Ipswich and East Suffolk
Clinical Commissioning Group

New Medicine Report	**Atomoxetine** **(First known as Tomoxetine)** **(Adopted by the CCG until review and further notice)**
Document Status	Post Suffolk D&TC
Traffic Light Decision	**RED**
Date of Last Revision	12.07.04
Approved Name	Atomoxetine
Trade Name	Strattera™
Manufacturer	Lilly
Legal Status	Licensed POM
Indication	Attention Deficit/Hyperactivity Disorder in children aged 6 years and over, adolescents and adults as defined by DSM-IV criteria or ICD-10 guidance
Dosage	Target dose for <70kg 1.2mg/kg/day Target dose for ≥70kg 80mg/day
Cost	£13.65 for 7 or £54.60 for 28 of any strength (10mg, 18mg, 25mg, 40mg and 60mg (28 tablet pack only))
Possible Number of Suffolk Patients	Up to 866 requiring treatment with medication
Number Needed to Treat	About 3 to 5 for beneficial effect at about

	2 months of treatment. Please see text
Treatment Alternatives	Diet Psychotherapy Dexamfetamine Methylphenidate Tricyclics
Future Alternatives	Adderall (™ in USA) a combination amphetamine product
Possible Future Indications	Nocturnal enuresis Depression Bipolar disorder Panic/Anxiety attacks

Reviewer's Comments

Atomoxetine is a new treatment for attention deficit/hyperactivity disorder (ADHD) which benefits from not being a Controlled Drug and having a once or twice daily dosage.

The evidence so far shows that it has a positive effect on symptoms over a short period of time but no trials are reported here which have lasted longer than 9 weeks.

Although one trial did compare the activity of atomoxetine with methylphenidate no results were reported as it was not a primary endpoint of the trial. It is therefore not possible to know whether the product is of equal value, less or more benefit than current treatment.

A number of side effects have been noted including loss of appetite, tiredness and an increase in somnolence.

Of greater concern is the effect on blood pressure and heart rate all of which are raised and on weight loss and possible a reduction in growth rate. It should be noted that these were seen over a very short timescale and although the p value showed significance it is not clear what will happen during longer term therapy. Thus patients being treated with atomoxetine will need to be closely monitored during any long term treatment.

Atomoxetine should be used as part of a total package of care which should include other measures including social support, educational assistance and psychological help with coping strategies.

It should be noted that there is a suggestion that some of the symptoms of ADHD may be affected by diet and steps should be taken to ensure that substances with the potential to aggravate ADHD should be avoided.

This product is licensed for use in adults and there seems to be an increase in the level of interest in ADHD in the adult population.

Evidence Reviewed

Paper, Review, Abstract etc.	Level of evidence
Spencer T, Heiligenstein JH, Biederman J et al Results from 2 proof-of-concept placebo-controlled studies of atomoxetine in children with attention deficit/hyperactivity disorder J Clin Psychiatry 2002;63:1140-1147	I
Michelson D, Allen AJ, Busner J et al Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomised placebo-controlled study Am J Psychiatry 2002;159:1896-1901	I
Michelson D, Faries D, Wericke J et al Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomised placebo-controlled dose-response study Pediatrics 2001;108(5)	I
Michelson D, Adler L, Spencer T et al Atomoxetine in adults with ADHD: two randomised, placebo-controlled studies Biol Psychiatry 2003;53:112-120	I
General Information provided by Lilly	

Level of evidence adapted from "Quick and Clean" : authorative health technology assessment for local health care contracting Andrew Stevens, Duncan Collin-Jones & John Gabbay Health Trends Vol 27 No 2 1995

Review

Atomoxetine is a selective norepinephrine reuptake inhibitor which has been found to have an effect in patients with attention deficit/hyperactivity disorder (ADHD). The mode of action is not known but it is apparent that atomoxetine affects the regulation of norepinephrine by its action as a potent inhibitor of the presynaptic norepinephrine transporter. It has minimal affinity for any other transporter or receptor systems.

In a trial reported by Michelson, Faries, Wernicke et al a total of 297 children and adolescents aged 8 to 18 with ADHD were treated in 13 centres across the USA. The authors are acknowledged in the paper as employees and shareholders of Lilly which also funded the trial.

Important exclusion criteria included IQ <80, serious medical illness, comorbid psychosis or bipolar disorder, history of a seizure disorder and ongoing use of psychoactive medication other than the study drug.

After a period of washout the patients were randomised to one of four arms placebo or atomoxetine at a dose of 0.5mg/kg/day or 1.2mg/kg/day or 1.8mg/kg/day taken in divided doses in the morning and late afternoon.

The outcomes were measured and are presented in Table 1. The primary outcome measure was defined as the ADHD-RS an 18 item scale based on a semi-structured interview with the parent (or primary caregiver). Each item corresponds with 1 of the 18 DSM-IV diagnostic criteria. Each item is given a score (0=never or rarely, 1=sometimes, 2=often, 3=very often) and the total score is the sum of all responses to each item. Please note that this is a 72 point scale with a maximum score of 54 and a minimum of 0.

Table 1
To show the change in score over 8 weeks for the primary end point measure the ADHD-RS

	Placebo	Atomoxetine 0.5mg/kg/day	Atomoxetine 1.2mg/kg/day	Atomoxetine 1.8mg/kg/day
N	83	43	84	82
ADHD-RS				
Total	-5.8	-9.9	-13.6	-13.5
Inattention subscale	-2.5	-5.1	-7.0	-6.8
Hyperactive/Impulsive subscale	-3.2	-4.8	-6.6	6.7

All scores for atomoxetine 1.2mg and 1.8mg per kg/day have a p value<0.05 pairwise comparison with placebo.

The authors note that it is difficult to interpret the results. It is not possible to determine the time to onset of initial response as the target dose of 1.2mg/kg/day was not reached until the third week and the dose of 1.8mg/kg/day was not reached until the fourth week of the 8 week trial. In addition the value of long-term therapy was not assessed so it was not possible to see whether the medication was a suitable therapeutic option compared with the current stimulants. However it can be seen that the 1.2mg and 1.8mg per kg per day doses were more effective than placebo and the low dose treatment.

In the trial sponsored by Lilly and reported by Michelson, Allen, Busner et al 171 children between the ages of 6 and 16 years who met the DSM-IV criteria for ADHD were randomly assigned to receive 6 weeks of treatment with either atomoxetine once daily or placebo. Important exclusion criteria included serious medical illness, a history of psychosis or bipolar disorder, alcohol or drug abuse within the last 3 months and ongoing use of psychoactive medication other than the study drug.

All patients entered a medication free evaluation period for a minimum of 5 days. Those patients assigned to the atomoxetine arm received a daily dose of 0.5mg/kg for the first 3 days followed by 0.75mg/kg for the remainder of the first week. The dose was then increased to 1.0mg/kg. Four weeks after randomisation patients with a CGI score >2 had a further dose increase to 1.5mg/kg/day.

The primary outcome measure was the total score on the ADHD-RS described above. Patient data was analysed on an intent to treat basis with the last score carried forward. The results are shown in Table 2

Table 2
To show the improvement in ADHD-RS and CGI severity scores for children treated with atomoxetine or placebo

	Placebo (n=83)		Atomoxetine (n=84)	
	Baseline mean	Change mean	Baseline mean	Change mean
ADHD-RS				
Total score	36.7	-5.0	37.6	-12.8
Inattentive symptoms	21.4	-2.9	21.9	-7.1
Hyperactive/Impulsive symptoms	15.3	-2.1	15.7	-5.7
% with a ≥25% reduction in total score from baseline		31.3%		59.5%
CGI severity score	4.6	-0.5	4.7	-1.2
% with remission endpoint CGI severity score of 1 or 2		9.6%		28.6%

The majority of patients were male and most were either mixed or inattentive subtype with very few in the hyperactive/impulsive subgroup.

The data shows that atomoxetine is superior to placebo in the treatment of ADHD over a 6 week period.

Using the data of % with a ≥25% reduction in total ADHD-RS score an NNT of 4 over 6 weeks can be calculated. Using the remission of severity CGI score the NNT changes to 5.

In a trial sponsored by Lilly and reported by Spencer et al 291 patients were entered into two multicentre trials at a total of 17 sites in the USA. Patients were aged at least 7 but under 13 with normal intelligence and met the DSM-IV diagnostic criteria for ADHD. Patients were excluded if they were characterised as poor metabolisers of CYP2D6 (the safety of use in this group had not been

established at the time but has since been shown to be of little or no problem). In addition patients were excluded if they weighed less than25kg at entry, had a documented history of bipolar I or II disorder or a history of psychosis, had any organic brain disease or a history of seizure disorder, were taking any psychotropic medication, had a history of drug or alcohol abuse within the last 3 months or had any significant prior or current medical conditions. Those patients with comorbid anxiety and or depressive disorders were able to participate.

Patients were enrolled into 1 of 2 double blind placebo controlled trials with identical design. There were three study periods 2-week medication washout, 9-week treatment period and 1-week single blind discontinuation phase. All atomoxetine patients achieved their maximum treatment dose by week 7 of the treatment phase.

Patients with previous exposure to psychostimulant medication were randomised with either atomoxetine or placebo and those who were treatment naïve were randomised to atomoxetine, placebo or methylphenidate. The inclusion of methylphenidate was to ensure that the study design worked should atomoxetine fail to show any positive improvement in the patients' scores, as one would expect methylphenidate to have some action and therefore produce a positive result in that arm of the trial. It was not intended to show as either a primary or secondary endpoint the relative efficacy of atomoxetine to methylphenidate and no results have been produced within the paper for the methylphenidate treatment arm. Although acknowledging that it was not designed to conclusively show this outcome it would have been of interest to see how the two compared.

The primary outcome measure for the trial was change on the ADHD-RS measure. A number of other measures were used as secondary end points. The results are shown in Table 3.

Table 3
To show the mean change from baseline in the various arms of 2 placebo-controlled studies of atomoxetine in children with ADHD

	Study 1				Study 2			
	Atomoxetine		Placebo		Atomoxetine		Placebo	
Measure	n	Change	n	Change	n	Change	n	Change
ADHD-RS								
Total score	64	-15.6	61	-5.5	63	-14.4	60	-5.9

Inattentive symptoms	64	-7.5	61	-3.0	63	-7.6	60	-3.0
Hyperactive/Impulsive symptoms	64	-8.0	61	-2.5	63	-6.9	60	-2.9
% with at least a 25% decrease in total ADHD-RS score		64.1%		24.6%		58.7%		40.0%
CGI severity score	64	-1.2	61	-0.5	63	-1.5	61	0.7
CPRS-ADHD Index	59	-5.7	54	-2.6	61	-8.8	60	-2.1

From the % with a decrease of at least 25% in ADHD-RS scores NNTs can be calculated giving a value of 3 for study group1 and 5 for study group 2 over a 9 week period.

Michelson also reports a study of the treatment of ADHD in adults with atomoxetine. This showed that atomoxetine was effective in reducing scores across a number of measures over a ten week treatment period. Several factors are suggested which may limit the interpretation of this trial but it none the less shows a possible route for treatment in adults with ADHD.

Adverse Effects etc.

For full details please see the SPC for this product.

In the trial by Michelson, Faries, Wernicke et al it was shown that all doses of atomoxetine were well tolerated compared to placebo although there were data to suggest that decreased appetite and increased somnolence were seen with an increase in the dose. There was evidence of change in vital signs and the change in weight as shown in Table 4. The authors suggest this is of potential importance. Further research is underway in respect of this finding. It is suggested that the change is no greater than would be seen in patients treated with methyphenidate.

Table 4
To show the changes in vital signs and weight over 8 weeks as described by Michelson et al

	Placebo	Atomoxetine 0.5mg/kg/day	Atomoxetine 1.2mg/kg/day	Atomoxetine 1.8mg/kg/day
N	83	43	84	81
Change in systolic BP mmHg	+2.1	+3.3	+4.4	+2.5
Change in diastolic BP mmHg	-1.4	+1.5	+2.8	+1.7
Change in pulse rate	+1.6	+5.8	+6.3	+8.3
Change in weight (Kg)	1.7	0.3	-0.4	-0.5

The trial reported by Michelson, Allen, Busner et al noted similar increases in blood pressure and pulse with a mean decrease in weight of –0.9kg compared with a mean increase of 0.8kg in the placebo group.

In addition the most frequently reported adverse events were gastrointestinal and increases in tiredness and fatigue.

The trial reported by Spencer gave the following results for vital signs and weight change during treatment as shown in Table 5

Table 5
To show the change in vital signs and weight, combined data as described by Spencer et al

	Placebo	Atomoxetine	P value
Change in systolic BP mmHg	+8.6	+10.8	
Change in diastolic BP mmHg	+8.3	+9.6	
Change in heart rate	+12.2	+13.0	<0.001
Change in weight (Kg)	+1.4	-0.5	<0.001
Change in temperature (C)	+0.03	+0.01	
Change in height (cm)	+1.1	+0.8	

A significantly higher percentage of patients in the active treatment group reported a decrease in appetite (22% vs 7% p<0.01).

Economic Information

It is suggested that ADHD affects 5% of school-aged children with a male to female ration of 4:1. The ratio may be skewed, as boys tend to exhibit hyperactivity and impulsivity whereas girls tend to exhibit inattention. It has been estimated that 1% of school children meet the diagnostic criteria for severe combined type ADHD.

The product is licensed for the treatment of children aged 6 years and over, adolescents and adults. The figures for the child population in Suffolk give age ranges of 5-9 and 10-14 so these have been used in the calculations to produce Table 6. Although it is acknowledged that some error will have occurred it is not felt that the actual figures will be too different.

It would be expected that children in the 1% group will be receiving some specialist treatment with many receiving current drug therapy. A small proportion of those may be treated with atomoxetine in the first instance.

Table 6
To show the estimated numbers of children with ADHD in Suffolk as described in the text.

PCT	Number of children aged 5 – 14years	5%	1%
Central	12,513	626	125
Ipswich	18,974	949	190
Suffolk Coastal	12,630	632	126
Suffolk West	27,078	1,354	271
Waveney	15,413	771	154
Total for Suffolk	86,609	4,330	866
Total for East Commissioning	44,117	2,206	441

The incidence rate for ADHD in adults has not been calculated.

The cost of current treatments is shown in Table 7

Table 7
To show the cost of current treatments for ADHD (MIMS July 2004 & DIZone)

Treatment name	Strength	Pack size	Cost(£)
Concerta XL	18mg	30	27.00
	36mg	30	36.75
Dexedrine	5mg	28	1.92
Equasyn and Tranquilyn (methylphenidate)	5mg	30	2.78
	10mg	30	4.99
	20mg	30	9.98
Ritalin	10mg	30	5.57
Strattera	10mg, 18mg, 25mg, 40mg, 60mg(28 only)	7	13.65
		28	54.60

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Charts to be used in the decision making process in Suffolk

Quality of Evidence categories	
I	Strong evidence from at least 1 RCT
II-1	Evidence from a well designed CT without randomisation
II-2	Evidence from well designed cohort or case controlled study
II-3	Evidence from multiple time series or dramatic results
III	Opinions of respected clinicians or expert committees
IV	Evidence inadequate

Cost utility categories	
	Per life year gain
A	Less than £3,000
B	£3,000 to £20,00
C	> £20,000
D	Negative life year

Key to Table at Right	
++	Strongly recommended
+	Recommended
-	Beneficial but high cost
X	Not recommended
0	Not proven

Recommendations informed by cost utility an evidence			
Quality of evidence	A	B	C
I	++ (high)	++	-
II	++	+	-
III	+	-	-
IV	0	0	0

Adapted from

“Quick and Clean” : authorative health technology assessment for local health care contracting
Andrew Stevens, Duncan Collin-Jones & John Gabbay
Health Trends Vol 27 No 2 1995

To Decide If A Medication Is To Be Used In Suffolk

Criterion	Tends to poor	2	Me
Quality of evidence in the papers reviewed	IV	III	I
Magnitude of effect inferred from the trials reviewed	Low		Me
Known Side Effect Profile	High		Me
Known Interactions	High		Me
Concern re Possible Side Effects Not Yet Uncovered	High		Me
Balance of Benefit To Harm (side effects toxicity interactions etc)	Poor		Me
NNT	High		Me
Comparison Of Effectiveness With Other Medicines In Use For The Same Condition	Poor		Me
Severity of Condition to be Treated	Trivial		Me
Cost Utility Score	D	C	
Recommendations informed by cost utility and quality of evidence	0	X	

To Decide Where A Medication Is To Be Used In Suffolk

Criterion		Red	Amber
Skills of the prescriber	Experience Of The Condition	Specific	Specific
	Diagnosis	Specific	Specific
	Monitoring Progress Of Treatment	Difficult	Specific
Therapy	Patient Selection	Difficult	Specific
	Initiation Of Treatment	Difficult	Difficult
	Dose Titration	Difficult	Specific
	Monitoring Of Side Effects	Complex	Easy
	Method Of Administration	Complex	Normal
	Discontinuation Of Treatment	Complex	Complex