MHRA

Medicines and Healthcare products Regulatory Agency

Safeguarding public health

RESTRICTED COMMERCIAL

NOT FOR PUBLICATION

ASSESSMENT REPORT

PAROXETINE (SEROXAT) - VARIATION ASSESSMENT REPORT – PROPOSAL TO CONTRAINDICATE IN ADOLESCENTS AND CHILDREN UNDER 18 YEARS WITH MAJOR DEPRESSIVE DISORDER

NAME OF ACTIVE SUBSTANCE:

Paroxetine

ORIGINATING MEMBER STATE: United Kingdom

CONTACT POINT IN THE MEMBER STATE FOR DISCUSSION ON ISSUE RAISED BY THE ASSESSMENT REPORT:

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DATE OF ASSESSMENT REPORT: 4 June 2003

1. INTRODUCTION

On 21 May 2003, GlaxoSmithKline submitted to MHRA a briefing document summarising clinical trial data on Seroxat (paroxetine) in the treatment of paediatric obsessive compulsive disorder, social anxiety disorder and major depressive disorder, in preparation for discussion of forthcoming variations to extend the indications to the paediatric age group. However, this submission also included results from trials in major depressive disorder in children and adolescents that raised both a serious safety concern in relation to use in major depressive disorder in adolescents and children as well as a concern over lack of efficacy in this population. Due to the serious nature of this issue, CSM advice was sought urgently on 29 May 2003. This assessment report provides a summary of previous CSM advice on SSRIs and suicidal behaviour, a detailed assessment of the clinical trial data submitted by the MAH and proposals from the Marketing Authorisation Holder to reflect the paediatric clinical trial data.

2. BACKGROUND

2.1 Depression in children and adolescents

Depression can be defined as depressed mood or loss of enjoyment plus three or four associated symptoms such as sleep disturbance, hopelessness and suicidality. It has only been since the 1970 and early 1980's that depression in childhood and adolescence has been recognised.

There are three main differences in depression in children compared with adults (Scott A et al. 2000):

- There are developmental issues that relate to the age differences in the presence of affective disorders
- Children have different cognitive abilities and this will give rise to differences in their experience of the cognitive features that are associated with adult depression.
- To apply adult criteria to children assumes that they are correctly able to report their experience of depression.

A UK Office of National Statistics survey (Meltzer H 2000) estimated that depression occurs in 0.2% of boys and 0.3% of girls between the ages of 5 and 10 years and 1.7% of boys and 1.9% of girls between the ages of 11 and 15 years.

The criteria for diagnosis of depression in children and adolescents is the same as the diagnosis for adults in both the ICD-10 and the DSM-IV-TR. Depressive symptoms are very common in adolescents and depression should therefore only be diagnosed when the following are present: significantly impaired social functioning, psychopathological symptoms such as a suicide attempt and significant suffering from the symptoms. The aetiological factors of depressive disorder in young people appear to be related to early adverse experiences and certain temperamental features. These factors may predispose young people to develop depression, especially in those genetically at risk.

Depression in childhood and adolescence differs from adult-onset depression in measures of cortisol secretion, serotonergic function, immune status and

neuropsychological function and in lack of response to tricyclic antidepressants. Children tend to show more irritability and overactivity than adults. It is not known whether this is due to an effect of the stage of the illness, heterogeneity in the type of mood disorder or an influence of developmental level. There also appear to be differences between childhood and adolescent depression. In comparison with adolescent depression, pre-adolescent depression is less likely to lead to adult depression, has more overlap with other disorders, shows a male preponderance and is more strongly associated with family dysfunction.

The features of obsessive-compulsive disorder in childhood are also affected by the stage of development. Compulsive behaviour is more prominent in younger children, probably because of the inability to verbalise both obsessive ideation and the "senselessness" of their actions.

2.2 Licensed status of anti-depressants in children in the UK

2.2.1 Tricyclic antidepressants:

None of the tricyclic antidepressants (amitriptyline hydrochloride, clomipramine hydrochloride, dothiepin hydrochloride, imipramine hydrochloride|) are licensed for use in children under 16 years. Amitriptyline and imipramine are licensed for use in children over 7 years for nocturnal enuresis.

2.2.2 Selective serotonin re-uptake inhibitors (SSRIs):

None of the SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine maleate, paroxetine, sertraline) are authorised for depression in children. Following a European article 30 harmonisation procedure in 2001, fluvoxamine has been authorised for children over 8 years and adolescents for obsessive-compulsive disorder (25 mg daily increased if necessary in steps of 25mg every 3-4 days to maximum 200mg daily in divided doses). Sertraline is also authorised for obsessive-compulsive disorder in children 6-12 years, 25mg daily increased if necessary in steps of 50mg at intervals of at least 1 week, maximum 200mg daily (and adolescents over 13 years).

It is important to note that in the U.S. fluoxetine has recently been authorised for the treatment of depression and obsessive-compulsive disorder in children aged 7-17 years. Currently there is on-going Article 30 procedure in the EU to harmonise the SPC across Europe. This does not include paediatric data as an article 30 procedure does not allow assessment of data to extend authorisation to new indication. However, the MAH, Lilley, has agreed to formally submit paediatric data previously submitted to the FDA, as a Type II variation to the MHRA, at completion of the Article 30 procedure to extend the indication of fluoxetine to children. This is likely to be in 2004. These paediatric data were assessed by the MHRA in November 2001 and presented to the Paediatric Medicines Working Group. It was initially intended that these recommendations would inform the UK position at European level discussions. The Working Group considered that the evidence for efficacy for the use in major depressive disorder and obsessive compulsive disorder was robust. There were concerns with regard to the long-term safety of fluoxetine, in particular with respect

to possible adverse effects on growth and decreased alkaline phosphatase levels. The Working Group considered that the evidence supported a paediatric indication for both obsessive compulsive disorder and major depressive disorder.

The Royal College of Paediatrics and Child Health formulary, Medicines for Children 1999, gives dosage recommendations for citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline but not escitalopram, for children aged 12-18 years, for the treatment of depression.

2.3 Treatment of depression in children and adolescents

Treatment is based on psychosocial interventions such as cognitive behavioural therapy (CBT), interpersonal psychotherapy and family interventions and pharmacotherapy.

Harrington (2002) suggests that cognitive behavioural therapy or interpersonal psychotherapy are probably the first choice treatment choice for moderate depression. Approximately one-third of clinically depressed adolescents do not respond to CBT and therefore patients should be re-assessed after 6-8 weeks to determine whether there has been a response. The next step should be a different line in treatment such as SSRI therapy. Less is known about the management of severe depression but a combination of medication and individual treatment is often necessary.

As there are currently no drugs licensed for treatment of depression in children, pharmacological treatment is based on off-label use of drugs licensed for adults. Rigorous evidence for the efficacy of treatment of depression in children and adolescents is lacking. Few trials separate data from children and adolescents.(Hazell P, 2002) This is important because children may have a different response to treatment than adolescents. Evidence for the efficacy of pharmacological treatment is also limited. A recent Cochrane systematic review of tricyclic antidepressants identified three trials of 64 pre-pubertal children. A statistically non-significant trend favouring placebo over active treatment was found. (Hazell P, 2002). As it has become clear that tricyclic antidepressants are not an effective treatment in either children or adolescents, pharmacological treatment has tended to focus on the use of SSRIs.

3. PREVIOUS CSM AND PHARMACOVIGILANCE WORKING PARTY ADVICE ON SSRIS AND SUICIDAL BEHAVIOUR

The following summarises the previous assessments of the issue of suicidal behaviour in association with SSRIs carried out in the UK and at the Pharmacovigilance Working Party of the Committee for Proprietary Medicinal Products.

CSM initially reviewed this issue following publication of case series by Teicher et al (1990) which stimulated scientific debate and intense media interest. In 1992 following further review an article was published in the UK drug safety bulletin

'Current Problems in Pharmacovigilance' which stated 'there is little to support the suggestion that fluoxetine induces suicidal or aggressive behaviour.

Following close monitoring of spontaneous adverse drug reaction reports, there was a UK exercise in 1998-2000 to develop harmonised safety information for all SSRIs. During this process, CSM advised that the core SPC should reflect the general clinical experience that suicidal behaviour increases in the early stages of treatment as with any antidepressant.

Dr David Healy, a psychiatrist in Wales, raised issue of suicidal behaviour with SSRIs in his publication 'A failure to warn' in 1999. CSM considered the available data in June 2000 and concluded that it was impossible to answer the question of whether SSRIs caused suicidal behaviour in a small subpopulation of patients. They considered that the issue should be kept under review and formally reviewed every 2-3 years.

CSM concluded that patient information leaflets for the SSRIs should be updated to include a warning that suicidal thoughts may occur or increase in the early stages of treatment and that urgent medical advice should be sought in the event of such symptoms.

UK presented the assessment on suicidal behaviour with SSRIs to the Pharmacovigilance Working Party (PhVWP) in 2000. All EU member states agreed with the scientific conclusions of the UK assessment however no other member state considered that updating the patient information to warn about the risk of suicidal behaviour was appropriate.

CSM considered data relating to suicidal behaviour, aggression and akathisia in December 2001 and concluded that:

- The evidence was not sufficient to confirm a causal association between SSRIs and suicidal behaviour, although an effect in a small high-risk population could not be ruled out.

- Akathisia should be added to SSRI Summary of Product Characteristics (SPCs).

This assessment report was then discussed at the PhVWP which agreed with the conclusions of the UK assessment report but considered that further discussion was required about the definition of akathisia.

On 21 November 2001 a group of CSM and external experts was called together to hear Dr David Healy present his research in relation to suicidal behaviour. This was principally a reanalysis of human volunteer studies on fluoxetine.

They concluded that:

- the evidence presented did not justify a change to the regulatory position
- changes to UK Seroxat Patient Information Leaflet (PIL) were required to clarify warnings on withdrawal reactions.

They recommended the following further work to investigate suicidal behaviour -

- General Practice Research Database study
- reanalysis of clinical trial data on fluoxetine

A further meeting of this expert group had been planned for March 2003. However the Seroxat User Group, a group of 4000 patients and former patients, called into question the independence of the members of the group in view of declarations of interest in the pharmaceutical industry of two members. Following legal advice the meeting of March was cancelled and the group dissolved.

The CSM convened a formal Expert Working Group on SSRIs in April 2003, the first meeting of which was on 23 May 2003.

Paediatric data

MHRA called the Marketing Authorisation Holder for Seroxat, GlaxoSmithKline (GSK) on 21 May 2003 to discuss various issues arising from the television programme Panorama, broadcast on 11 May 2003. It was at that meeting that the paediatric data relating to the use of Seroxat in children was raised. At that point the MAH were planning to request a variation to extend the indications for Seroxat to include the indications Social Anxiety Disorder and Obsessive Compulsive Disorder in children as well as the safety warnings in major depressive disorder. Following meetings with MHRA, GSK agreed to prioritise the safety variation from the extension of the indications.

4. DATA TO BE CONSIDERED

Three acute-phase clinical trials treating children (aged 7–11 years) and adolescents (aged 12–18 years) who have Major Depressive Disorder (MDD) have been submitted in support of this application – they are studies 329, 377 and 701. The Table below is an overall summary of the design of the studies: each is then described in more detail.

Study number	Treatment duration (weeks)	Design	Age range (years)	Paroxetine dosages (mg/day)	Number of patients
329	8	Randomised (1:1:1); double blind; parallel groups; placebo controlled and active (imipramine) controlled; flexible dose.	12 – 18	20 – 40	271
377	12	Randomised (2:1); double blind; parallel groups; placebo controlled; flexible dose.	13 – 18	20 – 40	274
701	8	Randomised (1:1); double blind; parallel groups; placebo controlled; flexible dose.	7 – 17	10 – 50	203

Study 329
The study was carried out in 10 centres in the US and 2 in Canada; all were university or hospital psychiatry departments. The first patient was given study medication in April 1994; the last patient was enrolled in March 1997; the last study visit was in May 1997.

The study had an acute phase lasting 8 weeks where all patients were treated, followed by a continuation phase in which 'responders' had the option to continue to receive blinded study medication for a further 6 months.

Patients had to be:
- aged between 12 years 0 months and 18 years 11 months (at the start of the study),
- currently experiencing an episode of major depression (according to DSM-III-R) which had been ongoing for at least 8 weeks,
- have a total score ≥ 12 on the 17-item HAM-D.

The primary objective was to compare the efficacy and safety of imipramine and paroxetine to placebo in the treatment of adolescents with unipolar major depression.

Efficacy parameters were:
- the Hamilton Depression Scale (HAM-D),
- the 9-item depression sub-scale of the Schedule for Affective Disorders and Schizophrenia for School-age Children – Lifetime Version (K-SADS-L),
- the Clinical Global Improvement (CGI),
- the Self-Perception Profile (SPP),
- the Autonomous Functioning Checklist (AFC),
- the Sickness Impact profile (SIP).

Safety parameters were:
- Adverse experiences,
- Vital signs and body weight,
- Clinical laboratory evaluations,
- Electrocardiograms (EKGs).

Demographics
275 patients were enrolled and randomised – 93 to paroxetine, 95 to imipramine, 87 to placebo. The table shows basic demographic details and a summary of the patient disposition, including major reasons for patients not completing the 8-week acute phase of the study.

Table 329-1

	Paroxetine (N=93)	Imipramine (N=95)	Placebo (N=87)
Age (yrs) mean	14.8	14.9	15.1
Female (%)	62%	59%	66%
Baseline HAM-D mean	19.0	18.3	19.2
Completed 8 weeks	72%	60%	76%
Reasons for withdrawal:			
Adverse event(s)	10%	32%	7%
Lack of efficacy	4%	1%	7%
Other reason(s)	14%	7%	10%

Efficacy Results

The Applicant has imputed missing values using the 'last observation carried forward' approach. This is considered reasonable and is commonly used in these types of studies. Any bias resulting from this is usually considered to be a bias towards the null hypothesis of no treatment effect, rather than potentially exaggerating any small differences. Particularly for the comparison of paroxetine with placebo, it is noted that the proportions of patients not completing 8 weeks were quite similar (28% and 24%).

Two primary endpoints were pre-specified:

The mean change from baseline in the HAM-D score and the proportion of patients with an end of treatment HAM-D score less than or equal to 8. The table below shows a summary of the results for these two primary endpoints.

Table 329-2

	Paroxetine (N=93)	Imipramine (N=95)	Placebo (N=87)
Mean change in HAM-D score (std error)			
Week 8 observed cases	−12.2 (0.88)	−10.6 (0.97)	−10.5 (0.88)
Week 8 last obs carried forward	−10.7 (0.81)	−8.9 (0.81)	−9.1 (0.83)
Percent 'responders' (n/N)			
Week 8 observed cases	81%(54/67)	73%(41/56)	65%(43/66)
Week 8 last obs carried forward	67%(60/90)	59%(55/94)	55%(48/87)

The differences between the active groups and placebo are summarised below with point estimates, 95% confidence intervals and *P*-values.

Table 329-3

	Paroxetine – Placebo diff (95% CI) P-value	Imipramine – Placebo diff (95% CI) P-value
Mean change in HAM-D score		
Week 8 observed cases	–1.7 (–4.1, 0.8) 0.15	+0.1 (–2.7, 2.5) 0.95
Week 8 LOCF	–1.7 (–3.9, 0.6) 0.13	+0.2 (–2.1, 2.5) 0.87
Percent 'responders'		
Week 8 observed cases	15% (0, 30) 0.05	8% (–8, 24) 0.36
Week 8 LOCF	12% (–3, 26) 0.11	3% (–11, 18) 0.61

Adverse Events

There were no deaths during the trial. 18 patients experienced serious adverse events (11 paroxetine, 5 imipramine and 2 placebo). A summary of the CNS-related adverse events that occurred in more than 5% of patients in any one (or more) treatment group and that were at least twice as common in the either of the active groups compared to the placebo group is shown below.

Table 329-4

Adverse Event % (n)	Paroxetine (N=93)	Imipramine (N=95)	Placebo (N=87)
Dizziness	24% (22)	47% (45)	18% (16)
Emotional lability	7% (6)	3% (3)	1% (1)
Hostility	8% (7)	3% (3)	0% (0)
Insomnia	15% (14)	14% (13)	5% (4)
Somnolence	17% (16)	14% (13)	3% (3)
Tremor	11% (10)	15% (14)	2% (2)

The Applicant has summarised these events for younger versus older children (less than 15 years and 15 years and above). Note that it is not evident from the protocol whether or not this was a pre-planned breakdown (and if it was, if the age of 15 was pre-planned). The table below shows this split of results for the event 'emotional lability':

Table 329-5

Adverse Event % (n/N)	Paroxetine (N=93)	Imipramine (N=95)	Placebo (N=87)
Emotional lability (all patients)	7% (6/93)	3% (3/95)	1% (1/87)
< 15 years	3% (1/39)	5% (2/38)	0*
≥ 15 years	9% (5/54)	2% (1/57)	1*

* number of patients randomised to placebo who were <15 years and who were ≥15 years is not given

Study 377

The study was carried out in 33 centres in Belgium, Italy, Spain, UK, Holland, Canada, South Africa, United Arab Emirates, Argentina and Mexico. The first patient was given study medication in April 1995; the last study visit was in May 1998.

After screening, all patients entered a 2-week single blind, placebo run-in period. Eligible patients were then randomised in the ratio 2 (paroxetine): 1 (placebo). The study lasted 12 weeks. After this (or if a patient withdrew early), patients had their dose tapered down to 10mg/day (over a period of up to 2 weeks) before ending the study.

Patients had to be:

- aged between 13 years 0 months and 18 years 11 months (at the start of the study),
- currently experiencing an episode of unipolar major depression (according to DSM-IV),
- have a total score < 69 on the C-GAS,
- have a score ≥ 16 on the MADRS.

The primary objective was to compare the efficacy of paroxetine and placebo in the treatment of adolescents with unipolar, major depression.

Efficacy parameters were–

Primary parameters:

- the proportion of patients with a 50% or greater reduction in MADRS score between baseline and study endpoint and
- the change from baseline to study endpoint in K-SADS-L depression subscale.

Secondary parameters:

- change from baseline in MADRS total score
- change from baseline in CGI severity of illness score
- CGI global improvement score
- change from baseline in BDI
- change from baseline in MFQ.

Safety parameters were:

- Adverse experiences,
- Vital signs,
- laboratory data.

Demographics

324 patients were screen of whom 286 were randomised – 187 to paroxetine, 99 to placebo. The ITT population (for efficacy and safety) includes 182 patients on paroxetine and 93 on placebo). The table shows basic demographic details and a summary of the patient disposition, including major reasons for patients not completing the 12 week acute phase of the study.

Table 377-1

	Paroxetine (N=182)	Placebo (N=93)
Age (yrs) mean (min=12*, max=19)	15.5	15.8
Female (%)	67%	66%
Baseline K-SADS-L mean	24.6	24.8
(min, max)	(11, 37)	(13, 36)
Completed 12 weeks	70%	74%
Reasons for withdrawal:		
Adverse event(s)	11%	8%
Lack of efficacy	5%	6%
Other reason(s)	14%	12%

* 3 patients were 12 years old on entry to the study (the minimum should have been 13)

Efficacy Results

The Applicant has imputed missing values using the 'last observation carried forward' approach. This is considered reasonable and is commonly used in these types of studies. Any bias resulting from this is usually considered to be a bias towards the null hypothesis of no treatment effect, rather than potentially exaggerating any small differences. Note that the proportions of patients not completing 12 weeks were quite similar (30% and 26%).

Two primary endpoints were pre-specified:

- the proportion of patients with a 50% or greater reduction in MADRS score between baseline and study endpoint and
- the change from baseline to study endpoint in K-SADS-L depression subscale.

Table 377-2

	Paroxetine (N=182)	Placebo (N=93)
Percent 'responders' (n/N)		
Week 12 observed cases	75% (94/126)	71% (47/66)
Week 12 last obs carried forward	60% (107/177)	58% (53/91)
Mean change in K-SADS-L score (std error)		
Week 12 observed cases	–10.8 (0.49)	–10.2 (0.63)
Week 12 last obs carried forward	–9.3 (0.54)	–8.9 (0.70)

The differences between the active groups and placebo are summarised below with point estimates, 95% confidence intervals and *P*-values.

Table 377-3

	Paroxetine – Placebo estimate* (95% CI) P-value
Percent 'responders'*[1]	
Week 12 observed cases	1.2 (0.6, 2.3) 0.67
Week 12 LOCF	1.1 (0.7, 1.9) 0.70
Mean change in K-SADS-L score*[2]	
Week 12 observed cases	–0.7 (–2.1, 0.8) 0.38
Week 12 LOCF	–0.4 (–2.0, 1.2) 0.62

* estimate (1) is the odds ratio for the MADRS 'responder' analysis
estimate (2) is the difference in means for the K-SADS-L analysis

Adverse Events

There were no deaths during the trial. 28 patients experienced serious adverse events (22 paroxetine and 6 placebo). A summary of the CNS-related adverse events that occurred in more than 5% of patients in any one (or more) treatment group and that were at least twice as common in the either of the active groups compared to the placebo group is shown below.

Table 377-4

Adverse Event % (n)	Paroxetine (N=182)	Placebo (N=97)
Dizziness	10% (19)	8% (7)
Emotional lability	4% (8)	3% (3)
Insomnia	5% (9)	3% (3)
Somnolence	9% (17)	7% (6)
Tremor	3% (6)	1% (1)

Study 701

The study was carried out in 40 centres in the US and 1 in Canada. The first patient was given study medication in March 2000; the last study visit was in January 2001.

After a 1-week screening phase, eligible patients were randomised equally to either paroxetine or placebo. The study then lasted 8 weeks. After this (or if a patient withdrew early), patients had their dose tapered down to 10mg/day (over a period of up to 2 weeks) before ending the study.

Patients had to be:

- aged between 7 years 0 months and 17 years 11 months (at the start of the study),
- currently experiencing an episode of major depression (according to DSM-IV),

The primary objective was to compare the efficacy of paroxetine and placebo in the treatment of children and adolescents with Major Depressive Disorder.
Secondary objectives were to compare the safety and tolerability of paroxetine versus placebo in the treatment of children and adolescents with MDD.

Efficacy parameters were–
Primary parameters:

- the change from baseline to study endpoint in Children's Depression Rating Scale–Revised (CDRS–R).

Secondary parameters:

- change from baseline in the CGI severity of illness item score,
- proportion of responders based on CGI (responder defined as '1' or '2' on the scale),
- change from baseline on the GAF scale,
- change from baseline in the Kutcher Adolescent Depression Rating Scale in the 12- to 17- year-old patients

Safety parameters were:

- Adverse experiences,
- Vital signs,
- laboratory evaluations,
- electrocardiograms,
- physical examination..

Demographics

305 patients were screened of whom 206 were randomised – 104 to paroxetine, 102 to placebo. The ITT population (for efficacy and safety) includes 101 patients on paroxetine and 102 on placebo). The table shows basic demographic details and a summary of the patient disposition, including major reasons for patients not completing the 8 week acute phase of the study.

Table 701-1

	Paroxetine (N=101)	Placebo (N=102)
Age (yrs) mean (min=7, max=17)	11.9	12.1
Female (%)	48%	47%
Baseline CDRS–R	60.7	62.6
(std dev)	(9.4)	(9.0)
Completed 8 weeks (all patients)	69%	77%
Reasons for withdrawal:		
Adverse event(s)	9%	2%
Lack of efficacy	8%	11%
Other reason(s)	14%	10%
Completed 8 weeks (children)	60%	87%
Completed 8 weeks (adolescents)	74%	69%

Efficacy Results

The Applicant has imputed missing values using the 'last observation carried forward' approach. This is considered reasonable and is commonly used in these types of studies. Any bias resulting from this is usually considered to be a bias towards the

null hypothesis of no treatment effect, rather than potentially exaggerating any small differences. It is of some concern that that the proportions of patients not completing 8 weeks were somewhat dissimilar (33% and 23%) and that there is a particularly large differential early-withdrawal rate in the children (as opposed to the adolescents).

The primary endpoint was pre-specified as the change from baseline to study endpoint in Children's Depression Rating Scale–Revised (CDRS–R).

Table 701-2

	Paroxetine (N=101)	Placebo (N=102)
Mean change in CDRS–R score (std error)		
Week 8 observed cases	–27.3 (1.5)	–26.5 (1.5)
Week 8 last obs carried forward	–22.6 (1.5)	–23.4 (1.6)

The differences between the active groups and placebo are summarised below with point estimates, 95% confidence intervals and *P*-values.

Table 701-3

	Paroxetine – Placebo difference (95% CI) P-value
Mean change in K-SADS-L score (all patients)	
Week 8 observed cases	–0.8 (–4.5, 2.9) 0.66
Week 8 LOCF	+0.8 (–3.1, 4.7) 0.68
Mean change in K-SADS-L score (children)	
Week 8 observed cases	+0.4 (–5.2, 6.1) 0.89
Week 8 LOCF	+5.3 (–0.1, 10.6) 0.05
Mean change in K-SADS-L score (adolescents)	
Week 8 observed cases	–1.4 (–6.5, 3.7) 0.58
Week 8 LOCF	–2.6 (–8.2, 3.1) 0.38

The company notes that there seem to be quite large differences between the young patients (children) and the older adolescents. However, the largest difference (which is not quite 'statistically significant at a conventional level of 0.05) is in the 'children' subgroup but *is in favour of placebo* with a *P*-value =0.054.

Adverse Events

A summary of the CNS-related adverse events that occurred in more than 5% of patients in either treatment group and that were at least twice as common in the paroxetine group compared to the placebo group is shown below. The table shows events that emerged during the 8 week treatment period, not those taper phase or in the 30 day follow-up period.

Table 377-4a – CNS events during treatment phase

Adverse Event % (n)	Paroxetine (N=101)	Placebo (N=102)
Dizziness	5% (5)	1% (1)
Insomnia	11% (11)	7% (7)
Nervousness	6% (6)	4% (4)
Somnolence	10% (10)	7% (7)

Table 377-4b – CNS events during taper phase

Adverse Event (n)	Paroxetine (N=101)	Placebo (N=102)
Anxiety	0	1
Depression	1	0
Emotional lability	1	0
Nervousness	1	0
Somnolence	0	1
Withdrawal syndrome	0	1

Table 377-4c – CNS events during follow-up phase

Adverse Event (n)	Paroxetine (N=101)	Placebo (N=102)
Agitation	0	1
Dizziness	2	0
Emotional lability	2	1
Manic depressive reaction	1	0
Nervousness	1	0
Psychosis	1	0
Somnolence	1	0

Note that it is not possible to combine the above tables into one summary table for the full study period. The same patient could appear in more than one phase with the same event.

Assessor's comments:

Overall Summary of Efficacy

The Applicant agrees that efficacy has not been demonstrated for the indication of MDD. None of the primary endpoints for any of the studies showed either statistically significant benefit for paroxetine over placebo, nor in any case were non-significant (in a statistical sense) differences suggestive of possible benefits of useful clinical magnitude (see Table 329-3, 377-3 and 701-3).

Overall Summary of Safety

In addition to the adverse event tables provided in the study report, the Applicant has also searched adverse event text for any event possibly associated with suicide, suicide attempt, suicidal ideation, etc. As has been noted for each study, none had any deaths (due to any cause) so there were no completed suicides.

Adverse event text was searched in the following way:

Preferred term is '*emotional lability*'
and the verbatim term includes any reference to:
'*attempt*'
'*cut*'
'*gas*'
'*hang*'
'*hung*'
'*jump*'
'*mutilat*' [includes '*mutilate*', '*mutilated*', '*mutilation*']
'*overdos*'
'*self damag*' or '*self-damag*'
'*self harm*' or '*self-harm*'
'*self inflict*' or '*self-inflict*'
'*self injur*' or '*self-injur*'
'*shoot*'
'*slash*'
'*suic*'
or the preferred term is '*overdose*' or '*intentional overdose*'.

All events found were screened for obvious cases that should not be included (e.g. the term 'acute' might be wrongly picked up because it contains the letters 'cut'). It is possible that other terms could also be indicative of suicidal attempt or ideation, in particular the terms 'try' 'tried' were not included (although 'attempt' was).

The Applicant labels all events discovered by the above search strategy as being 'possibly related to suicidality'. The table below shows the number of cases in these paediatric trials in MDD for paroxetine and placebo.

	Paroxetine % (n/N)	Placebo % (n/N)	Relative Risk (95% CI)	P-value
'On therapy' period	3.7% (14/378)	2.5% (7/285)	1.5 (0.6, 3.4)	0.50
'On therapy' + 30 day follow-up	5.3% (20/378)	2.8% (8/285)	1.9 (0.8, 4.2)	0.12

The Applicant then goes on to further include events screened by the same search strategy in paediatric trials of obsessive compulsive disorder and social anxiety disorder. When adding these to the MDD data from above, the absolute rates in both active and placebo groups reduced. This is because whilst the denominators approximately double, the numerators (i.e. the number of cases in the OCD and SADF trials) only increase by a few patients. The Applicant presents the following results:

	Paroxetine % (n/N)	Placebo % (n/N)	Relative Risk (95% CI)	P-value
'On therapy' period	2.4% (18/738)	1.1% (7/647)	2.3 (0.9, 5.4)	0.07
'On therapy' + 30 day follow-up	3.4% (25/738)	1.2% (8/647)	2.7 (1.2, 6.0)	0.01

In conclusion, with respect to safety – and suicidality in particular – even the non-statistically significant increases seen in the depression-only tables give rise for concern given the high upper end of the 95% confidence interval for the relative risk (upper limits of 3.4 and 4.2). With regards the 'all studies' data, the Applicant dismisses the results limited to 'during therapy' as 'not statistically significant'. Although the *P*-value is 0.07 (which does not quite reach the conventional, although arbitrary, level of 0.05), the 95% confidence interval for the relative risk ranges from 0.9 to 5.4. This means that any possibility of a protective effect is minimal, but the excess risk could be over 5-fold.

5. DISCUSSION

Overall the data raise serious concerns about hostility, emotional lability and suicidal behaviour in children using paroxetine, and particularly adolescents. There is no good evidence of efficacy in major depressive disorder in the population studied. Therefore the balance of risks and benefits in this population is clearly negative.

These data have implications for other populations treated with paroxetine. The issue of suicidal behaviour with SSRIs has been reviewed on a number of occasions in the past by CSM with the conclusion that no causal relationship can be established, however an effect in a small subgroup of patients cannot be ruled out. These are the first clinical trial data to show a clear increase in suicidal behaviour versus placebo.

The possibility of a class effect should be considered, although review of fluoxetine application for paediatric depression did not reveal safety concerns in this area and the FDA have licensed fluoxetine for the treatment of depression and obsessive-compulsive disorder for children aged 7-17 years.

6. REGULATORY ACTION

The following actions are proposed or under way in view of the potential risk to public health:

i) UK national variation for Seroxat

The statements that have been proposed for addition to the UK SPC by the MAH are attached at Annex 1. CSM considered this issue at its meeting of 29 May 2003 and advised that efficacy in major depressive disorder in patients under the age of 18 had not been demonstrated, and that the clinical trial data represented a significant safety issue. They considered that the balance of risks and benefits of Seroxat in children

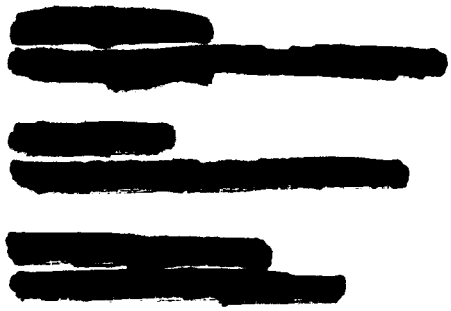
with major depressive disorder was clearly negative and that Seroxat should be contraindicated in this group of patients. In summary these include changes to the Indications (section 4.1), Posology (section 4.2), Contraindications (section 4.3) and Adverse effects (section 4.8) of the SPC.

ii) Communications to health care professionals and the public

A package of communications is under development to inform health care professionals, patients and the public of new data and action to be taken. It is proposed that there should be co-ordinated timing of release of information.

iii) European referral

This will achieve a harmonised European position. It is important because of the need to communicate a clear message to prescribers and the public and because of the number of products licensed through the European mutual recognition procedure.



4 June 2003

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ANNEX 1 – CHANGES TO UK SPC

Section 4.1

Children/adolescents

Seroxat is not indicated for use in children and adolescents under the age of 18 years.

In particular, controlled clinical studies failed to demonstrate efficacy and do not support the use of Seroxat in the treatment of children and adolescents with Major Depressive Disorder (See sections 4.3, Contra-Indications and 4.8, Undesirable effects).

Section 4.2

Special Patient Populations

Children/adolescents: The efficacy and safety of Seroxat in chilkdren and adsolescents under the age of 18 years have not been established. Controlled clinical studies failed to demonstrate efficacy and do not support the use of Seroxat in the treatment of children and adolescents with Major Depressive Disorder (See sections 4.3, Contra-Indications and 4.8, Undesirable effects).

Section 4.3

Seroxat should not be used in children and adolescents under the age of 18 years with Major Depressive Disorder. (See section 4.8, Undesirable effects).

Section 4.8

Adverse events from paediatric clinical trials

In paediatric clinical trials the following adverse events were reported at a frequency of at least 2% of patients and occurred at a rate of at least twice that of placebo: decreased appetite, tremor, sweating, hyperkinesia, hostility, agitation, emotional lability (including crying, mood fluctuations, self-harm, suicidal thoughts and attempted suicide. Suicidal thoughts and suicide attempts were mainly observed in clinical trials of adolescents with Major Depressive Disorder.)

In studies that used a tapered withdrawal regimen, symptoms reported during the taper phase or upon discontinuation of paroxetine at a frequency of at least 2% of patients and that occurred at a rate of at least twice that of placebo were: nervousness, dizziness, nausea, emotional lability (including crying, mood fluctuations, self-harm, suicidal thoughts and attempted suicide) and abdominal pain.