the subsequent 6-month reporting period 27 November 2004 to 26 May 2005 identified 98 possible cases of seizure events. A total of 61 of these reports are not discussed further by the MAH since they were considered not to be seizure events upon review (category 5).

According to the MAHs assessment of reported seizure events, there are only four cases (4/183 + 0/37 reports) of seizure events in which the role of atomoxetine can not be excluded. These four patients have no prior history of seizure disorders. Thus, there is some evidence to suggest that atomoxetine causes seizure in patients with no prior history of seizure

The MAH exclude a causal role of atomoxetine in 50/183 and 13/37 reports of seizure events due to a prior history of seizure. Upon review it can be seen that a small number of these reports followed a similar pattern in that the patients had been seizure free for some time before atomoxetine was started, subsequently experienced an increase in seizure frequency upon starting atomoxetine, and, in those cases where outcome is provided, have remained seizure free following discontinuation of atomoxetine.

The MAH has concluded that there is insufficient evidence at present to establish a causal association between atomoxetine and the seizure events reported. The MAH states that the reporting rate of seizure events is consistent with the background prevalence and incidence of seizures in the child and adolescent ADHD population. However, this should be interpreted with caution since the reporting rates are based on spontaneous data which is subject to under-reporting. The MAH proposes to continue to closely monitor future reports of seizure associated with the use of atomoxetine.

**Assessor's comments:**
There were four reports in which the role of atomoxetine in new onset seizure could not be excluded. Furthermore there are a number of reports in which atomoxetine is temporally associated with an aggravation of the patient's pre-existing seizure disorder.

***Observational Study Data***
The MAH undertook a health claims database analysis to examine the incidence of seizures in the general paediatric population and various subgroups, including those with and without ADHD. The results are provided at Annex 7. The study also aimed to evaluate a possible association between ADHD medications and new-onset seizures.

Population
Paediatric patients in the Ingenix Research Database. The patients were divided into a number of different groupings:

- **General paediatric sample** (20% random sample of those with at least 1 year continuous enrolment and without any history of seizure or anti-convulsant medication in the 1 year baseline period. (134,888 patients)

- **Non ADHD group** – drawn from the general sample above (127,778 patients)
  - Psychiatric diagnosis group (5127 patients)
  - No psychiatric diagnosis group (122,651 patients)

- **ADHD group** – drawn from the full database of those with at least 1 year continuous enrolment and without any history of seizure or anti-convulsant medication in the 1 year baseline period (34,727 patients)
    - Treated ADHD ( 28,979 patients)
    - Untreated ADHD (5,748 patients)

Study design

This was a retrospective cohort study using the Ingenix Research Database fro 1/1/2003 to 31/12/2003. The outcome of interest was non-febrile new-onset seizure defined using a claims based algorithm. Time on drug analysis was used to determine the incidence of first medical claim of seizure occurring during time on ADHD therapy compared with time off therapy.

Analyses were carried out with atomoxetine separated from other ADHD treatment, and stratified by prior treatment with any ADHD therapy in the baseline period.

Results

*Demographics*

Within the general population there were 49% female and 51% male patients, with 58% of patients in the 6-12 yrs category and 42% aged 13-17 years.

Within the ADHD population there were 26% female and 74% males reflecting the known epidemiology of this condition. The age breakdown for treated ADHD patients was similar to that for the general population. For the untreated ADHD population there were 66% in the younger age-group and 34% in the older age-group.

**Table F17: Adjusted relative risk of first medical claim of seizure with time on ADHD therapy stratified by use of any ADHD therapy in baseline**

| | Combined (N=34,727) | | | Prior Use (N=28,225) | | | No Prior Use (N=6,502) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Adj RR* | 95% C.I. | | Adj RR* | 95% C.I. | | Adj RR* | 95% C.I. | |
| **ADHD Treatment Type** | | | | | | | | | |
| **Atomoxetine** | | | | | | | | | |
| Current | 1.1 | 0.6 | 2.1 | 1.2 | 0.4 | 2.6 | 2.5 | 0.9 | 7.1 |
| Recent | 0.8 | 0.0 | 9.4 | 1.2 | 0.1 | 5.3 | NA | NA | NA |
| Past or None | ref | - | - | ref | - | - | ref | - | - |
| **Other ADHD Therapy** | | | | | | | | | |
| Current | 0.8 | 0.6 | 1.3 | 1.7 | 0.9 | 3.4 | 0.7 | 0.2 | 2.0 |
| Recent | 0.9 | 0.4 | 1.9 | 2.0 | 0.8 | 5.1 | NA | NA | NA |
| Past or None | ref | - | - | ref | - | - | ref | - | - |
| **Demographics** | | | | | | | | | |
| Female, Ages 6-12 | 1.7 | 0.9 | 3.3 | 1.5 | 0.6 | 3.3 | 1.7 | 0.6 | 4.8 |
| Female, Ages13-17 | 1.4 | 0.7 | 3.0 | 1.9 | 0.8 | 4.2 | 0.4 | 0.1 | 3.5 |
| Male, Ages 6-12 | 1.6 | 1.0 | 2.7 | 1.5 | 0.8 | 2.8 | 1.5 | 0.6 | 3.5 |
| Male, Ages13-17 | ref | - | - | ref | - | - | ref | - | - |
| **Seizure Risk Factors** | | | | | | | | | |
| Congenital | 1.2 | 0.5 | 2.4 | 1.0 | 0.3 | 2.5 | 1.5 | 0.4 | 4.9 |
| No Congenital | ref | - | - | ref | - | - | ref | - | - |
| CNS | 4.6 | 3.0 | 7.0 | 5.3 | 3.1 | 8.9 | 3.3 | 1.6 | 7.0 |
| No CNS | ref | - | - | ref | - | - | ref | - | - |
| Systemic | 1.1 | 0.7 | 1.6 | 1.2 | 0.7 | 1.9 | 0.9 | 0.5 | 1.9 |
| No Systemic | ref | - | - | ref | - | - | ref | - | - |
| Substance | 1.6 | 1.2 | 2.6 | 2.0 | 1.1 | 3.3 | 2.2 | 0.9 | 5.4 |
| No Substance | ref | - | - | ref | - | - | ref | - | - |

*Adj RR = multivariable relative risk adjusted for all of the covariates above

**Table F21: Nested case control - adjusted odds ratios for treatment stratified by prior use in baseline period**

| | Combined (N=1,100) | | | Prior Use (N=846) | | | No Prior Use (N=254) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Adj OR[1] | 95% C.I. | | Adj OR[1] | 95% C.I. | | Adj OR[1] | 95% C.I. | |
| **ADHD Treatment Type** | | | | | | | | | |
| **Atomoxetine** | | | | | | | | | |
| Current | 1.1 | 0.5 | 2.4 | 1.2 | 0.4 | 3.1 | 2.6 | 0.5 | 12.1 |
| Recent | 0.5 | 0.1 | 4.4 | 0.7 | 0.1 | 5.0 | NA | NA | NA |
| Past or None | ref | - | - | ref | - | - | ref | - | - |
| **Stimulants** | | | | | | | | | |
| Current | 0.8 | 0.5 | 1.3 | 1.4 | 0.7 | 2.7 | 0.4 | 0.1 | 1.8 |
| Recent | 1.3 | 0.5 | 3.6 | 2.2 | 0.7 | 6.8 | NA | NA | NA |
| Past or None | ref | - | - | ref | - | - | ref | - | - |
| **Bupropion** | | | | | | | | | |
| Current | 2.7 | 0.6 | 11.8 | 4.1 | 0.9 | 18.7 | NA | NA | NA |
| Recent | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Past or None | ref | - | - | ref | - | - | ref | - | - |

[1] Adj OR = multivariable odds ratios adjusted for ADHD treatment, age, gender, all seizure risk factor categories, outpatient visits, hospitalizations, calendar quarter, and geographical region.

[2] Adj OR = multivariable odds ratios adjusted for ADHD treatment, age, gender, all seizure risk factor categories except for congenital, outpatient visits, hospitalizations, calendar quarter, and geographical region.

**Assessors Comments:** There is clear evidence of an increased risk of first claim seizure in patients exposed to atomoxetine who have no prior ADHD therapy use. The relative risk in this group from the cohort study is 2.5 (95% CI: 0.9- 7.1), with a similar odds ratio in the nested case-control study of 2.6 (0.5-12.1). Whilst these are not formally statistically significant, they are certainly suggestive of a signal of seizures related to therapy in this group.

This increased risk is not seen in those who have prior use of ADHD therapies and as these patients constitute the majority of treated ADHD patients the combined results reflect these figures.

It is possible that patients are selectively prescribed atomoxetine if there is a history of seizure risk, for example a family history of seizures, which may not be recorded in the database. It is also possible that patients susceptible to seizures on therapy will have been identified during prior treatment with other therapies. Either of these could lead to channelling of high risk patients.

However, there is no evidence for this channelling in this study and therefore the results should be interpreted as providing evidence of a signal of increased risk of seizures in previously untreated patients until further evidence emerge.

**Assessor's overall comments on seizure:**
The pre-clinical and clinical trial data for atomoxetine do no suggest that atomoxetine is proconvulsive however seizures have been the most frequently reported serious adverse event for atomoxetine since it was launched. The spontaneous reporting rate of seizure-related events remains higher than expected based on clinical trial data however the clinical trials excluded patients with a prior history of seizure disorder. The spontaneous reporting data together with the observational health claims database study suggest that atomoxetine is is related to seizures in both patients with and without a prior history of seizure disorder.

The SPC should be updated to include warnings about the risk of de novo seizures and aggravation of seizure disorders in section 4.4 (Special Warnings and Precautions for Use), 4.8 (Undesirable Effects) and 4.9 (overdose).

## 6.2 Comparative safety with other treatments for ADHD

Atomoxetine is a specific noradrenaline reuptake inhibitor and is the first ADHD drug in its class. It differs substantially from existing medicinal products licensed for this indication (i.e. CNS stimulants including amphetamines and methylphenidate) and from other agents used occasionally off label for ADHD including desipramine and clonidine.

In particular it is claimed to have important advantages in its adverse effect profile and abuse potential compared with the CNS stimulants used for this condition.

## 6.2.1 Methylphenidate

Methylphenidate is a central nervous system stimulant whose mode of therapeutic action is not fully understood but is thought to be due to cortical stimulation and possibly to stimulation of reticular activating system. It is a piperidine derivative structurally related to amphetamine with two chiral centres. In the UK it has controlled drug status, which imposes restrictions on prescribing and handling.

Ritalin was the first methylphenidate containing product to be licensed for the treatment of ADHD. Other available methylphenidate containing products are Equasym and the modified-release preparations Concerta XL and Esquasym XL. Methylphenidate products are indicated as a part of a comprehensive treatment programme for attention ADHD in children over 6 years of age where remedial measures alone prove insufficient. Treatment must be under the supervision of a specialist in childhood behavioural disorders. Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10.

The adverse effects of methylphenidate are commonly symptoms of overstimulation of the CNS and include insomnia, nightmares, nervousness, restlessness and irritability. The safety profile of long term methylphenidate therapy is not well-established and this reflected in the product information for prescribers which advises that patients requiring long-term therapy should be carefully monitored.

Methylphenidate accounts for approximately 90% of overall ADHD prescribing in the UK.

### 6.2.1.1 Clinical trial data – Comparative Efficacy and Safety Study of atomoxetine and methylphenidate (Study LYBR)

Study B4Z-MC-LYBR was a multi-centre, randomised, double-blind study that compared the safety and efficacy of atomoxetine and methylphenidate in paediatric outpatients with ADHD.

***Study Objectives***

The primary objective of this study was to test the hypothesis that atomoxetine is noninferior to methylphenidate as assessed using conventional symptom measures - ADHDRS-IV-Parent:Inv (Attention-Deficit/Hyperactivity Disorder Rating Scale-IV Parent Version: Investigator-Administered and Scored). This objective was assessed by comparing the response rates (with response defined as a ≤40% reduction from baseline to endpoint in the ADHDRS-IV-Parent:Inv total score) for the atomoxetine and methylphenidate treatment groups using the following prespecified definition: if the 1 sided 95% lower confidence limit of the difference in responders (atomoxetine minus

methylphenidate) was greater than -18%, atomoxetine was declared noninferior to methylphenidate.

Secondary objectives included comparison of the safety and efficacy of atomoxetine and methylphenidate as assessed by treatment emergent adverse events, and comparison of the efficacy of atomoxetine and methylphenidate on the Conners' Parent Scale-Revised: short Form (CPRS-R:S).

***Study Design and selection criteria***

A total of 330 children aged 6 through to 16 years of age who met the DSM-IV criteria for ADHD (any subtype) were recruited. Diagnosis was confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL) semi-structured interview. Criteria for enrolment included a cut-off score of ≥25 for boys or ≥22 for girls, or >12 for a specific subtype on ADHDRS-IV-Parent:Inv as well as CGI-ADHD-S (Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity) score of ≥4 at both Visit 1 and 2.

The study consisted of three study periods. After an initial screening and washout period, individuals were randomised in a double-blind fashion to atomoxetine (n=164) or methylphenidate (n=166). Those receiving atomoxetine began therapy at a target dose of 0.8mg/kg/day, administered once daily, and were titrated up to a maximum dose of 1.8 mg/kg/day, based on the physician's assessment of symptoms response. Those receiving methylphenidate began therapy at a target dose of 0.2mg/kg/day, administered twice daily, and were titrated up to a maximum dose of 0.6 mg/kg/day, based on the physician's assessment of symptoms response. Following the second study period, subjects entered a discontinuation phase that included one follow-up visit. At this visit and assessment of safety and tolerability after drug discontinuation was conducted.

Key exclusion criteria included:

- Individuals who had previously participated in an atomoxetine study;
- Individuals who had failed to experience some benefit in ADHD signs and symptoms on methylphenidate or amphetamine;
- Those with a history of bipolar I or II disorder, psychosis, or a pervasive developmental disorder;
- Those determined by the investigator to be at serious suicidal risk;
- Individuals diagnosed with Tourette's Disorder or motor tics, or those who have a family history of Tourette's Disorder.

The following safety information was collected:

Adverse events – collected and recorded on the CRF at each visit regardless of relationship to study drug. Captured as actual term and coded to MedDRA by blinded Lilly personnel.

Laboratory data – Standard laboratory tests were conducted at regular intervals including routine chemistry, haematology and urinalysis tests.

Vital signs – these were collected during the study and included blood pressure (systolic and diastolic), heart rate, weight and height.

ECGs – measured at baseline (to determine eligibility for study entry) and at the end of study periods 2 and 3.

Concomitant therapies – were reviewed and recorded at each visit

***Safety Evaluation***

The mean final prescribed dose for individuals receiving atomoxetine was 1.37 mg/kg/day, and the mean maximum dose was 1.44 mg/kg/day. While for those receiving methylphenidate the mean final prescribed dose was 0.52 mg/kg/day and the mean maximum dose was 0.53 mg/kg/day. The duration of therapy was similar in both groups (atomoxetine 58.17 days, methylphenidate 61.58 days).

Overall completion rates in both arms were high but the methylphenidate group had a higher completion rate than the atomoxetine group (91.6% vs 84.1%; p=0.044). The percentage of patients who discontinued treatment due to adverse events was statistically significantly higher in the atomoxetine group compared with the methylphenidate group (11% vs 3.6%; p=0.011). Approximately one half of the individuals who discontinued atomoxetine treatment due to adverse events did so early in the treatment period. The adverse events that most frequently led to discontinuation were anorexia (5 atomoxetine, 1 methylphenidate), decreased appetite (2 atomoxetine, 2 methylphenidate), nausea (1 atomoxetine, 1 methylphenidate) and abdominal pain (2 atomoxetine).

Analysis of adverse events included the 330 individuals who took at least 1 dose of study drug. A total of 142 individuals in the atomoxetine group experienced at least one adverse event compared with 112 in the methylphenidate group; this difference was statistically significantly (86.6% vs 67.5%; p<0.001). A total of 9.8% of individuals in the atomoxetine group experienced adverse events that were considered severe, which is similar to the 7.8% seen in the methylphenidate group.

The most common adverse events occurring in ≥5% of individuals are detailed in table 12 below. Significantly more individuals in the atomoxetine group experienced anorexia, somnolence, nausea, vomiting and dizziness compared with those in the methylphenidate group.

**Table 12**

| Adverse events | Atomoxetine n (%) | Methylphenidate n (%) | Fischer's exact pvalue |
|---|---|---|---|
| Anorexia | 61 (37.2) | 42 (25.3) | 0.024 |
| Decreased appetite | 46 (28.0) | 32 (19.3) | 0.07 |
| Somnolence | 43 (26.2) | 6 (3.6) | <0.001 |
| Nausea | 33 (20.1) | 17 (10.2) | 0.014 |
| Headache | 25 (15.2) | 16 (9.6) | 0.135 |
| Dizziness | 25 (15.2) | 12 (7.2) | 0.024 |
| Vomiting | 19 (11.6) | 6 (3.6) | 0.007 |
| Abdominal pain | 15 (9.1) | 15 (9.0) | 1.00 |
| Fatigue | 13 (7.9) | 5 (3.0) | 0.055 |
| Pyrexia | 11 (6.7) | 17 (10.2) | 0.324 |
| Cough | 11 (6.7) | 10 (6.0) | 0.825 |
| Upper respiratory tract infection | 9 (5.5) | 11 (6.6) | 0.818 |
| Irritability | 7 (4.3) | 10 (6.0) | 0.620 |
| Rhinorrhoea | 7 (4.3) | 10 (6.0) | 0.620 |
| Insomnia | 5 (3.0) | 9 (5.4) | 0.414 |

Other adverse events of note include:

Hepatic disorders- There was only case of raised ALT and this occurred in an individual receiving methylphenidate.

Cardiac disorders - Palpitations (2 atomoxetine, 4 methylphenidate) and tachycardia (2 atomoxetine) were the only cardiac disorders that were reported. There were also cases of chest pain (2 atomoxetine, 4 methylphenidate) and chest discomfort (1 atomoxetine), however, the information available does not allow determination of whether these cases were cardiac in origin.

Neurological disorders – There was one case of focal motor convulsion in a [redacted] who discontinued from the study after having received atomoxetine for 1 month. The investigator considered that the convulsion was possibly related to atomoxetine. There were no seizures in the methylphenidate group.

Psychiatric disorders – these include anger (6 atomoxetine, 1 methylphenidate), nervousness (5 atomoxetine, 3 methylphenidate), mood swings (1 atomoxetine, 2 methylphenidate) and excitability (2 methylphenidate).

In relation to the information collected on laboratory data, statistically significant differences in mean change scores were seen for alkaline phosphatase (ALP) and creatine phosphokinase (CPK). The mean decreases in ALP observed in both treatment groups were small. In relation to CPK there was a mean decrease in the atomoxetine group and a mean increase in the methylphenidate group. More patients in the methylphenidate group

had abnormally high CPK values compared with the atomoxetine group (13.2% vs 9.0%) but this difference did not reach statistical significance.

Data collected on vital signs showed statistically significant increases in diastolic and systolic blood pressure and temperature in patients receiving atomoxetine or methylphenidate but there was no significant difference between the groups. There was a statistically significantly decrease in patients weight in both treatment groups with the weight loss in the atomoxetine group being significantly lower than that seen in the methylphenidate group.

With regard to ECG changes there were no statistically or clinically meaningful changes in QT intervals between treatment groups.

### 6.2.1.2 Meta-analysis of Suicide-related Events in Paediatric Active Comparator-Controlled ADHD Clinical Trials

Following discussion of the risk of suicidal ideation associated with atomoxetine at the October meeting of the CHMP Pharmacovigilance Working Party the MAH was requested to provide a meta-analysis of suicide-related events in paediatric active comparator-controlled ADHD clinical trials (namely studies HFBD, HFBK, LYAV, LYBI and LYBR). All studies involved treatment with the active comparator methylphenidate. The analyses were conducted using the same methodologies as the meta-analysis submitted on 15 September 2005 which first identified an increase risk of suicidal ideation in children treated with atomoxetine compared to placebo. The two methodologies are the FDA-defined approach and the Lilly (PSWG)-defined approach (see Annex 1 for further information).

Using the FDA-defined approach, table 13 below provides the results for suicide-related events in paediatric, active comparator-controlled trials.

**Table 13. Suicide-Related Events (FDA-defined approach)**

| | Code 1[a] | | Code 2[b] | | Code 3[c] | | Code 4[d] | | Code 5[e] | | Code 9[f] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | ATX n/N | MPH n/N | ATX n/N | MPH n/N | ATX n/N | MPH n/N | ATX n/N | MPH n/N | ATX n/N | MPH n/N | ATX n/N | MPH n/N |
| HFBD | 0/65 | 0/20 | 0/65 | 0/20 | 0/65 | 0/20 | 1/65 | 0/20 | 0/65 | 0/20 | 0/65 | 0/20 |
| HFBK | 0/64 | 0/18 | 0/64 | 0/18 | 0/64 | 0/18 | 0/64 | 0/18 | 1/64 | 0/18 | 1/64 | 0/18 |
| LYAV | 0/44 | 0/41 | 0/44 | 0/41 | 0/44 | 0/41 | 0/44 | 1/41 | 0/44 | 0/41 | 0/44 | 0/41 |
| LYBI | 0/222 | 0/220 | 0/222 | 0/220 | 0/222 | 0/220 | 0/222 | 0/220 | 0/222 | 0/220 | 0/222 | 0/220 |
| LYBR | 0/164 | 0/166 | 0/164 | 0/166 | 0/164 | 0/166 | 0/164 | 0/166 | 0/164 | 0/166 | 0/164 | 1/166 |
| **TOTAL** | **0/559** | **0/465** | **0/559** | **0/465** | **0/559** | **0/465** | **1/559** | **1/465** | **1/559** | **0/465** | **1/559** | **1/465** |

Abbreviations: ATX = atomoxetine; MPH = methylphenidate.

[a] Code 1 = Completed suicide

[b] Code 2 = Suicide attempt

[c] Code 3 = Preparatory acts toward imminent suicidal behavior

[d] Code 4 = Suicidal ideation

[e] Code 5= Self-injurious behavior, intent unknown

[f] Code 9= Not enough information (non fatal)

Table 14 provides the results of the meta-analysis for suicide-related events in the pediatric ADHD studies.

**Table 14 : Meta-Analysis of Suicide-Related Events in Acute Pediatric Active Comparator-Controlled Atomoxetine Studies – ADHD (FDA-Defined Approach)**

| Outcome | Atomoxetine | | | Methylphenidate | | | MHRR [a] (95% CI) p-value | MHID [b] (%) (95% CI) p-value |
|---|---|---|---|---|---|---|---|---|
| | No. of events | N | % | No. of events | N | % | | |
| Code 1,2,3,4: suicidal behavior or ideation | 1 | 559 | 0.18 | 1 | 465 | 0.22 | 0.52 (95% CI; 0.06, 4.54) P = 0.556 | -0.12 (-0.62, 0.38) P = 0.649 |
| Code 4: Suicidal ideation | 1 | 559 | 0.18 | 1 | 465 | 0.22 | 0.52 (95% CI; 0.06, 4.54) P = 0.556 | -0.12 (-0.62, 0.38) P = 0.649 |
| Code 1,2,3,4,5,6,9: possible suicidal behavior or ideation | 3 | 559 | 0.54 | 2 | 465 | 0.43 | 0.62 (95% CI; 0.14, 2.73) P = 0.528 | -0.14 (-0.88, 0.60) P = 0.713 |

a MHRR=Mantel-Haenszel risk ratio stratified by study. It is the estimate of the percentage among atomoxetine-treated patients over the percentage among methylphenidate-treated patients.

B MHID=Mantel-Haenszel incidence difference stratified by study. It is the estimate of the percentage among atomoxetine-treated patients minus the percentage among methylphenidate-treated patients in percentage units.

As illustrated in the tree plot (Figure 1), a risk ratio of 0.52 (95% CI; 0.06, 4.54) is derived from the paediatric, active comparator-controlled studies meta-analysis for FDA codes 1, 2, 3, or 4, which include all events related to either suicidal behaviour or ideation.

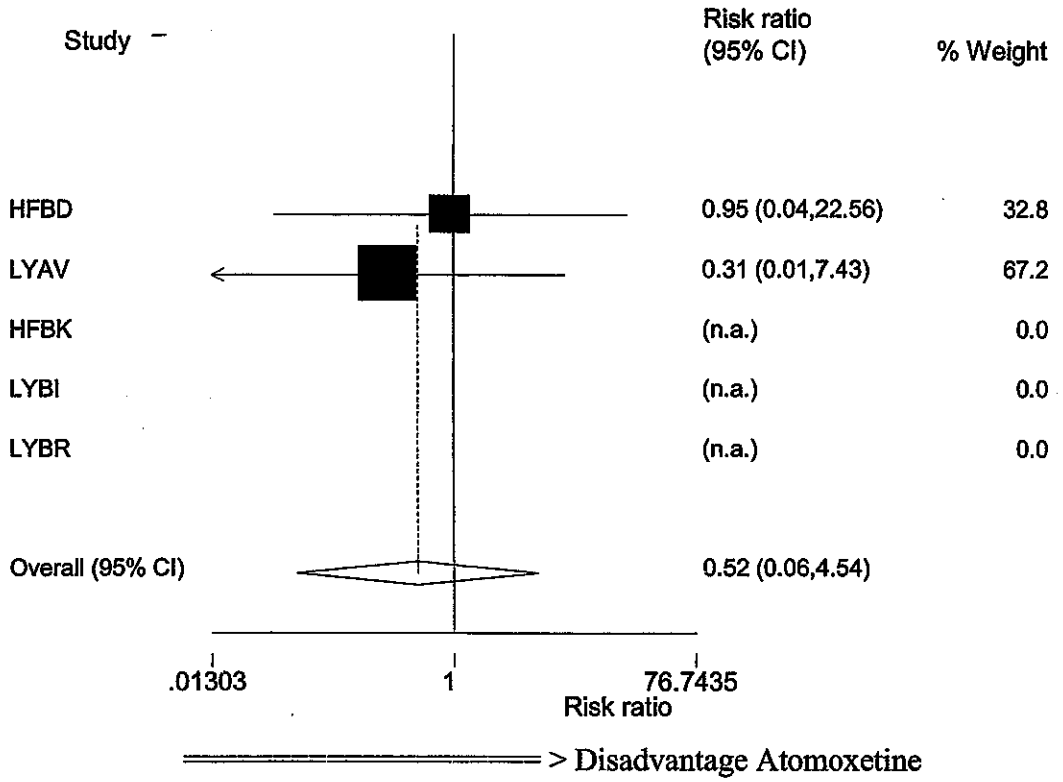



Figure 1

There are a total of 5 patients who experienced a potentially suicide related event in the active comparator controlled trials. Two of these patients (one atomoxetine, one methylphenidate) had insufficient information to adequately characterise their intent. Of the remainder, two were treated with atomoxetine and one with methylphenidate.

There were no studies in which there was more than one patient with a potentially suicide related event, which means that the individual trials do not have the power to detect this outcome reliably. Due to the small number of events in both treatment arms, there is insufficient information in this meta-analysis to establish whether there is a difference in risk of suicide related events between methylphenidate and atomoxetine.

A further meta-analysis carried out using a strategy defined by the MAH (PSWG defined approach – see Annex 1 for details of methodology) gave broadly similar results.

The meta-analysis results as provided by the MAH do not suggest that there is a difference in risk between the two treatments. However, if a standard 'correction factor' has been applied to both study arms when there are zero events in one arm, this may

provide an inaccurate summary of the risks. For example, study HFBD had 1 event in the atomoxetine arm (65 patients) and 0 events in the methylphenidate arm (20 patients). Simply adding 0.5 to each arm will produce a crude relative risk of 0.92

Results from a crude pooled analysis of the data we have conducted are provided in the table below for comparison with the meta-analysis results.

| FDA defined categories | Crude relative risk | 95% CI |
|---|---|---|
| 1 to 4 | 0.83 | 0.05 – 13.26 |
| 1 to 5 | 1.66 | 0.15 – 18.29 |
| 1 to 5, 9 | 1.25 | 0.21 – 7.44 |

These results suggest that the meta-analysis relative risk estimates provided by the MAH may be lower than would be expected given the data provided in table 13 above.

The MAH confirmed that the methodology used to calculate relative risks when there are zero events in one study arm was the method of adding 0.5 to the number events and to the number of non-events for each treatment prior to calculating the risk ratio.

### 6.2.1.3 Clinical trial data – Concerta XL

The Concerta XL Summary of product characteristics provides an overview of its safety profile during the clinical trials submitted in support of its licence application. In these clinical trials (n=469), approximately 62% of patients experienced at least one adverse reaction. The most commonly reported undesirable effects were headache (26%), loss of appetite (14%), insomnia (14%), and stomach ache (12%).

Other adverse reactions experienced are shown below.

*Body as a whole*: Common: ADHD aggravated, asthenia. Uncommon: chest pain, fever, accidental injury, malaise, pain.

*Cardiovascular system disorders*: Common: hypertension. Uncommon: migraine, tachycardia.

*Digestive system disorders*: Common: nausea and/or vomiting, dyspepsia. Uncommon: diarrhoea, faecal incontinence, increased appetite.

*Metabolic and nutritional system disorders*: Common: weight loss.

*Musculoskeletal system disorders*: Uncommon: leg cramps.

*Nervous system disorders*: Common: dizziness, somnolence and twitching (tics). Uncommon: hyperkinesia, speech disorder and vertigo.

*Psychiatric disorders:* Common: anxiety, depression, emotional lability, hostility and nervousness. Uncommon: abnormal dreams, apathy, confusion, hallucinations, sleep disorder, thinking abnormal, suicide attempt.

*Respiratory system disorders*: Uncommon: cough increased, epistaxis.

*Skin system disorders*: Common: rash. Uncommon: alopecia, pruritus, urticaria.

*Special senses*: Uncommon: diplopia.

*Urogenital system disorders*: Uncommon: urinary frequency, haematuria, urinary urgency.

Of note is the psychiatric disorders system organ class which lists suicide attempts as having occurred uncommonly (≥0.1% to <1%) in these trials. This may represent only one or two events in this relatively small trial population but was obviously of sufficient concern to warrant mention in the SPC. Upon further clarification with the MAH (Janssen-Cilag Ltd) it transpires that it was a single post-marketing spontaneous case of completed suicide reported in the US which led to the inclusion of this statement in the SPC. This case was submitted with the original Marketing Authorisation Application for Concerta XL. The case involves a [redacted] patient with ADHD and a history of depression. The patient had been receiving sertraline for approximately eight months when Concerta XL 36mg daily was initiated. Within 1 month of starting Concerta the patient committed suicide. The patient's father and maternal great-grandfather had also previously committed suicide.

### 6.2.1.4 UK Spontaneous Reporting Data

Up to 22 September 2005 a total of 481 reports of 897 reactions have been received in association with all methylphenidate containing products in the UK since October 1964. The majority of the reported reactions (60%) belong to the following five system organ classes (SOCs) - Psychiatric disorders, Nervous system disorders, General disorders, Skin and subcutaneous disorders and Blood and lymphatic disorders.

Overall the most commonly reported reactions include hallucinations (n=31), aggression (n=23), headache (n=21), nausea and/or vomiting (n=20), anorexia/decreased appetite (n=18), drug ineffective (n=17), rash (n=14), abdominal pain (n=13) and insomnia (n=12), abnormal behaviour (n=12) and alopecia (n=12). These suspected adverse drug reactions (ADRs) are similar to the most commonly reported ADRs in clinical trials.

*Psychiatric disorders*
The most commonly reported psychiatric disorders are listed in the table below. Mainly these are recognised reactions or may reflect the underlying disease.

| Reaction | Number of reports |
|---|---|
| Hallucinations | 31 |
| Aggression | 23 |
| Insomnia | 12 |
| Abnormal behaviour | 12 |
| Tic | 11 |
| Confusion | 7 |
| Psychotic disorder | 7 |
| Nightmares/sleep terrors | 7 |
| Depression | 5 |
| Mood disorders | 5 |
| Suicidal ideation | 5 |

*Suicide attempts/ suicidal ideation*
A total of 5 reports of suicidal ideation and 3 reports of suicide attempt have been received. In addition there have been 3 reports of overdose.

Four of these reports (1 suicide attempt and 3 suicidal ideations) are from a literature article that presents the findings of an audit survey of service provision. The impact was examined of a mass media public education campaign about ADHD and the use of methylphenidate. Short, medium and long-term effects were also investigated. A total of 3 reports of suicidal behaviour and 5 reports of suicide attempt were included in the results tables. The information provided is limited and does not allow a decision about causality to be made in these cases.

The remaining two suicide attempts involve a [redacted] and a [redacted]. In the first case the individual had a history of emotional instability [redacted]. In the second case, within two months of starting treatment the [redacted] experienced low mood and marked depression and [redacted]. [redacted] recovered after drug withdrawal.

The two reports of suicidal ideation involve a [redacted] and a [redacted]. In the first case the [redacted] experienced depression and suicidal feelings after 18 months on methylphenidate. [redacted] recovered after drug withdrawal but this also coincided with a change in [redacted]. In the second case it was reported that after an unspecified time on methylphenidate [redacted]. The night time dose was stopped and behaviour improved.

*Overdose*
The first case involves a [redacted] who took up to 10 tablets [redacted]. [redacted] subsequently died due to cerebral oedema possibly as a result of a hypertensive crisis. The second case relates to a male patient whose [redacted] gave [redacted] a higher than prescribed dose (54mg instead of 36mg). He experienced hallucinations and displayed choroidal/extrapyramidal

movements. The third case involves [redacted] (under 16 years of age) who is reported to be abusing methylphenidate; very limited information has been provided in this case.

*Drug dependence/abuse*
There have been two reports of drug dependence and two reports of drug abuse received.

The first case of drug dependence contains very little information – a [redacted] patient was reported to be addicted to methylphenidate after 4 months of treatment. The second case of drug dependence involves a [redacted] who had received methylphenidate for narcolepsy for 6 years and became dependent on it. [redacted] subsequently managed to successfully withdraw from treatment.

The first case of drug abuse contains very little information other than to say that the patient who is less than 16 years of age is reported to be abusing methylphenidate. The second case of drug abuse is described in the overdose report above.

The methylphenidate product information does contain warnings that the chronic abuse of Ritalin can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour.

*Nervous system disorders*
The most commonly reported reactions in this SOC are headache (n=21), seizures (n=18), Dizziness (n= 9), tremor (n=7) and dysarthria (n=4). These are recognised reactions and listed in the methylphenidate product information.

*General disorders*
The most commonly reported reactions in this SOC are drug ineffective (n=17), chest pain/discomfort (n=16), drug withdrawal syndrome (n=6), pyrexia (n=5) and asthenic conditions (3 asthenia, 2 malaise and 1 fatigue). There are also two reports of growth retardation. Chest pain, fever, fatigue and malaise are recognised reactions and listed in the product information.

*Skin and subcutaneous disorders*
The most commonly reported reactions in this SOC are rash (n=14), alopecia (n=12), urticaria (n=8), photosensivity reactions (n=5) and hyperhidrosis (n=4). With the exception of photosensitivity reactions these are recognised reactions that are listed in the methylphenidate product information.

*Blood and lymphatic disorders*
The reported reactions in this SOC include neutropenia (n=32), leukopenia (n=15), thrombocytopenia (n=5) and anaemia. These are recognised reactions and listed in the methylphenidate product information, which recommends periodic full blood counts, differential and platelet counts during prolonged therapy.

*Hepatic disorders*
A total of 7 reports of hepatic disorders have been received. These are 3 reports of jaundice, 2 of hepatitis and 1 report each of hepatosplenomegaly and 1 Gilbert's

syndrome. Abnormal liver function tests and hepatitis are recognised reactions and listed in the methylphenidate product information.

*Cardiac disorders*
A total of 39 reports of cardiac disorders have been received. The most commonly reported reactions in this SOC are palpitations (n=9), arrhythmia (n=6), cyanosis (n=5) and tachycardia (n=2). Tachycardia, palpitations and arrythmias are recognised reactions and listed in the methylphenidate product information.

*Fatal reports*
Seven of the reports had a fatal outcome, which is equivalent to approximately 1.5% of all reports received in association with methylphenidate. Where cause of death is provided (6 reports) the reported causes of death are cardiomegaly, cardiac arrest, fibrosarcoma, cerebral haematoma and cerebral oedema. These reports also include a report of fatal neonatal respiratory distress syndrome following maternal use of methylphenidate.

### 6.2.1.5 US spontaneous reporting data

At a recent FDA Paediatric Advisory the FDA presented to the meeting a review of the spontaneous reporting data held on its Adverse Event Reporting System (AERS) database in relation to Concerta from market approval (1 August 2000) to 4 January 2005.

The following are the top 20 reported events in association with the use of Concerta in children and adolescents: drug ineffective (54), headache (52), aggression (45), insomnia (44), pharmaceutical product complaint (42), abnormal behaviour (41), condition aggravated (36), abdominal pain (35), anorexia (32), vomiting (31),hallucinations (30), anxiety (26), drug effect decreased (25), agitation (24), nausea (24), chest pain (23), depression (21), muscle twitching (21), suicidal ideation (20), drug interaction (19).

Whilst the top 20 reported events in association with the use of Concerta in adults are: nausea (19),agitation (17), completed suicide (14), insomnia (14), pharmaceutical product complaint (12), somnolence (12), intentional overdose (10), coma (9), convulsion (9), drug ineffective (9),vomiting (9), tremor (8), back pain (7), confusional state (7), depressed level of consciousness (7), diarrhoea (7), disorientation (7), dizziness (7), drug withdrawal syndrome (7) and heart rate increased (7).

The FDA has also reviewed in more detail the spontaneous reports submitted during the first year after Concerta received paediatric market exclusivity in the US. A total of 164 reports were retrieved by this search but 2 involved adults, 5 were duplicate reports and 14 involved other methylphenidate containing products. This resulted in 135 reports associated with Concerta. These reports included 13 reports of suicidal thoughts or behaviour (8 suicidal ideation, 3 suicide attempts and 2 suicidal gestures). Two of the reports of suicidal ideation were considered by the FDA to be strongly confounded by the concomitant sertraline that had recently been added to the child's treatment. Only limited information is available on the remaining reports of suicidal thoughts and behaviour but

they are not considered by the FDA to be strongly confounded – the time to onset in these cases varied greatly from 1 day to 2 years.

The FDA concludes that psychiatric adverse events represent the main area of unlabeled adverse events. The FDA notes that the current labelling includes information on pre-exacerbations of underlying conditions (anxiety, tension and agitation, and behavioural and thought disorders in psychotic patients) but consider that newly-emergent psychiatric adverse events are not adequately labelled and therefore further review of these events is required and consideration should be given to amending the product information.

#### 6.2.1.6 Responses to NUI on reports of Suicidal Behaviour associated with Methylphenidate in European Member States

As agreed during the November 2005 meeting of the Pharmacovigilance Working Party a Non Urgent Infofax (NUI) was circulated to all Member States to obtain information on what, if any reports of suicidal behaviour they have received in association with the methylphenidate containing products authorised in their countries. A tabular overview of the responses received from 13 Member States is attached at Annex 10. At least one methylphenidate containing product is licensed in the majority (11 out of 13) of Member States who responded. The licensed indications are mainly ADHD but some in Member States Ritalin is authorised indicated for the treatment of narcolepsy. In most countries there is a general trend towards increasing usage of methylphenidate in the last few years.

A total of 13 reports of suicide attempt, 9 reports of suicidal ideation and 2 reports of completed suicide have been received in [redacted]. Five of the reports of suicide attempt were potentially confounded by previous history or underlying disease and in a further 3 cases the suicide attempt occurred in the context of a psychotic episode. Generally it appears that where Concerta and Equasym are licensed the product information contraindicates use in patients with current or a history of suicidal tendency. The Concerta product information lists suicide attempt as a potential side effect in section 4.8. With the exception of the product information in the Netherlands, the Ritalin(e) product information only contains information about transient depressed mood in section 4.8.

### 6.2.2 Dexamphetamine

Dexamphetamine a stereoisomer of amphetamine, is an indirect-acting sympathomimetic with alpha- and beta-adrenergic activity. It has marked stimulant effect on the CNS, particularly the cerebral cortex. In the UK it is indicated for children with refractory hyperkinetic states under the supervision of a physician specialising in child psychiatry.

#### 6.2.2.1 UK Spontaneous reporting data

Up to 22 September 2005 a total of 50 reports of 88 reactions have been received in association with all dexamphetamine containing products. Approximately one half of the

reported reactions belong to the following system organ classes (SOCs) - Psychiatric disorders, Nervous system disorders and Cardiac disorders.

*Psychiatric disorders*
The most commonly reported psychiatric disorders are psychotic disorder (n=5), hallucinations (n=3) and insomnia (n=2). There is also 1 report of intentional self-injury and 1 of drug dependence. The first case relates to intentional self-harm in a schizophrenic patient who was using illicit drugs such as cannabis and amphetamines. The second case is of a [redacted] who became dependent on dexamphetamine after 2 years of treatment. Psychotic disorders and insomnia are recognised reactions and listed in the product information and there are also warnings about the drug dependence.

*Nervous system disorders*
The most commonly reported nervous system disorders are amnesia (n=3) and seizures (n=2). Seizures are recognised reactions and listed in the SPC.

*Cardiac disorders*
The most commonly reported reactions in this SOC are palpitations (n=3), atrial fibrillation (n=2), supraventricular tachycardia (n=2), myocardial infarction (n=2), congestive cardiac failure (n=2) and congestive cardiomyopathy (n=2). Tachycardia, palpitations, increases in blood pressure and very rare reports of cardiomyopathy are recognised reactions and listed in the SPC. In Canada, concerns about very rare reports of sudden death in children and adults taking Adderall ( a combination preparation of amphetamine salts) has led to its withdrawal from the Canadian market. It has subsequently been returned to the market.

*Hepatic disorders*
There is one report of hepatic congestion. This was in an individual who developed congestive cardiomyopathy and myocardial infarction.

*Fatal reports*
Five reports had a fatal outcome, which is equivalent to approximately 10% of all reports received in association with dexamphetamine. Where cause of death is provided (4 reports) the reported causes of death are pulmonary embolism (n=2) and 1 report each of cerebral artery thrombosis and coronary artery thrombosis.

In the two cases of pulmonary embolism and the case of coronary artery thrombosis there is limited information on which to judge what role dexamphetamine may have played in these cases. The case of cerebral artery thrombosis in a 36 year old patient who the post mortem noted had been on dexamphetamine for 6 years and an oral contraceptive for at least 6 days prior to [redacted] death.

**Assessor's comments (comparative safety):**
Methylphenidate and dexamphetamine are alternative therapies authorised for ADHD. Usage data from the UK indicate that extended release methylphenidate is the most widely prescribed treatment for ADHD followed by immediate release methylphenidate,

dexamphetamine and then atomoxetine. During the period 1/7/2004 to 30/6/2005, the total number of patient years exposed to methylphenidate is estimated to be just over 45,000 patient years, with approximately 2,500 patient years exposed to atomoxetine and 6,500 patient years exposed to dexamfetamine.

A meta-analysis of suicide-related events in paediatric active-comparator-controlled ADHD clinical trials does not suggest that there is a difference in risk of suicide-related events between the atomoxetine and methylphenidate, however the correction methods used by the MAH may provide an inaccurate summary of the risks and there are too few events to come to any firm conclusions. Thus whilst the results do not suggest a difference in risk they are not reassuring either.

The comparative safety and efficacy of atomoxetine and methylphenidate was examined in study LYBR. The percentage of patients who discontinued treatment due to adverse events was statistically significantly higher in the atomoxetine group compared with the methylphenidate group (11% vs 3.6%; p=0.011). The adverse events that most frequently led to discontinuation were anorexia, decreased appetite, nausea and abdominal pain and are recognised adverse effects of both drugs. The number of patients who experienced one or more adverse events was statistically significantly greater in the atomoxetine group compared with the methylphenidate group (86.6% Vs 67.5%; p<0.001) however the number of severe adverse events was similar between the groups (9.8% atomoxetine vs 7.8% methylphenidate). Of note, there was a statistically significant decrease in weight in both treatment groups with the weight loss in the atomoxetine group being significantly lower than that seen in the methylphenidate group.

With respect to psychiatric disorders there were differences between the two groups – atomoxetine was associated with more cases of anger, and nervousness, whilst methylphenidate was associated with more cases of mood swings and excitability.

There were no clinically significant differences between atomoxetine and methylphenidate with respect to reported cardiac disorders (including effects on blood pressure and ECG changes), hepatic disorders and seizure disorders. With regard to the latter it is of note that there was one reported case in the atomoxetine group and none in the methylphenidate group. No conclusions can be drawn from these results however given the small number of cases.

From the UK spontaneous reporting data presented, psychiatric reactions, nervous system disorders and general conditions are in the top 5 most frequently reported system organ classes for all three drugs. The two other SOCs which were in the 5 most frequently reported SOCs for atomoxetine but not for methylphenidate or dexamphetamine were gastrointestinal disorders and investigations. The majority of these reports are of nausea, vomiting, and abdominal pain and abnormal liver function tests. Skin disorders and blood and lymphatic disorders are in the 5 most frequently reported SOCs for methylphenidate but not for atomoxetine or dexamphetamine. The cardiac disorders SOC is in the top 3 SOCs for dexamphetamine, however it is not in the top 5 SOCs for either atomoxetine or methylphenidate.

Based on the UK spontaneous reporting data, the most commonly reported reactions for

atomoxetine and methylphenidate are remarkably similar and include nausea, vomiting, headache, and aggression.

It is important to note that the spontaneous reporting data for atomoxetine, methylphenidate, and dexamphetamine can only be used to detect trends in reporting rates for any given reported reaction. Numerical comparisons should not be made between reactions associated with the different drugs. Confounding factors such as variations in the level of reporting (which can depend on the age of the drug, promotion/publicity surrounding the drug) and the extent of usage of the drug mean that any comparison made is likely to be misleading.

The four key safety issues identified and discussed above for atomoxetine (suicidal behaviour and other psychiatric reactions, seizures, hepatotoxicity and cardiovascular adverse effects) are recognised adverse effects of methylphenidate. Seizures and cardiovascular adverse reactions are recognised to occur with dexamphetamine as well as other serious adverse events such as psychosis, intracranial haemorrhage, toxic hypermetabolic state, rhabdomyolysis, and renal damage.

# 7.0 DISCUSSION

*Efficacy*
Due to the small number of patients included in the studies and their primary objectives very limited information on comparative efficacy can be obtained from studies LYAU, LYAV and LYBM. Study LYBR was multi-centre, randomised, double-blind study comparing the safety and efficacy of atomoxetine and methylphenidate in 330 children. Whilst this study has limitations and design/analysis issues that mean it is not completely applicable to the use of atomoxetine in the EU it does support what has been seen previously in that there is trend in favour of greater efficacy for methylphenidate. It is recommended that further large, well-designed studies are warranted to help clearly establish the comparative efficacy of atomoxetine to alternative treatment for ADHD.

*Overall safety profile*
The review of the available safety data suggests that generally the most commonly reported reactions in association with atomoxetine are recognised reactions and are listed in the product information. Spontaneous reporting data suggest that the safety profiles for atomoxetine and methylphenidate are similar, however, it is difficult to make direct comparisons from the data given the considerably different length of times that these products have been marketed. It is of note that some more recent direct comparative data (clinical study LYBR) provides some indication that atomoxetine may not be as well tolerated as methylphenidate. However, atomoxetine could be considered to have some important advantages over alternative treatments in terms of its apparent lack of abuse potential and that it can be used in patients with co-morbid tic disorders.

Review of the currently available safety data for atomoxetine has identified four key safety issues which may impact on the overall risk:benefit balance of atomoxetine in children and adolescents with ADHD. These four key safety issues are the previously

identified issues of suicidal ideation/behaviour (and other psychiatric reactions) and hepatotoxicity, and the newly identified signals of seizure and cardiac adverse reactions (in particular QTc interval prolongation). Further reported reactions have been identified that require further review and assessment are blood dyscrasias; cerebrovascular accident; serious skin disorders including erythema multiforme and Stevens Johnson Syndrome; urinary tract haemorrhage; testicular pain, testicular disorder and testicular atrophy; parasthesia/hypoaesthesia; speech disorder/dysarthria; dyskinesia, dystonia, extrapyramidal disorders and tremor; myalgia and arthralgia. Those adverse events identified which could potentially impact on the overall risk:benefit balance of atomoxetine if upon review they were considered to be causally related, are cerebrovascular accident and serious skin reactions. The MAH has been requested to provide further review of these safety signals and an assessment of the data will be provided in an addendum report prior to the January 2006 meeting of the PhVWP. The review also identified that the occurrence of Raynaud's phenomenon appears to be causally related to atomoxetine use. Whilst this is not considered to substantially impact on the risk:benefit balance it should be added to the SPC in section 4.8 as potential side effect.

*Suicidal behaviour*

With regard to the risk of suicidal thoughts and attempts, the data from clinical trial and spontaneous reports support the action taken with Urgent Safety Restriction to update the SPC to include warning about the risk of suicidal behaviour. Whilst the meta-analysis of suicide-related events paediatric active-controlled studies does not suggest that atomoxetine is associated with a greater risk than methylphenidate, due to the low number of events and therefore lack of adequate power it not possible to rule such an increased risk. Methylphenidate products are recognised to potentially cause worsening of underlying depression and suicide attempt is listed as a potential side effect for some methylphenidate products (Concerta) and is contraindicated in patients with severe depression and a history of suicidal tendency. This contraindication may result in atomoxetine being preferentially prescribed in patients who are at high risk of suicidal behaviour and if such 'channelling' occurs it may skew the spontaneous reporting rates of these events. The same cannot be said of the clinical trial data which initially raised the signal of suicidal behaviour in association with atomoxetine. In the atomoxetine paediatric clinical trials co-morbid conditions including depression and anxiety disorders were not exclusion criteria and this was considered appropriate given that it is representative of the population likely to receive atomoxetine in clinical practice. However, the number of patients with co-morbid psychiatric disorders in the trials was relatively low. Patients with a history of bipolar disorders and those considered to be a serious suicidal risk however were excluded. Therefore, it may be considered appropriate that use of atomoxetine is also contraindicated in patients with severe depression and those considered with a history of suicidal tendency.

*Hepatic disorders*

In January 2005, following the review of the available on hepatic reactions the atomoxetine SPC was updated to contain warnings about the risk of rare, idiosyncratic hepatic reactions. The more recent data confirms the very rare nature of the liver injury and the potentially severe nature of the events. It does not, however, allow better characterisation of these hepatic reactions over and above what is already known and

therefore does not suggest that further updates to the product information are necessary or are likely to minimise this risk.

*Seizure disorders*
The pre-clinical and clinical trial data for atomoxetine do not suggest that atomoxetine is proconvulsive but it is of note that patients with a history of seizure disorder were excluded from these clinical trials. Spontaneous reporting data show that seizures have been the most frequently reported serious adverse events for atomoxetine since it was first launched. Seizures are recognised to occur in association with methylphenidate use and there are warnings in the product information about this risk and that treatment should be stopped if seizures occur. Although there is not data to support this it is possible that atomoxetine may be preferentially prescribed to patients who are a high risk of seizures and that this may skew the spontaneous reporting rates of seizure disorder. The results of an observational health claims database study suggest that atomoxetine use is associated with the occurrence of seizures in patients with and without a prior history of seizure disorder. Together these data indicate that it may be advisable to update the atomoxetine product information to include a warning in section 4.4 about the risk of aggravation of underlying seizure disorders and/or new onset seizure as well as updates to section 4.8 (Undesirable effects) and section 4.9 (Overdose).

*Cardiovascular disorders*
Atomoxetine is recognised to increase noradrenergic tone and effects such as orthostatic hypotentison, palpiations, tachycardia and increases in blood pressure, which are all listed in the SPC. However, a review of spontaneous reports of cardiac disorders has highlighted the significant number of reports of QTc interval prolongation that have been received since atomoxetine was first launched. A review of the data from the WHO Uppsala monitoring centre has also raised concerns about the potential for atomoxetine to cause QTc interval prolongation and that this may be more marked when atomoxetine is used with concomitant medicinal products that are known to be substrates or inhibitors of CYP2D6. There is also some suggestion from the spontaneous reporting data that QTc prolongation may be more likely in association with higher/overdoses of atomoxetine. Together with the earlier concerns from pre-clinical data, these spontaneous reports do not rule out the possibility that at the very least, atomoxetine may cause QT interval prolongation in situations where steady state plasma levels of atomoxetine are increased. In order to determine the potential for atomoxetine to cause QTc interval prolongation at therapeutic doses further pre-clinical studies may be necessary and it may be advisable that ECG data are routinely collected in clinical trials. The MAH has also been requested to provide further review of cases reported as 'unspecified arrhythmias' and central ischaemia and an assessment of the data will be provided in an addendum report prior to the January 2006 meeting of the PhVWP.

Overall the available safety and efficacy data suggest that the balance of risks and benefits of atomoxetine in the treatment of ADHD remains favourable. It may, however, be considered that further amendments to the product information and/or restrictions on use are required in order to optimise its safe use. Furthermore, studies to better define the comparative efficacy of atomoxetine in relation to alternative treatments and additional

amendments to the Pharmacovigilance Risk Management Plan to better characterise the safety profile and minimise the risk may be warranted.

## 8.0 REGULATORY OPTIONS

The following regulatory options are open for consideration by the Pharmacovigilance Working Party in relation to atomoxetine (Strattera). Options ii) and iii) are not mutually exclusive.

**i) No action (other than the update to the product information already agreed)**
This option should be considered if the balance of risk and benefits is considered to be favourable and the action taken to date to update the product information (Urgent Safety restriction to include warnings about suicidal behaviour) accurately reflects the safety profile and sufficiently addresses the known risks.

**ii) Further update of the product information and strengthening of warnings.**
This option should be considered if the balance of risks and benefits is considered to be favourable but further amendments are considered necessary in order to accurately reflect the safety profile and optimise its safe use.
The following are possible areas where updates to the SPC may be required:

Section 4.3 (Contraindications) – contraindicate use in patients with severe depression and a history of suicidal behaviour
Section 4.4 (Warnings and Precautions for Use) – addition of warning about the risk of aggravation of underlying seizure disorders and new onset seizure
Section 4.8(Undesirable effects) – addition of Raynaud's phenomen, aggression, hostility and emotional lability.
Section 4.9 (Overdose) – amendments to this section to reflect the potential for QT prolongation in overdose

**iii) Restriction of use**
Strattera is already restricted to initiation and supervision by or under the supervision of a physician with appropriate knowledge and experience in treating ADHD. However, this restriction could be made more prominent in the SPC by moving this from section 4.2 (Posology and Administration) to Section 4.1 (Therapeutic indications), which would also mean that this is consistent with the position for both methylphenidate and dexamphetamine. A further restriction on use that could be considered is in patients who have previously failed or are intolerant of other treatment for ADHD, i.e. second-line therapy. This should be considered if there is clear evidence that the safety profile of atomoxetine is less favourable than that of alternative treatments.

**iv) Immediate Suspension of the Marketing Authorisation**
Immediate suspension of the Marketing Authorisation pending further investigation/evaluation of the risk is appropriate if the balance of risks and benefits is clearly negative and there are urgent, significant safety and public health concerns where lesser measures are not considered to provide adequate safeguards.

**v) Revocation of the Marketing Authorisation**

Revocation of the Marketing Authorisation with rights of appeal for the Marketing Authorisation Holder should be considered if the balance of risks and benefits is clearly negative and the product proves harmful in the normal conditions of use.

[redacted]

**9 December 2005**

# ANNEX 1

# European AR on MAH Meta-Analyses of Clinical Trial Data (Suicide)

MHRA

Medicines and Healthcare products Regulatory Agency

Safeguarding public health

# ASSESSMENT REPORT

## STRATTERA (atomoxetine) - Increased risk of suicidal behaviour

| | |
|---|---|
| **Invented name of the pharmaceutical products in the Member State** | Strattera |
| **Name(s) of the active substance(s) (INN)** | atomoxetine |
| **Pharmacotherapeutic classification (ATC Code)** | centrally acting sympathomimetics (N06BA9) |

| | |
|---|---|
| **Reference No** | UK/H/0686/01-06 |

| | |
|---|---|
| **Reference Member State** | UK |
| **Member States concerned** | DE, NL, NO |

| | |
|---|---|
| **Marketing Authorisation holder's name and address** | Eli Lilly and Company Limited<br>Kingsclere Road<br>Basingstoke<br>Hampshire<br>RG21 6XA<br>United Kingdom |
| **Marketing authorisation number** | PL 00006/0374-0379 |

| | |
|---|---|
| **Date of this Report** | 23 September 2005 |

**STRATTERA▼ (atomoxetine): INCREASED RISK OF SUICIDAL BEHAVIOUR**

**1. ISSUE**

The MHRA has been informed by the Marketing Authorisation Holder for Strattera (Eli Lilly) of an analysis of double blind, randomised, placebo-controlled clinical trial data for atomoxetine which has identified a statistically significant increased risk of suicidal behaviour with atomoxetine compared to placebo in children with ADHD. Lilly have submitted a Type II variation (30 day procedure) to update section 4.4 (Special Warnings and Special Precautions for Use) of the Summary of Product Characteristics (SPC) and the corresponding section of the Patient Information Leaflet (PIL), with respect to suicidal behaviour.

On discussion with CMS it has been agreed that these new data call into question the overall balance of risks and benefits for atomoxetine in its licensed indication and a full risk:benefit review is warranted. In the interim it has been agreed that warnings about the risk of suicidal behaviour with atomoxetine should be added via and Urgent Safety Restriction (USR) procedure to allow timely communication of the risk to health professionals and patients. This report provides an overview of the new analysis and proposes SPC changes to be implemented via a USR.

**2. BACKGROUND**

Strattera (atomoxetine) is authorised for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents aged 6 years and over as part of a comprehensive treatment regime. Atomoxetine is a highly selective and potent inhibitor of the pre-synaptic noradrenaline transporter without directly affecting the serotonin or dopamine transporters.

Atomoxetine is authorised in the EU under the Mutual Recognition Procedure (MRP) with the UK as lead Member State (RMS) and Germany, the Netherlands and Norway as Concerned Member States (CMS). Marketing Authorisation applications are currently ongoing in a further 22 CMSs under a second-wave MRP.

In January 2005, following reports of severe liver injury associated with the use of atomoxetine, the SPC and PIL were updated via an expedited variation procedure to warn of the risk of liver injury with the advice to stop treatment immediately if liver injury is suspected.

Atomoxetine was included in the recent EU Article 31 referral of paediatric use of antidepressants. Following review of the data submitted by Lilly on 22 February 2005, the EU Committee on Human Medicinal Products (CHMP) concluded that there was no signal of an increased risk of suicide related behaviour in the atomoxetine studies however there was an increased risk of hostility and emotional lability.

The two new analyses of atomoxetine clinical trial data which identified an increased risk of suicidal behaviour with atomoxetine compared with placebo in children with ADHD were performed by the MAH at the request of the FDA. The full report is attached at Annex 1.

## 3. OVERVIEW OF THE DATA

### *3.1 Methodology*

Since the completion of the Article 31 procedure, Lilly have performed two further analyses of atomoxetine clinical trial data. The MAH state that data from 8 paediatric placebo-controlled trials were included in Lilly's response to the Article 31 Referral. The two new analyses include data from a further 4 paediatric placebo-controlled studies (3 in ADHD and 1 in enuresis) and 9 adult placebo-controlled studies (3 ADHD, 6 Major Depressive Disorder). Furthermore, for these new analyses, a more comprehensive search of the database, which included the comments field as well as the reaction term fields, was conducted.

The two new separate meta-analyses employ different methods – the first set of meta-analyses are carried out using the FDA-defined outcome definitions, and the second set of meta-analyses are carried out using outcome definitions derived by Lilly's internal Psychobehavioural Safety Working Group (PSWG). The two methods and their differences are described in more detail in Section 5 of the attached full report (Annex 1).

All meta-analyses were carried out on 12 paediatric studies and 9 adult studies separately. The meta-analyses have been carried out using the Mantel-Haenszel risk ratio and Mantel Haenszel incidence difference methods.

### *3.2 Results*

***Paediatric studies***

The results of the meta-analysis of suicide-related events in the paediatric studies for all conditions (ADHD and enuresis) utilising the FDA-defined approach are provided in **Table 1** below.

**Table 1. Meta-analysis of Suicide-Related Behaviours in Acute Paediatric Placebo-Controlled Atomoxetine Studies – All conditions (FDA-defined approach).**

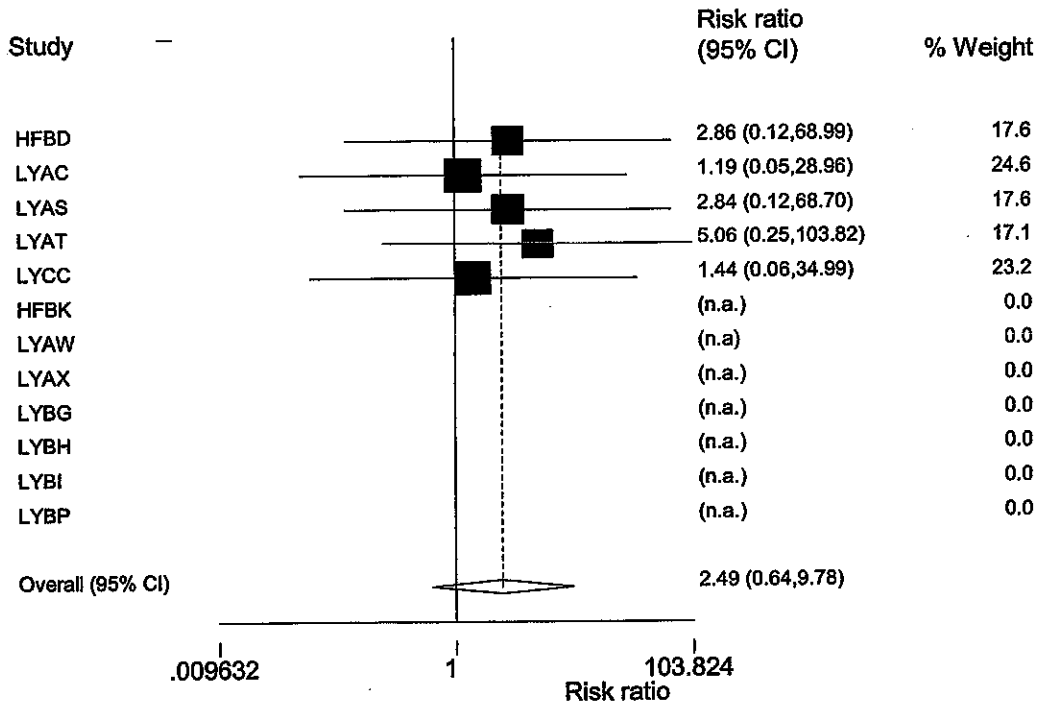
| Outcome | Atomoxetine | | | Placebo | | | MHRR [a] (95% CI) p-value | MHID [b] (%) (95% CI) p-value |
|---|---|---|---|---|---|---|---|---|
| | No. of events | N | % | No. of events | N | % | | |
| Code 1,2,3,4: Suicidal behavior or ideation | 6 | 1357 | 0.44 | 0 | 851 | 0 | 2.49 (0.64, 9.78) p=0.190 | 0.52 (0.12,0.91) p=0.010 |
| Code 1,2,3: Suicidal behavior | 1 | 1357 | 0.07 | 0 | 851 | 0 | 1.19 (0.049, 28.96) p=0.914 | 0.06 (-0.07, 0.19) p=0.398 |
| Code 4: Suicidal ideation | 5 | 1357 | 0.37 | 0 | 851 | 0 | 2.92 (0.63, 13.57) p=0.172 | 0.46 (0.09,0.83) p=0.016 |
| Code 1,2,3,4,5,6,9: Possible suicidal behavior or ideation (or not enough information known) | 9 | 1357 | 0.66 | 3 | 851 | 0.35 | 1.43 (0.56, 3.65) p=0.457 | 0.38 (-0.26, 1.03) p=0.244 |

[a] MHRR = Mantel-Haenszel risk ratio stratified by study. It is the estimate of the percentage among atomoxetine-treated patients over the percentage among placebo-treated patients.

[b] MHID = Mantel-Haenszel incidence difference stratified by study. It is the estimate of the percentage among atomoxetine-treated patients minus the percentage among placebo-treated patients in percentage units.

**Figure 1** below shows the risk ratios by study for suicide behaviour or ideation (FDA-defined approach).

**Figure 1. Suicide behaviour or Ideation (FDA Derived): Risk Ratios by Study Atomoxetine vs Placebo Paediatric Studies, All Conditions (Forest Plot from STATA)**




There were 12 paediatric studies included in the meta-analysis, however only 5 of these had any suicide behaviour or ideation events recorded, as defined by FDA codes 1-4. The risk ratio from the meta-analysis of suicide behaviour or ideation for atomoxetine compared to placebo was 2.49 (0.64, 9.78)

The studies with no suicide related events recorded can only be included in the meta-analysis using the Mantel Haenszel incidence difference methodology. The incidence difference from the meta-analysis of suicide behaviour or ideation for atomoxetine compared to placebo was 0.52% (0.12, 0.91).

More suicide-related events (6 events from 5 trials) were identified using the FDA search criteria than the PSWG criteria and so the PSWG defined method is not discussed further in this preliminary report. The PSWG paediatric analyses can be found in Section 6.2.2 (page 33) of the full report (Annex 1).

There was no real pattern in terms of time to onset of these events, which occurred at the following times into the treatment period – day 9, day 10, day 17, day 25, day 28 and day 31.

***Adult studies***

There were 9 adult studies included in the meta-analysis, however only 6 of these had any suicidal behaviour or ideation events recorded, as defined by FDA codes 1-4. The risk ratio from the meta-analysis of suicide behaviour or ideation for atomoxetine compared to placebo was 1.19 (0.57, 2.52)

The studies with no suicide related events recorded can only be included in the meta-analysis using the Mantel Haenszel incidence difference methodology. The incidence difference from the meta-analysis of suicide behaviour or ideation for atomoxetine compared to placebo was 0.28% (-0.47, 1.02).

The increased risk does not appear to be reflected in adult patients. Further details of the adult analyses can be found in section 6.3 (page 35 onwards) of the MAH's full report (Annex 1).

## 4. OTHER DATA

***UK spontaneous reports of suicidal behaviour***

The MHRA has received 11 reports (12 reactions) of suicide-related behaviour suspected to be associated with the use of atomoxetine in the UK since its launch in July 2004. These are: Intentional overdose (1) suicidal depression (1), suicidal ideation (8) and suicide attempt (2).

Usage data from the UK indicate that approximately 2200 patients have been treated with atomoxetine since UK launch in July 2004.

***Spontaneous reports in other EU member states***

The responses to the Rapid Alert dated 19th September indicate that 3 cases of suicidal behaviour have been reported in other EU member states. These include completed suicide (1), suicide attempt (1) and suicidal ideation (1).

A cumulative review of all spontaneously reported cases worldwide will be requested from the MAH as part of the more detailed review.

## 5. DISCUSSION

Two new meta-analyses of clinical trial data for atomoxetine in children with ADHD indicate a statistically significant increased risk of suicidal ideation or behaviour with atomoxetine compared with placebo (Mantel-Haenszel risk ratio 2.49 (0.64, 9.78; p=0.190), Mantel-Haenzsel incidence difference 0.52 (0.12, 0.91 p=0.010)). The age range of children experiencing these events was 7 to 12 years. There does no appear to be any real pattern in terms of time to onset of events.

The fact that the risk ratio in the paediatric analysis does not reach statistical significance, whereas the incidence difference does is likely to be due to the fact that a number of studies cannot be used in the former meta-analysis because there are no suicide behaviour or ideation events recorded.

Overall, the signal seems to be fairly strong of an increased risk of this rare outcome in clinical trial of atomoxetine Vs placebo in paediatric patients. The size of the increased risk is reflected in the risk ratio and incidence difference which suggest that the risk is doubled in patients exposed to atomoxetine compared to placebo, leading to an excess incidence of approximately 5 per thousand patients. It is important that this risk is reflected in the prescribing information and in information provided for patients.

Spontaneous data in the UK indicates a high reporting rate for suicidal behaviour which is of concern.

The two meta-analyses of nine double blind, randomised, placebo-controlled clinical trials of atomoxetine in adults do not indicate an increased risk of suicidal behaviour in adults receiving atomoxetine. Atomoxetine is not authorised for use in adults in the EU.

In January 2005, the SPC and PIL for atomoxetine were updated to warn of the risk of severe liver injury and this included the advice that treatment with atomoxetine should be stopped immediately if liver injury is suspected. We consider that the risk of liver injury and the newly identified risk of suicidal behaviour associated with the use of atomoxetine in children with ADHD warrant a full risk:benefit evaluation of this product in its licensed indication.

## 6. CONCLUSION

Two new meta-analyses of twelve double blind, randomised, placebo-controlled clinical trials of atomoxetine in children with ADHD indicate a statistically significant increased risk of suicidal behaviour with atomoxetine compared with placebo (Mantel-Haenszel risk ratio = 2.49 (0.64, 9.78)). The risk ratio and incidence difference suggest a doubling of the risk of suicidal behaviour or ideation in patients exposed to atomoxetine compared to placebo, leading to an excess of approximately 5 per thousand patients.

The same signal is not observed in adults.

The product information for atomoxetine should be updated through a USR procedure to reflect the increased risk of suicidal ideation or behaviour associated with atomoxetine treatment in children with ADHD. The wording proposed by the MAH in the Type II variation submitted on 15 September 2005 is not considered acceptable. Alternative wording for section 4.4 of the SPC is proposed in section 8 of this assessment.

This newly identified risk, together with the risk of severe liver injury associated with atomoxetine warrant a full risk:benefit evaluation of atomoxetine in its licensed indications. It is important that the risk:benefit evaluation also considers the concern about the potential risk of seizures in association with atomoxetine and the available data on the efficacy of atomoxetine compared to existing ADHD treatments.

## 7. RESPONSES TO RAPID ALERT DATED 19th SEPTEMBER 2005

On 19th September the UK circulated a Rapid Alert to Member States concerning the new signal of an increased risk of suicidal behaviour associated with atomoxetine. The following information was requested from MSs:

1) What is the usage of atomoxetine in your country?
2) Have you had any reports of suicidal behaviour associated with atomoxetine? If yes please provide a line listing
3) Do you agree with the proposal for an urgent safety restriction in week commencing 26 September to add warnings about suicidal behaviour?

Responses have been received from 17 MSs. The responses have been tabulated and the table is attached in Annex 2. All MSs agree with the proposal for an urgent safety restriction.

## 8. PROPOSED SPC WORDING

**Section 4.4 (Special Warnings and Special Precautions for Use**

*"Suicide related behaviours (suicide attempts and suicidal ideations) have been reported in patients treated with atomoxetine. In double blind clinical trials, suicide related behaviours occurred at a frequency of 0.44% in atomoxetine treated patients (6 out of 1357, one case of suicide attempt and five of suicidal ideation). There were no events in the placebo group (n=851). The age range of children experiencing these events was 7 to 12 years. It should however be noted that the number of adolescent patients included in the clinical trials was low.*

*Hostility (predominantly aggression, oppositional behaviour and anger) and emotional lability were more frequently observed in clinical trials among children treated with Strattera compared to those treated with placebo.*

*Patients who are being treated for ADHD should be carefully monitored for the appearance or worsening of suicide-related behaviour, hostility and emotional lability. As with other psychotropic medication, the possibility of rare, serious psychiatric adverse effects cannot be excluded."*

**Section 4.8 (Undesirable Effects)**

*"Suicidal ideation or attempts have been reported (see section 4.4, Special Warnings and Precautions for Use)."*

[redacted]

**23rd September 2005**

# ANNEX 2

# Repeat Use Mutual Recognition Procedure (MRP) Assessment Report (dated 8th June 2005)

MHRA

Medicines and Healthcare products Regulatory Agency

Safeguarding public health

# Mutual Recognition Procedure No. UK/H/686/01-06/E01

## Reference MS: UK

# ASSESSMENT REPORT (REPEAT USE)

## for

## STRATTERA™ 5MG
## STRATTERA™ 10MG
## STRATTERA™ 18MG
## STRATTERA™ 25MG
## STRATTERA™ 40MG
## STRATTERA™ 60MG

According to Article 28.4 of Directive 2001/83/EC

**Confidential Appendices**



*Total pages: 167*

# 16 I. INTRODUCTION

## *16.1I.1 GCP Aspects*

The clinical expert has provided the following statement in respect of Good Clinical Practice:

As required by EU Directive 91/507/EEC, I have assessed the conduct of these studies with respect to their compliance with Good Clinical Practice (GCP) guidelines (CPMP/ICH/135/95). In my opinion, the reported protocol violations have neither prejudiced nor compromised the safety of the patients participating in atomoxetine trials. Additionally, the reported protocol violations have not adversely affected the data integrity of these studies. Thus, I am satisfied with the sponsor's rigorous approach to the careful and regular monitoring of the studies included in this application.

This is satisfactory.

## *16.2I.2 Orphan Medicinal Products*

Not applicable.

## *16.3I.3 Therapeutic Class*

Centrally Acting Sympathomimetics ATC code N06BA9

## *16.4I.4 Background*

Strattera is a New Active Substance developed by the applicant for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children, adolescents and adults. It is the first ADHD drug in its class, a specific noradrenaline reuptake inhibitor. As such it differs substantially from existing medicinal products licensed for this indication (i.e. CNS stimulants including amphetamines and methylphenidate) and from other agents used occasionally off label for ADHD including desipramine and clonidine. In particular it is claimed to have important advantages in its adverse effect profile and abuse potential compared with the CNS stimulants used for this condition.

Atomoxetine is structurally unrelated to the CNS stimulants and to existing agents that block the noradrenaline reuptake transporter (e.g. the tricyclic antidepressant desipramine). It has minimal affinity for other transporters or receptors, although its main metabolite shows modest inhibition of the serotonin reuptake transporter. Atomoxetine's mechanism of action is therefore very different from that of the stimulants licensed for ADHD, which work via effects on central dopaminergic pathways.

Attention-Deficit/Hyperactivity Disorder is a chronic condition characterised by "inattention and/or hyperactivity-impulsivity that is more frequent and severe than expected in individuals at a comparable level of development." Its onset is in early childhood and in many cases it persists into adolescence and adulthood where it is associated with adverse long term outcomes in academic and social function including poor employment history and criminality. Treatment is by a combination of psychosocial and pharmacological treatments. The clinical expert report (section 2.5.1.2) provides an overview of the clinical features and diagnostic criteria of ADHD.

This is a controversial condition for which expert opinion and clinical practice shows considerable geographic variation. It is most widely recognised and treated in the USA where the American Psychiatric Association reports a prevalence of 3-5% in school-aged children. Issues relating to ADHD itself are therefore critical in interpreting clinical data on treatments for this condition, in particular for assessing the external validity of these studies and their applicability to the European population of individuals diagnosed with ADHD. These issues will be discussed more fully in the efficacy section of this assessment report.

The UK National Institute for Clinical Excellence (NICE) provided guidance on the use of methylphenidate for ADHD in childhood in 2000. It provides background information on ADHD and a number of issues covered in this document are relevant to the current application.

### 16.5I.5 Regulatory Status

There have been no other marketing authorisation applications for this product in the EEA. Marketing Authorisations were granted in the UK on 27 May 2004. It was approved in the USA on 26 November 2002 and it is also registered in Australia, Mexico and Argentina. Marketing authorisation applications are pending in Canada and New Zealand.

### 16.6I.6 Indications

Strattera is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents and adults (see 5.1). Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10.

### 16.7I.7 Dose and Dose Regimen

For oral use. Strattera can be administered as a single daily dose in the morning. Patients who experience unwanted effects when taking Strattera as a single daily dose may benefit from taking it as twice daily evenly divided doses in the morning and late afternoon or early evening.

Dosing of Children and Adolescents up to 70 kg Body Weight—Strattera should be initiated at a total daily dose of approximately 0.5 mg/kg. The initial dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance dose is approximately 1.2 mg/kg/day (depending on the patient's weight and available dosage strengths of

atomoxetine). No additional benefit has been demonstrated for doses higher than 1.2 mg/kg/day.

In children and adolescents under 70 kg body weight, the safety of single doses over 1.8 mg/kg/day and total daily doses above 1.8 mg/kg have not been systematically evaluated.

Treatment must be initiated by or under the supervision of a physician with appropriate knowledge and experience of childhood and/or adolescence behavioural disorders (for example, paediatrician or child/adolescent psychiatrist).

Dosing of Children and Adolescents over 70 kg Body Weight and Adults - Strattera should be initiated at a total daily dose of 40 mg. The initial dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance dose is 80 mg. No additional benefit has been demonstrated for doses higher than 80 mg (see 5.1).

The maximum recommended total daily dose in children and adolescents over 70 kg and adults is 100 mg.

In children and adolescents over 70 kg body weight and adults, the safety of single doses over 120 mg and total daily doses above 150 mg have not been systematically evaluated.

Treatment must be initiated by or under the supervision of a psychiatrist with appropriate knowledge and experience of adult ADHD.

Strattera may be taken with or without food and it can be discontinued without tapering the dose.

Special Populations
Hepatic Insufficiency: For patients with moderate hepatic insufficiency (Child-Pugh Class B), initial and target doses should be reduced to 50% of the usual dose. For patients with severe hepatic insufficiency (Child-Pugh Class C), initial dose and target doses should be reduced to 25% of usual dose.
Renal Insufficiency: subjects with end stage renal disease had higher systemic exposure to atomoxetine than healthy subjects (about a 65% increase), but there was no difference when exposure was corrected for mg/kg dose. Strattera can therefore be administered to ADHD patients with end stage renal disease or lesser degrees of renal insufficiency using the usual dosing regimen. Atomoxetine may exacerbate hypertension in patients with end stage renal disease.

Elderly and paediatric patients less than 6 years of age: not evaluated.

### *16.8I.8 Consideration for Paediatric Use*

This product has been fully developed for paediatric use in accordance with the Note for Guidance on Clinical Investigation of Medicinal Products in Children. Compliance with

the provisions of this guideline will be considered fully in the main body of this assessment report.

### 16.9I.9 Scientific Advice

The applicant sought Scientific Advice from the CPMP in June 2000 and June 2001. The applicant has followed most of the advice given by the CPMP and this will be discussed in the efficacy and safety sections in the main body of this assessment report. National Scientific Advice meetings were held at the MCA in 1999 and in January 2003. In addition meetings were held with BfArM and the MEB in 1999 (national scientific advice) and January 2003 (pre-submission dialogue).

### 16.10I.10 Organisation of the Medical Assessment Report

Following the initial assessment of these applications a number of major potential issues relating to safety and efficacy were identified. These were all resolved. The medical assessment report is presented in such a way that the issues raised during the assessment process are apparent to the reader. Outstanding issues and questions addressed to the company during the assessment process are inserted into the appropriate sections of the original assessment report followed by the company's summary of response and then the assessment of the response. The following external expert opinions provided by the applicant during the UK national licensing procedure for assessment by MHRA and Committee on Safety of Medicines (CSM), and mentioned in the body of this report, are included in the updated dossier, Cardiovascular Safety Report and Addendum to Cardiovascular Safety Report [redacted]; Expert Opinion on ADHD in adults [redacted]

## 17 II.Pharmacokinetics

### 17.1II.1 Introduction

The pharmacokinetics of atomoxetine were investigated in 26 studies involving over 300 adults and 30 children, predominantly using the product proposed for marketing or a bioequivalent formulation. The clinical pharmacology and disposition of atomoxetine was initially characterised in the 1980s. However all of the studies except the ethanol interaction study were conducted in recent years in accordance with GCP guidelines. All but one (HFBC) of the clinical pharmacology studies were performed in adults, with pharmacokinetic bridging data to children. This approach is consistent with CPMP and ICH guidelines and is acceptable.

The following studies were performed (healthy adults unless stated):

| Study title status | Nature of study | Numbers by EM/PM |
|---|---|---|
| HFBH | $^{14}$C Metabolism Study | 4 EM and 3 PM |
| HFBJ | Single and Multiple Dose PK and Safety Study | 16 EM and 11PM |
| LYAE | Multiple Dose PK and Safety Study | 10 EM and 6 PM |
| LYBJ | Once-Daily PK Study in PMs | 9 PM and 1 EM |

| | | |
|---|---|---|
| HFBC | Safety and PK Study in Paediatric ADHD Patients | 30 EM |
| HFBM | PK in End Stage Renal Disease | 13 EM |
| HFBN | Effect of Hepatic Impairment Child-Pugh B - C | 20 EM |
| LYAN | PK and Safety in Japanese Subjects | part A: 23 EM; part B: 26 EM |
| HFBP | Desipramine Interaction Study | 22 EM |
| LYAJ | Midazolam Interaction Study | 8 PM |
| HFBL | Paroxetine Interaction Study | 22 EM |
| LYAY | Fluoxetine Interaction Study | 19 EM, 1 PM |

EM = CYP2D6 Extensive metaboliser; PM = CYP2D6 Poor metaboliser.

The most notable pharmacokinetic feature of the drug is that it is predominantly metabolised by CYP2D6 and therefore its clearance is highly affected by CYP2D6 polymorphism. This has important implications for efficacy and safety.

The four main PK studies in healthy adults are reported in the following sections. The pharmacodynamic and tolerability data, in particular the cardiovascular effects, from these studies are reported in the PD section of this assessment report (III.2). An overview of the main PK parameters is presented in section II.6 of this assessment report.

### *17.2II.2 14 C Radiolabel Study HFBH*

7 adult male subjects (4 extensive metabolisers and 3 poor metabolisers) dosed to steady state were administered 14 C-atomoxetine in order to identify and quantify the major metabolites of atomoxetine in plasma, urine, and faeces and to evaluate differences between extensive and poor CYP2D6 metabolisers.

In both extensive and poor metabolisers, atomoxetine was primarily cleared by oxidative metabolism and nearly all its metabolites were renally eliminated. The primary oxidative (Phase I) metabolite produced by both extensive and poor metabolisers is 4-hydroxyatomoxetine, which is subsequently conjugated to produce the primary ultimate metabolite of atomoxetine, 4-hydroxyatomoxetine-O-glucuronide.

The same major metabolites of atomoxetine are produced regardless of CYP2D6 metabolic status, although the rate of metabolic elimination is substantially slower in poor metabolisers. The proportion of the dose excreted as 4-hydroxyatomoxetine-derived metabolites was greater in extensive metabolisers (85%) than in poor metabolisers (45%). The relative amount of metabolites derived from secondary routes of biotransformation (such as N-desmethylatomoxetine and 2-hydroxymethylatomoxetine) was greater in the poor metabolisers (55%) than in extensive metabolisers (15%). Atomoxetine and 4-

hydroxytomoxetine-O-glucuronide are the principle circulating species in plasma of extensive metabolisers, while atomoxetine and N-desmethylatomoxetine are the principle circulating species in poor metabolisers. Very little atomoxetine was excreted into the urine unchanged (<3%) regardless of CYP2D6 metabolic status.

### 17.3II.3 Study HFBJ - Single and Multiple Dose PK and Tolerability

This placebo controlled, randomised study evaluated the effect of CYP2D6 status on the safety, pharmacokinetics and dose proportionality of single (10 to 120mg) and multiple (40mg twice daily) oral doses of atomoxetine in 27 healthy adults (14 men and 13 women). 16 extensive metabolisers and 11 poor CYP2D6 metabolisers were studied. A single-dose escalation phase (placebo, 10mg, 30mg, 60mg, 120mg) was followed by a multiple-dose phase (40mg daily for 7 days).
Key single dose PK parameters are presented below for both extensive and poor metabolisers.

**Extensive Metabolisers** Arithmetic mean (CV%)

| | 10 mg (n=16) | 90 mg (n=15) | 120 mg (n=15) |
|---|---|---|---|
| Cmax (ng/mL) | 84.54 (37.4) | 812.55 (30.2) | 1053.18 (31.4) |
| t1/2 hrs | 4.20 (2.18-7.50) | 5.62 (3.75-8.55) | 5.16 (3.68-7.53) |
| AUC0-t | 0.509 (69.9) | 5.47 (71.5) | 7.42 (65.5) |
| CL/F (L/hr/kg) | 0.356 (47.0) | 0.289 (41.5) | 0.278 (40.2) |

**Poor Metabolisers** Arithmetic mean (CV%)

| | 10 mg (n=11) | 90 mg (n=11) | 120 mg (n=11) |
|---|---|---|---|
| Cmax (ng/mL) | 171.44 (20.3) | 1517.81 (21.7) | 2233.04 (36.4) |
| t1/2 hrs | 19.9 (15.6-24.5) | 21.4 (15.2-27.0) | 21.6 (14.1-26.8) |
| AUC0-t | 4.19 (20.4) | 36.6 (20.9) | 51.6 (19.2) |
| CL/F (L/hr/kg) | 0.0345 (21.6) | 0.0352 (22.5) | 0.0332 (18.9) |

Cmax and AUC were dose-linear in both. Plasma clearance in poor metabolisers was only 10-12% of that in extensive metabolisers. Cmax was approximately doubled and AUC 7 to 8 times higher in poor metabolisers.

Key steady-state PK parameters are presented below for both extensive and poor metabolisers. Cmin was the parameter that differed most between extensive and poor metabolisers, being 16 times higher in the latter group. Cmax was approximately four times higher whilst AUC was 7 times higher in poor metabolisers.

| | Extensive metabolisers (N = 6) | Poor metabolisers (N = 6) |
|---|---|---|
| Css,min | 69.47 (133.6) | 1116.59 (21.5) |
| Css,max | 526.52 (67.3) | 1948.79 (19.8) |
| AUC0-t | 2.59 (77.8) | 18.6 (21.4) |
| t1/2 b | 5.23 (2.97-7.81) | 24.4 (19.4-31.1) |

### 17.4II.4 Study LYAE - Multiple Dose PK

This was a single-centre, single-blind, placebo-controlled, multiple-dose escalation study in 16 healthy adult subjects (10 extensive metabolisers and 6 poor metabolisers; 11 men and 5 women) to evaluate the safety, tolerability and pharmacokinetics of gradually increasing multiple-dose regimens (placebo, 30, 45, 60, 75mg twice daily) of atomoxetine. Each dose was given for a period of 5 days, sufficient to achieve steady state even in poor metabolisers. Steady state plasma levels of atomoxetine, 4-hydroxyatomoxetine, and N-desmethylatomoxetine were determined for each individual at each dose level. The values for the 45mg b.d. dose (approximately the target dose proposed in the SPC) are presented below:

AUC (mcg hr/ml) of atomoxetine and its principal metabolites at steady state, 90mg/day

| | Extensive metabolisers | Poor metabolisers |
|---|---|---|
| Atomoxetine | 1.97 | 18.0 |
| N-desmethylatomoxetine | 0.110 | 9.00 |
| 4-hydroxyatomoxetine | 0.124 | 0.0228 |

Plasma concentrations (mean AUCs) for the 4-hydroxyatomoxetine metabolite were much lower than for the parent drug regardless of CYP2D6 metaboliser status. Levels in poor metabolisers were approximately 20% of those in extensive metabolisers.

However after 5 days of dosing mean AUCs of N-desmethylatomoxetine were 80 times higher in poor metabolisers compared with extensive metabolisers. The applicant has presented data on "steady state" Cmin, Cave, Cmax, AUC0-t and Tmax for these metabolites. There is no information however on the rate of elimination of either metabolite except that the plasma concentration – time curves show no apparent change in plasma levels over the 12 hour period following dosing in poor metabolisers. There is therefore no indication that these data represent the steady state situation for the metabolites and the potential for accumulation has not been addressed in this study.

### 17.5II.5 Study LYBJ – Once Daily Dosing Steady-State PK in Healthy Poor Metabolisers

The applicant states that in extensive metabolisers near-complete elimination of atomoxetine would occur within the 24-hour dosing interval and that therefore once-daily dosing should mimic single-dose pharmacokinetics. This was an open-label 2-centre study in 10 healthy adults (5 men and 5 women), intended to investigate the steady-state pharmacokinetics and possibility for accumulation in poor metabolisers with once-daily dosing of atomoxetine 120mg. It was the only multiple-dose clinical pharmacology study in which the dose was administered once daily.

A 60mg dose was given on the first day rising to 80mg on days 2 and 3, and 120mg daily on days 4 to 7. Blood samples for atomoxetine assay were obtained before and at various time points after each dose. This study did not however measure plasma levels of atomoxetine's metabolites. Key PK parameters are presented below, in comparison with data normalised to the same daily dose (120mg) from a twice daily divided dose in study HFBJ.

| | Study LYBJ – once daily | Study HFBJ – twice daily |
|---|---|---|
| Css,min | 937.60 (51.6) | 1674.89 (21.5) |
| Css,max | 3912.73 (29.2) | 2923.18 (19.8) |
| AUC0-t | 50.6 (38.7) | 55.8 (21.4) |
| t1/2 b | 23.3 (15.3-41.4) | 24.4 (19.4-31.1) |

At steady state following once daily dosing, peak atomoxetine plasma levels (Cmax) were about 30% higher and trough levels (Cmin) about 45% lower compared to data from previous studies with divided twice-daily dosing. Extent of exposure (AUC) was not significantly changed. The applicant states that the PK parameters were as predicted from single-dose data.

17.5.1.1.1.1.1.1 Assessor's Comment

*With once daily dosing Cmin fell to only 24% of Cmax compared with a figure of 57% for twice daily dosing, representing a considerably increased fluctuation of plasma levels. If there is no PK-PD hysteresis and therapeutic activity falls in parallel with plasma levels (which is not necessarily the case), there would be potential for loss of therapeutic effect at the end of a 24 hour dosing interval even in poor metabolisers.*

## 17.6II.6 Overview of Pharmacokinetics in Healthy Adults

The applicant has presented integrated analyses for both extensive and poor metabolisers across the adult clinical pharmacology studies. The mean values for the key PK parameters for extensive metabolisers and poor metabolisers are presented in the tables below.

| | Extensive metabolisers | Poor metabolisers |
|---|---|---|
| Cmax (ng/mL) | 568 | 1165 |
| CL/F (L/hr/kg) | 0.352 | 0.0337 |
| t1/2 (hrs) | 3.56 | 20.6 |
| Vz /F (L/kg) | 1.82 | 1.01 |
| MRT (hrs) | 5.32 | 26.8 |
| Css,avg (ng/mL) | 249 | 2537 |
| Css,max (ng/mL) | 667 | 3223 |
| Percent Fluctuation (%) | 245 | 58.4 |
| Vss /F (L/kg) | 1.88 | 0.92 |

CL/F = total clearance of drug from plasma/bioavailability, also defined as apparent plasma clearance
C max = maximum observed plasma concentration;
C ss,avg = average steady-state plasma concentration;
C ss,max = maximum observed steady-state plasma concentration;
MRT = mean residence time
t 1/2 = apparent terminal elimination half-life
V ss /F = volume of distribution at steady state/bioavailability
V z /F = volume of distribution/bioavailability (single dose data)

The key PK features in healthy adults are as follows:

### 17.6.1 Absorption

- Atomoxetine is rapidly and near-completely absorbed from the gastrointestinal tract in both extensive and poor metabolisers of CYP2D6. The absolute oral bioavailability of atomoxetine is moderately affected by CYP2D6 polymorphism due to the occurrence of some first pass metabolism in extensive metabolisers. After single oral doses, Cmax is 2-fold higher in poor metabolisers compared to extensive metabolisers. Median Tmax was approximately 1 hour and 2.5 hours in extensive and poor metabolisers respectively.
- Pharmacokinetics are dose- proportional over a dose range of 10-120mg in both poor and extensive metaboliser adult subjects. Clearance decreased slightly with increasing dose but the 90% confidence interval of the dose-proportionality analysis for AUC was contained within the interval (0.8, 1.25).
- In a clinical pharmacology study data showed drugs that elevate gastric pH (antacids, omeprazole) appeared to have no effect on bioavailability.

### 17.6.2 Distribution

- The mean apparent volume of distribution was 1.8 l/kg in extensive metabolisers and 1.0 1.8 l/kg in poor metabolisers.
- Atomoxetine is approximately 98% bound to albumin. The N-desmethylatomoxetine metabolite is 99% bound whilst 4-hydroxyatomoxetine to plasma protein was 67% bound. In vitro drug-displacement studies demonstrated that atomoxetine did not affect the binding of warfarin, acetylsalicylic acid, phenytoin, and diazepam to human albumin. Significant interactions resulting from plasma protein displacement are not anticipated.

### 17.6.3 Metabolism and Elimination

- Atomoxetine's predominant metabolic route is via CYP2D6 and hence clearance is substantially reduced in CYP2D6 poor metabolisers (approximately 7% of the Caucasian population). In poor metabolisers apparent plasma clearance (CL/F) is about one tenth of the value for extensive metabolisers.
- The metabolites of atomoxetine are almost exclusively eliminated by excretion in the urine. Regardless of CYP2D6 metabolic status, very little atomoxetine was excreted unchanged in the urine (<3%).
- In both poor and extensive metabolisers, the principal oxidative metabolites are N-desmethylatomoxetine and 4-hydroxyatomoxetine. In poor metabolisers these metabolites are formed by several lower affinity isoforms of cytochrome P450, but at a much slower rate than by CYP2D6. The hydroxylated metabolite undergoes subsequent glucuronidation, forming the primary ultimate metabolite of atomoxetine, 4-hydroxyatomoxetine-O-glucuronide.
- After single oral doses, elimination half-life is approximately 6-fold longer in poor metabolisers compared to extensive metabolisers. At steady state, peak plasma levels (Css,max ) were on average 5-fold higher and mean plasma levels (Css,avg) on average 10-fold higher.
- In extensive metabolisers the majority of the dose is excreted as 4-hydroxytomoxetine-derived metabolites (85%). However in poor metabolisers only 45% is metabolised via this primary route and secondary routes of biotransformation (including N-

desmethylatomoxetine- and 2-hydroxymethylatomoxetine-derived metabolites) account for 55% of the dose (approximately 15% in extensive metabolisers).

- Steady state plasma concentrations of 4-hydroxyatomoxetine are low compared to atomoxetine in both poor and extensive metabolisers (<0.2% and <2% of atomoxetine AUC respectively).
- However the mean AUC of N-desmethylatomoxetine was approximately 54% of atomoxetine in poor metabolisers compared with a figure of 7% for extensive metabolisers. Although the contribution of this metabolic pathway to the overall metabolism of atomoxetine was still relatively minor in poor metabolisers (approximately 6% of the total dose), N-desmethylatomoxetine accumulates in the plasma because it must undergo CYP2D6 mediated hydroxylation (and subsequent O-glucuronidation) prior to its excretion. Accumulation of the N-desmethyl metabolite would therefore be a potentially important issue with long term dosing of poor metabolisers if this metabolite possesses pharmacological activity. However, no pharmacological activity across numerous neuronal receptor and channels has been associated with this metabolite. The clinical significance of the higher plasma exposures in poor metabolisers to atomoxetine and its demethylated metabolite are considered in the pharmacodynamics section of this report.

## *17.7II.7 Pharmacokinetics in the Paediatric Population*

### 17.7.1 Study HFBC - Safety and PK of Atomoxetine in Paediatric Patients with ADHD

Study HFBC was a single-centre, open-label, dose-titration study. It evaluated the single-dose (10mg) and steady-state (20 - 45 mg twice daily for a mean duration of 68 days, range 8 to 100 days) pharmacokinetics of atomoxetine and its two principal oxidative metabolites in 30 ADHD patients aged 7 to 13. The single-dose phase studied 5 males and 2 females and the steady state phase studied 13 males and 3 females. All patients were genotyped as CYP2D6 extensive metabolisers. For both single-dose and steady-state analyses blood samples were taken immediately prior to the morning dose and at 1, 2, 4, 8, 12, and 24 hours (a second dose was not given during this 24 hour period).

As in adults, absorption was rapid following oral administration (Tmax 1-2 hours). The plasma concentration-time profiles and values for half-life, plasma clearance and apparent volume of distribution were very similar after a single dose and after multiple twice daily dosing indicating minimal accumulation. At steady state the AUC of atomoxetine was at least 20 times greater than the AUC for N-desmethylatomoxetine and 4-hydroxytomoxetine, indicating minimal accumulation of these metabolites.

The table below contains mean values for single-dose and steady-state PK parameters.

| Pharmacokinetic Parameter (mean) | Single-dose (n = 7) | Steady-state (n = 16) |
|---|---|---|
| Dose | 10mg | 20 - 45 mg twice daily |
| mg/kg | 0.272 | 0.951 |
| Cmax | 533 | 584 |
| Tmax | 2.00 hr | 1.73 hr |
| t1/2 (elimination half-life) | 3.12 | 3.28 |
| CL/F (L/hr)<br>(L/hr/kg) | 17.3<br>0.455 | 20.3<br>0.477 |
| Vz/F (L)<br>(L/kg) | 74.4<br>1.96 | 95.9<br>2.25 |

*CL/F = total clearance of drug from plasma/bioavailability (apparent plasma clearance)*
*V z /F = volume of distribution/bioavailability (apparent volume of distribution)*

*Assessor's Comment*
*This study shows that the single-dose and steady-state PK parameters in children and adolescents with ADHD are comparable to the mean values seen in healthy adults. The principal deficiency with this study is that it studied only extensive metabolisers and therefore provides no information on the group that is of most concern, i.e. poor metabolisers. In particular the potential for accumulation of N-desmethylatomoxetine in this population is not known.*

## 17.7.2 Population Pharmacokinetic Analysis

Mean clearance and volume of distribution estimates for atomoxetine were evaluated in 420 paediatric ADHD patients in five Phase Ib - 2 studies (HFBD, HFBE, HFBF HFBK, and HFBC) using a population approach. The analyses included the effects of CYP2D6 genotype, body weight, plasma albumin, body weight and food. The data were consistent with those obtained from the analysis of Study HFBC. The following are the key findings:

- Paediatric poor metabolisers had a 9-fold lower mean clearance than extensive metabolisers, which is essentially the same difference as seen in adults.
- AUC, clearance and volume of distribution were all largely proportional to body weight. This supports the weight-based dosing regimen (milligram/kilogram) proposed in the SPC. As expected dosing according to body weight (1 mg/kg regimen) resulted in a narrower range of AUC values than a fixed dose regimen. This was true for both poor and extensive metabolisers.
- In children the administration of atomoxetine with food decreased the rate of absorption (Cmax reduced by 9%) but not AUC. This is not considered to be clinically significant.
- Pharmacokinetics were proportional across the dose range evaluated of 5 to 45 mg (0.08 to 1.74 mg/kg).
- Age, gender and race did not influence PK independently of body weight (range 7-15 years).
- Albumin, total bilirubin and alanine aminotransferase (ALT) levels were not associated with a significant effect on atomoxetine pharmacokinetics.

PK data from the paediatric patients from Study HFBC and the paediatric population analysis were compared with the adult data from the clinical PK integrated analysis. No significant differences were apparent and the pharmacokinetics of atomoxetine in adults and children appear to be similar.

*Assessor's Comment*
*Conventional and population pharmacokinetic analyses in the paediatric patient population indicate that the pharmacokinetics of atomoxetine in adults and children are similar. In both populations, body weight and CYP2D6 status were the key variables. The applicant proposes dosing of atomoxetine in paediatric patients based on patient body weight. This is reasonable as dose proportionality was demonstrated when analysed on a mg/kg basis. However, as with adults, there is a lack of data on the potential for accumulation of N-desmethylatomoxetine in poor metabolisers.*

## *17.8II.8 Special Populations*

### 17.8.1 Study HFBM: Single Dose PK of Atomoxetine in Subjects with End Stage Renal Disease

This open-label, single-dose study conducted evaluated the influence of severe renal impairment on the PK of atomoxetine, 4-hydroxyatomoxetine, N-desmethylatomoxetine, and their glucuronide conjugates. 13 adult subjects (6 ESRD, 7 healthy; 4 men and 9 women) received a single 20mg oral dose of atomoxetine.
Atomoxetine Cmax was 7% greater and AUC 64% greater in ESRD subjects than in the healthy control subjects. However the renally impaired subjects had a significantly lower body weight. Weight adjusted values for atomoxetine clearance were 0.42 and 0.47 l/kg/hr in ESRD and normal subjects respectively. This is not a clinically important difference. The AUC of 4-hydroxyatomoxetine-O-glucuronide, a renally excreted metabolite with no known pharmacological activity, increased as expected in the renally impaired subjects but levels of the primary oxidative metabolites did not. The applicant's proposal that no dose adjustment is necessary in patients with renal insufficiency is acceptable.

### 17.8.2 Study HFBN - Single Dose PK of Atomoxetine in Subjects with Liver Disease

This open-label, single-dose study conducted evaluated the influence of moderate and severe hepatic impairment (Child-Pugh B and C) on the PK of atomoxetine. 11 adult liver disease patients and 11 healthy adult subjects (14 men and 8 women), all CYP2D6 extensive metabolisers, received a 20mg single oral dose of atomoxetine. Plasma levels of atomoxetine, 4-hydroxatomoxetine, N-desmethylatomoxetine, and their glucuronide conjugates, and the in vitro plasma protein binding of atomoxetine were measured. The metabolic activity of CYP2D6 (debrisoquine metabolic ratio) and liver blood flow (sorbitol clearance) were also correlated with atomoxetine clearance.

The study medication was well tolerated by all subjects. Reduced clearance and prolonged half-life, of atomoxetine and the glucuronide conjugate of 4-hydroxyatomoxetine, and a decrease in mean atomoxetine plasma protein binding was seen in hepatically impaired subjects compared to healthy controls. Atomoxetine

exposure (AUC) was increased in subjects with moderate (2-fold increase) and severe (4-fold increase) hepatic impairment. The atomoxetine pharmacokinetics and cardiovascular changes noted in HI subjects were however less than those exhibited by healthy subjects with CYP2D6 poor metaboliser genotype.

This single-dose study does not provide adequate safety information about chronic dosing and patients with significant hepatic impairment may be potentially more sensitive to the haemodynamic effects of atomoxetine. The applicant recommends a 50% dosage reduction in patients with moderate hepatic impairment (Child-Pugh Class B), and a 75% dosage reduction in patients with severe hepatic impairment (Child-Pugh Class C). This seems reasonable.

### 17.8.3 Study LYAN – Single and Multiple Dose PK in Healthy Japanese Male Adults

This study showed no clinically meaningful difference in the pharmacokinetics of atomoxetine and 4-hydroxyatomoxetine between the Japanese and US populations. It was however conducted exclusively in extensive metabolisers and there is therefore no information on Japanese poor metabolisers.

*17.8.3.1.1.1.1.1 Sub-Group Analyses for Potential Factors Affecting PK Parameters*

Of the covariates were examined in the integrated analysis of PK data, albumin concentration, alcohol use, sex, single dose/steady state, and racial origin did not affect atomoxetine pharmacokinetics. CYP2D6 genotype and dose proportionality are discussed elsewhere. Minor PK differences only were correlated with age and smoking status.

## *17.9 II.9 Interactions*

In vitro metabolic and interaction studies were used to design the following programme of four clinical drug interaction studies in the appropriate CYP2D6 populations.

### 17.9.1 HFBP Desipramine Interaction Study

This study investigated the potential for atomoxetine to inhibit the CYP2D6 metabolic pathway, using desipramine as a probe drug (CYP2D6 substrate). It was conducted exclusively in extensive metabolisers. Atomoxetine did not affect the single-dose pharmacokinetic parameters of desipramine, and therefore it is concluded that atomoxetine does not inhibit CYP2D6-mediated metabolism. Steady-state pharmacokinetics of atomoxetine were not significantly influenced by a single dose of desipramine. The combinations were safe and well tolerated and no clinically relevant changes in orthostatic blood pressure or heart rate were seen.

### 17.9.2 Study LYAJ Midazolam Interaction Study

This study was conducted exclusively in poor metabolisers (4 men and 4 women) to evaluated the ability of atomoxetine (60mg twice daily) to inhibit CYP 3A4 metabolic pathway using midazolam as a probe drug, and to evaluate the length of QTc intervals.

Poor CYP 2D6 metabolisers are most likely to show a CYP 3A4 mediated interaction. Only modest changes (approximately 16%) in midazolam pharmacokinetics were seen and it is concluded that atomoxetine is not a significant inhibitor of CYP 3A4 metabolism. QTc intervals after atomoxetine were not significantly different from baseline.

### 17.9.3 HFBL Paroxetine Interaction Study

This sequential study was conducted in 22 healthy extensive metaboliser adults (17 men and 5 women) to evaluate the effect of a potent CYP2D6 inhibitor (paroxetine 20 mg once daily) on the steady-state pharmacokinetics of atomoxetine (20mg twice daily). PK parameters of paroxetine were not affected by atomoxetine. Atomoxetine Cmax, AUC, and half-life increased approximately 3.5-, 6.5-, and 2.5-fold, respectively, in the presence of paroxetine. The effect of paroxetine therefore approached but did not equal that seen in genetically poor CYP2D6 metabolisers.

### 17.9.4 LYAY Fluoxetine Interaction Study

This 4-period, sequential study of atomoxetine and fluoxetine (a potent CYP2D6 inhibitor) at steady-state concentrations, in 20 healthy adults (15 men and 5 women) was conducted to evaluate the effect of fluoxetine on the steady-state PK of atomoxetine. Fluoxetine pre-treated subjects were given atomoxetine 10 mg, 45 mg, and 75mg twice daily for up to 5 days. There was no placebo control.
Mean clearance at steady-state was 0.05 l/ hr/kg for all dose levels. This compares with mean values of 0.35 and 0.034 l/ hr/kg reported for extensive and poor metabolisers respectively. Hence coadministration of fluoxetine reduces atomoxetine clearance almost to the level seen in genetically poor CYP2D6 metabolisers. One subject was a poor metaboliser; however, the subject discontinued the study and a PK evaluation could not be completed for this subject.

### 17.9.5 Pharmacokinetic Conclusions

1. In extensive metabolisers the PK profile of atomoxetine is well characterised and is generally favourable. Its elimination half life of 3.5 hours is short for a drug intended for once daily administration. However it is plausible that its therapeutic activity may persist after plasma levels have fallen in the latter part of the dosing interval if fluctuations in receptor binding do not parallel fluctuations in plasma levels. Therefore justification for once daily dosing will depend on pharmacodynamic and clinical data.
2. Substantially reduced clearance of atomoxetine is seen with interactions with CYP 2D6 inhibitors (e.g. paroxetine and fluoxetine) and in genetically poor CYP 2D6 metabolisers (who constitute 7% of the Caucasian population). The magnitude of the reduction of atomoxetine clearance produced by paroxetine and fluoxetine approached but did not exceed that observed in genetic poor metabolisers. In both of these categories of patients, plasma clearance is reduced by approximately 90%. At steady state peak plasma levels (Css,max) are approximately 5-fold higher and mean plasma levels (Css,avg) approximately 10-fold higher compared with extensive metabolisers.

3. Safety issues could potentially arise not only from an increase in total drug exposure (AUC) and higher peak levels (Cmax) of the parent drug, but also from elevated levels of the N-desmethyl metabolite. After 5 days of dosing in poor metabolisers the mean AUC of N-desmethylatomoxetine was 80 times higher than in extensive metabolisers, and was 50% of the AUC of the parent drug. However it is possible that accumulation of this metabolite might continue long after 5 days if its elimination half life is substantially more than 24 hours. This information is not available. Little change in the plasma concentration of N-desmethylatomoxetine was seen in the 12 hour period after dosing and it therefore might have a long half life. It is reassuring that N-desmethylatomoxetine shows little activity at transporter and receptor systems. Nevertheless other significant pharmacological activity cannot be ruled out and the applicant should provide data on the clearance and potential for accumulation of N-desmethylatomoxetine in CYP 2D6 poor metabolisers.
4. In vitro studies indicate that, due to the number of alternative metabolic pathways of atomoxetine in CYP2D6 poor metabolisers, coadministration of cytochrome P450 inhibitors, regardless of isoform inhibition selectivity, would not be expected to increase the plasma concentrations of atomoxetine in poor metabolisers. This seems reasonable and additional clinical studies to confirm this do not appear to be necessary.
5. In vivo and in vitro studies showed that atomoxetine does not inhibit or induce CYP3A4, CYP1A2, CYP2D6, and CYP2C9. Atomoxetine has little or no effect on the metabolism of other drugs in either poor or extensive CYP2D6 metabolisers

### 17.9.6 Outstanding Issues – Pharmacokinetics

**(Following the initial assessment of these applications the following outstanding issues and questions were addressed to the company. They are followed by the company's summary of response and then the MHRA's assessment of the response).**

1. **The applicant should provide data on the clearance and potential for accumulation of N-desmethylatomoxetine in CYP 2D6 poor metabolisers, and the possible clinical significance. After 5 days of dosing in poor metabolisers the mean AUC of N-desmethylatomoxetine was 80 times higher than in extensive metabolisers, and was 54% of the AUC of the parent drug. The possibility should be addressed of accumulation of this metabolite after this time as it appears to have a long half life. Data showing the elimination half life of N-desmethylatomoxetine in poor and extensive metabolisers should be clearly presented. It is reassuring that N-desmethylatomoxetine shows little activity at transporter and receptor systems. Nevertheless other significant pharmacological activity cannot be ruled out and the possible clinical significance of the substantially higher exposure to N-desmethylatomoxetine in poor metabolisers should be discussed.**

## 17.9.7 Company's Response (Summary)

As noted by the MHRA and CSM, *N*-desmethylatomoxetine shows little affinity for neuronal receptors and would not produce pharmacological or side effects due to direct interaction. Additionally, this metabolite has negligible activity at the human cardiac $I_{Kr}$ (hERG) channel at maximum unbound plasma concentration in CYP2D6 poor metaboliser (PM) subjects (as discussed in response to preclinical Question 8). Exposure comparisons of unbound metabolite made between animals and human PM subjects at a dose of 1.8 mg/kg/day (i.e., greater than the maximum recommended therapeutic dose of 1.2 mg/kg/day), demonstrate that dogs have higher exposures to *N*-desmethylatomoxetine than PM subjects. Further, *N*-desmethylatomoxetine accumulated in dogs proportionally to levels seen in human PM subjects. Reassuringly, as discussed in the response to Question 8, the nonclinical data show no adverse effects in dogs.

Concerning its potential for accumulation, *N*-desmethylatomoxetine plasma concentrations in PM subjects reach steady state conditions following approximately 7 days of twice daily (BID) dosing; similar time to reach steady-state is expected following once daily (QD) dosing. Furthermore, data from paediatric PM patients following up to approximately 400 days on therapy demonstrate that there is no further accumulation in the plasma following chronic therapy.

With regard to elimination half-life, in CYP2D6 extensive metaboliser (EM) subjects, *N*-desmethylatomoxetine circulated in plasma at low concentration compared to atomoxetine and showed a slightly longer half-life than atomoxetine (6.6-8.3 hr vs. 4.2-5.6 hr). In PM subjects, *N*-desmethylatomoxetine plasma concentrations were higher compared to EM subjects, and showed a longer half-life (approximately 36-40 hr) compared to atomoxetine (20-24 hr). Nevertheless, the biotransformation and excretion of *N*-desmethylatomoxetine is analogous to that of atomoxetine in both EM and PM subjects.

Since the accumulation of *N*-desmethylatomoxetine occurs in individuals in which atomoxetine also accumulates, it is impossible to separate the effects of parent from its metabolite. Thus appraising the overall safety profile of atomoxetine in PM subjects accurately represents the influence of the parent as well as the metabolite. To that effect, comprehensive data from the clinical studies provide evidence that differences between EM and PM patients in circulating *N*-desmethylatomoxetine do not pose a safety concern, as attested by the acceptable safety profile and tolerability of atomoxetine in PM patients. The initial MAA included extensive analyses of all relevant safety parameters by CYP2D6 metabolic status, including a subset of PM patients with doses greater than 1.2 mg/kg/day (i.e. those patients with highest presumed exposures), with no evidence of serious safety concerns present in PM but not EM patients.

Further, up-to-date one year post-marketing safety data in over one million patients have not revealed any clinically significant issues (Appendix F.2 PSUR). A cumulative review of cardiovascular safety as suggested by the MHRA (PSUR Appendix 14.2), also

evaluated by [redacted], confirms that atomoxetine and its metabolites have no effect on cardiac repolarisation (Annex 1).

Thus, with little pharmacological activity, negligible activity at the hERG channel at maximum unbound plasma concentrations in PM subjects, and no associated toxicity or serious safety concerns in nonclinical and clinical studies, as well as in extensive post-marketing safety data, the higher exposure to *N*-desmethylatomoxetine in PM subjects has no impact on clinical safety.

**Assessor's Comment**

The new information confirms the following:

1. In poor metabolisers the half-life of *N*-desmethylatomoxetine was 36-40 hr, compared to 20-24 hr for the parent drug.

2. Steady state plasma concentrations of *N*-desmethylatomoxetine are approximately the same as for the parent drug (fig. 1.3 in the response document).

3. There is no significant accumulation of *N*-desmethylatomoxetine after 7-10 days (figs. 1.1, 1.2).

4. Updated post-marketing safety data in over one million patients including a cumulative review of cardiovascular safety do not reveal any clinically significant issues.

This is generally reassuring. The preclinical assessor was satisfied about the lack of important pharmacological activity of *N*-desmethylatomoxetine at the steady state plasma concentrations observed in poor metabolisers, thus this point was cleared.

## *17.10III Pharmacodynamics*

### *17.11III.1 Primary Pharmacology and Mechanism of Action*

The primary pharmacological effect of atomoxetine is central noradrenaline reuptake inhibition. *In vitro* studies are considered by the pre-clinical assessor. Investigation of the primary pharmacodynamics of atomoxetine in the proposed indication is otherwise only possible by clinical studies as no in vivo surrogate endpoints for noradrenaline reuptake inhibition exist. No clinical data are available on possible genetic or other inter-individual differences in the primary pharmacodynamic activity of atomoxetine. The inter-

individual variability in clinical response to atomoxetine is likely to reflect other differences in subject characteristics and psychopathology as well as genetic PK differences.

## *17.12III.2 Secondary Pharmacology*

The main secondary pharmacological activity of atomoxetine, predicted from its known pharmacodynamic activity and seen in early human studies, is its effect on the cardiovascular system (haemodynamic effects), mediated by an increase in noradrenergic tone. Cardiovascular parameters were recorded routinely in the Phase I (PK/safety) studies. Cardiovascular data from the two that included a placebo control and studied poor metabolisers are reported here briefly. The safety section of this report considers the pooled haemodynamic (BP, HR) data from the clinical trial programme

### 17.12.1 Study HFBJ - Pharmacokinetics and Safety in Poor Metabolisers

Single doses of atomoxetine, between 10 and 120 mg, produced dose related increases in standing heart rate of up to 20 beats per minute (bpm). At each dose level the changes were of a similar magnitude in poor and extensive metabolisers. Orthostatic changes in systolic blood pressure and heart rate were not clinically significant in either poor or extensive metabolisers.

Study LYAE

In this placebo-controlled, multiple-dose escalation study, 16 healthy adult subjects (10 extensive metabolisers and 6 poor metabolisers; 11 men and 5 women) received gradually increasing multiple-dose regimens (30, 45, 60, 75 mg twice daily each for 5 days) of atomoxetine. The heart rate responses to the same doses of atomoxetine were similar in poor and extensive metabolisers, despite higher plasma concentrations in the poor metabolisers. Pre-dose heart rate at steady state was also not higher in poor metabolisers. Both groups experienced orthostatic tachycardia (mostly asymptomatic) and both showed attenuation of the cardiovascular stimulating effects of atomoxetine over each 5-day dosing regimen.

## *17.13III.3 Relationship between Plasma Concentration and Effect*

Since no in vivo surrogate endpoint for noradrenaline reuptake inhibition exists, the relationship between plasma concentration and effect was investigated using the primary clinical endpoint from the dose-response study LYAC. The relationship between systemic exposure (AUC) and efficacy was similar to that between dose and efficacy. This is not surprising since AUC is essentially proportional to dose.

## *17.14III.4 Pharmacology of Principal Metabolites*

The pharmacological selectivity and potency of the principal oxidative metabolites, 4-hydroxyatomoxetine and N-desmethylatomoxetine, were evaluated for inhibition of the monoamine reuptake transporters, as well as the principal central receptor systems. These data are considered in greater detail by the preclinical assessor.

### 17.14.1 4-hydroxyatomoxetine

Steady state plasma concentrations of 4-hydroxyatomoxetine are low compared to atomoxetine in both poor and extensive metabolisers (<0.2% and <2% of atomoxetine concentrations respectively). 4-hydroxyatomoxetine possesses similar inhibitory activity at the noradrenaline transporter to that of atomoxetine and also shows some inhibitory activity at the serotonin transporter. It shows very little relative affinity for other receptor systems.

### 17.14.2 N-desmethylatomoxetine

Steady state plasma levels of N-desmethylatomoxetine were approximately 7% of atomoxetine levels for extensive metabolisers but 54% of atomoxetine levels in poor metabolisers. N-desmethylatomoxetine shows much less inhibitory activity at the noradrenaline transporter than atomoxetine. It shows very little relative affinity at the serotonin transporter and at other receptor systems.

17.14.2.1.1.1.1.1 Assessor's Comment

*This is quite reassuring. Neither principal metabolite is likely to make a significant contribution to pharmacodynamic activity either at the noradrenaline reuptake transporter or the other transporter and receptor systems studied. Although 4-hydroxyatomoxetine shows significant activity (but less than atomoxetine) its plasma levels are very low in all subjects. Although plasma levels of N-desmethylatomoxetine are much higher in poor metabolisers it appears to have little pharmacodynamic activity.*

## *17.15III.5 Pharmacodynamic Interactions with Other Medicinal Products or Substances*

Three double-blind, randomised, drug interaction studies on the effect of atomoxetine on the haemodynamic effects of sympathetic agonists (salbutamol), CNS stimulants (methylphenidate) and alcohol in healthy adult subjects are presented.

### 17.15.1 Sympathomimetics

Study HFBO was a crossover study to evaluate of the effect of oral chronic atomoxetine dosing (60mg twice daily) on haemodynamic parameters after a single intravenous dose of salbutamol in 13 healthy adult male extensive metabolisers in a primarily Asian population. Atomoxetine augmented the heart rate, systemic vascular resistance, and diastolic/systolic blood pressure changes following a single intravenous dose of salbutamol.

The applicant's proposed SPC includes the following warning:

> *Salbutamol: atomoxetine should be administered with caution to patients being treated with systemically administered (oral or intravenous) salbutamol (or other beta$_2$ agonists) because the action of salbutamol on the cardiovascular system can be potentiated.*

*Pressor Agents: Because of possible effects on blood pressure, atomoxetine should be used cautiously with pressor agents.*

*Drugs that Affect Noradrenaline: Drugs that affect noradrenaline should be used cautiously when co-administered with atomoxetine because of the potential for additive or synergistic pharmacological effects.*

This is generally appropriate. However, the warning should not be limited to *systemically administered* salbutamol, since high dose nebulised salbutamol can also produce high systemic levels. Specific advice should be given in respect of systemic decongestants (e.g. pseudoephedrine). The wording on the SPC was revised to reflect both these points as given in final approved SPC.

### 17.15.2 Methylphenidate

Study LYAP was a 3 period crossover study in 12 extensive metaboliser Asian men. It evaluated the haemodynamic effects of atomoxetine (60mg single dose and twice daily to steady state) and methylphenidate (60mg single dose and once daily to steady state), alone and in combination. Heart rate, blood pressure, systemic vascular resistance and plasma noradrenaline concentrations were measured.

Atomoxetine and methylphenidate both produced measurable haemodynamic changes, the most prominent of which was an elevation of heart rate. Atomoxetine generally produced smaller changes than methylphenidate, both after single dose and at steady state.

Dosing to steady state with atomoxetine did not result in haemodynamic changes additional to those produced by methylphenidate alone.

The magnitude of the haemodynamic changes produced by atomoxetine were similar following a single dose and at steady state.

Chronic methylphenidate increased intra-day maximum heart rate by 20 bpm. The combination of drugs given chronically increased intra-day maximum heart rate by 16 bpm when compared to placebo; this increase was similar to that with methylphenidate alone but appeared greater than with atomoxetine alone (9 bpm, p=0.066). Chronic dosing of atomoxetine and methylphenidate in combination was generally well tolerated in the population studied.

Plasma noradrenaline concentrations were increased following dosing with methylphenidate but not atomoxetine.

The applicant's proposed SPC includes the following statement, which is satisfactory.

*Methylphenidate: Co-administration of methylphenidate with atomoxetine did not increase cardiovascular effects beyond those seen with methylphenidate administration alone.*

### 17.15.3 Alcohol

Study E002 was a crossover study investigating the psychomotor effects of ethanol after pre-treatment with atomoxetine (40mg twice daily for 5 days) or placebo in 12 healthy adults (6 men and 6 women) of known CYP2D6 phenotype, both poor and extensive metabolisers. There was no evidence of a pharmacodynamic interaction with alcohol in

either poor metabolisers or extensive metabolisers. Atomoxetine was generally well tolerated in all subjects, although a greater incidence of adverse events was reported in poor metabolisers. No difference in atomoxetine tolerability was seen following administration of alcohol.

### 17.15.4 Pharmacodynamic Data from Interaction Studies Reported in the PK Section

No pharmacodynamic interactions were observed when atomoxetine was administered with alcohol (ethanol), desipramine, fluoxetine, or midazolam. However, combination therapy with paroxetine in extensive metabolisers appeared to produce greater orthostatic tachycardia and blood pressure falls compared to atomoxetine therapy alone. Orthostatic HR changes showed the following changes; combination 32 bpm, atomoxetine 19 bpm, and paroxetine 15 bpm. Mean orthostatic systolic BPs of these subjects were also affected in the same sequence; combination therapy drops (-17 mmHg) were greater than those following atomoxetine treatment (-10 mmHg) which exceeded drops following paroxetine treatment (-7 mmHg). Paroxetine is not known to exhibit cardiovascular effects at the dose given and therefore the cardiovascular changes are likely to be due to elevated atomoxetine levels resulting from the PK interaction. Why this was not also seen with the fluoxetine study is unclear.

### 17.15.5 Other Anticipated Interactions

The applicant's proposed SPC includes the following contraindication:

> *Atomoxetine should not be used in combination with monoamine oxidase inhibitors (MAOI). Atomoxetine should not be used within a minimum of 2 weeks after discontinuing therapy with MAOI. Treatment with MAOI should not be initiated within 2 weeks after discontinuing atomoxetine.*

The applicant has not specifically investigated this combination. This is appropriate given the known primary pharmacodynamic activity of atomoxetine.

## *17.16 Pharmacodynamic Conclusions*

The primary pharmacological effect of atomoxetine is relatively pure central noradrenaline reuptake inhibition, the drug having little pharmacodynamic activity at other receptors/transporters. The main metabolites appear to be relatively inactive; in particular the N-desmethyl metabolite, which is the only one that appears to have significant potential to accumulate in poor metabolisers, shows very little relative affinity at other receptors or transporters. The possibility that it might have any other significant pharmacological effect is considered by the preclinical assessor.

The only major secondary pharmacodynamic effects identified are the cardiovascular effects mediated by an increase in noradrenergic tone, in particular moderate increases in heart rate and diastolic and systolic blood pressure. In addition, orthostatic tachycardia and mild hypotension, sometimes associated with dizziness, were seen in a minority of

subjects. These topics were adequately reflected in the final approved SPC. The fact that these cardiovascular effects appear to be of smaller magnitude than those produced by methylphenidate, which is licensed in the requested indication, is reassuring. Cardiovascular safety is considered in more detail in section IV.
Similarly the only major secondary pharmacodynamic interaction identified is the additional increase in heart rate and systolic blood pressure produced by salbutamol. This can be extrapolated to other sympathomimetics without the need for further data. Some changes were made to the advice in section 4.5 of the proposed SPC relating to sympathomimetics and to "drugs that affect noradrenaline" (relevant examples should be given).

There are no outstanding pharmacodynamic issues.

# 18 IV CLINICAL EFFICACY

## *18.1 IV.1 Introduction*

The clinical trial programme included the following controlled studies designed to assess efficacy (numbers enrolled into each treatment group in brackets):

*18.1.1.1.1.1.1 Short Term Controlled Studies*

Two exploratory 9 week, randomised, double-blind, placebo-controlled studies in children/adolescents dosed twice daily, assessed primarily in the home setting:

| | |
|---|---|
| **HFBD** | Atomoxetine (65) vs. placebo (62) vs. methylphenidate (20, for study design validation purposes) |
| **HFBK** | Atomoxetine (64) vs. placebo (62) vs. methylphenidate (18, for study design validation purposes) |

One 8 week randomised, double-blind, placebo-controlled dose-response study (twice daily dosing) in children/adolescents, assessed primarily in the home setting:

| | |
|---|---|
| **LYAC** | 0.5 (44), 1.2 (84), 1.8 (85) mg/kg/day vs. placebo (84) |

Three Phase III randomised, double-blind, placebo-controlled studies in children/adolescents dosed once daily:

| | | | |
|---|---|---|---|
| **18.1.1.1.1.2** | **LYAT** | Atomoxetine (85) vs. placebo (86) | - home setting (6 weeks) |
| **18.1.1.1.1.3** | **LYBG** | Atomoxetine (133) vs. placebo (64) | - home setting (8 weeks) |
| **18.1.1.1.1.4** | **LYAW** | Atomoxetine (101) vs. placebo (52) | - school setting (7 weeks) |