Medicines and Healthcare products Regulatory Agency

Safeguarding public health

PRELIMINARY ASSESSMENT REPORT

STRATTERA (atomoxetine) – Risk Benefit Assessment

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 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.	

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).

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.

[redacted]

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 (MAH meta-analyses)
  - Post-marketing data: studies, usage data, spontaneous ADR reports, PSUR data
  - Published literature
- Observational data

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

5.0 BENEFIT EVALUATION

5.1

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).

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

6.1.2 Clinical Trial data

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

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 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:

Cardiorespiratory arrest
Myocardial infarction
Death, drug level increased
Death
Hepatic failure, renal insufficiency, vomiting, prothrombin time prolonged
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 (Death, Drug level increased) involved a 41-year old female patient with unknown medical history. She 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 her home; she had been dead for 4 days. Although the correct amounts of medications were found in her 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 involved a female patient of unknown age and unknown medical history. She 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

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.

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**

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.

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 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 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).

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.

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.

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.

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.

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.

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:

This seems completely inappropriate given that the MedDRA lower level term 'Intentional overdose' codes to the MedDRA preferred term 'non-accidental overdose'.

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.

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.

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.

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

and a cumulative review of spontaneous reporting data to 30 September 2005.

nd the November issue of the WHO

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

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 Novemb[illegible] 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.

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.

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.

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.

Two of the 'non-medically significant' cases may also indicate a dose response effect of atomoxetine on QT interval prolongation.

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.

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.

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 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.

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.

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.

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 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.

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%**

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

The causes of death in the three previously assessed fatal cases were given as acute viral myocarditis (12-year old male); cardiomegaly, complications of alcoholism (hepatic cirrhosis), mitral valve degeneration and morbid obesity (45-year old male); and liver congestion consistent with dilated cardiomyopathy (16-year old male). The fourth case concerning a 26-year old male 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 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

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),

6.1.5.3 Psychiatric Disorders

Clinical Trial Data

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.

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

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 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 12 year old male 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 (

. 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.

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 [redacted] following the healthcare professional communication concerning this newly identified risk.

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.

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).

summary of the data is provided below and the full assessment can be found in Annex 7 of this report.

Preclinical Data

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.

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.

6.2.1.3 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.

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 21 year old female and a 6 year old male. In the first case the individual had a history of emotional instability and following the discovery that she was pregnant she took 5 tablets as part of a suicide attempt. In the second case, within two months of starting treatment the boy experienced low mood and marked depression and tried to throw himself out of a window. He recovered after drug withdrawal.

The two reports of suicidal ideation involve a 6 year old and a 16 year old male. In the first case the boy experienced depression and suicidal feelings after 18 months on methylphenidate. He recovered after drug withdrawal but this also coincided with a change in his family circumstances which may have also contributed to improvement. In the second case it was reported that after an unspecified time on methylphenidate he wanted to kill himself and others. The night time dose was stopped and behaviour improved.

<u>*Overdose*</u>
The first case involves a 16 year old male who took up to 10 tablets which he was given by a friend who had been prescribed methylphenidate for ADHD. He subsequently died due to cerebral oedema possibly as a result of a hypertensive crisis. The second case relates to a male patient whose mother gave him a higher than prescribed dose (54mg instead of 36mg). He experienced hallucinations and displayed choroidal/extrapyramidal

movements. The third case involves a male (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 female patient was reported to be addicted to methylphenidate after 4 months of treatment. The second case of drug dependence involves a 33 year old female who had received methylphenidate for narcolepsy for 6 years and became dependent on it. She 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 Belgium, Denmark, France, Ireland, Netherlands, Portugal, Spain and UK. 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 46 year old female 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 fribrillation (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 her death.

Assessor's comments (comparative safety):
Methylphenidate and dexamphetamine are alternative therapies authorised for ADHD.

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

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.

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 review also identified that the occurrence of Raynaud's phenomenon appears to be causally related to atomoxetine use.

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.

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.

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

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.

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.

Overall the available safety and efficacy data suggest that the balance of risks and benefits of atomoxetine in the treatment of ADHD remains favourable.

9 December 2005