10. QUESTION 10: BENEFIT-RISK ASSESSMENT IN ALL INDICATIONS AND POPULATIONS

A critical review of the benefit-risk balance for your paroxetine containing medicinal product(s) in all indications and populations. This should address possible risk reduction by changes to the SPC or other measures.

Response

10.1. Introduction

The benefit-risk balance for paroxetine in the treatment of depressive illness and various anxiety disorders is critically reviewed, based upon the information provided in this Article 31 response and possible risk reduction strategies are discussed.

The response is presented as follows:

- Summary of benefits – The efficacy and benefits of paroxetine and its effect on morbidity and mortality associated with the above disorders are outlined by reviewing data from rigorous clinical trials as well as from a perspective that is analogous to normal clinical practice.
- Summary of risks – A summary of the safety and risk profile of paroxetine is described, with particular emphasis on the adverse events which are the main subject of this Article 31 referral.
- Benefit-Risk of paroxetine –The key points from the preceding summaries are discussed in terms of the benefit-risk relationship for paroxetine.
- Risk reduction strategies – Various methods for positively altering the benefit-risk balance for paroxetine are presented and discussed.
- Overall Conclusion.

10.1.1. Background

- Depression is the most common psychiatric disorder. It is a chronic and recurrent disorder with a published lifetime prevalence of up to 17% [Kessler, 1994]. Depressive illness and anxiety disorders can result in significant impairment of daily functioning alongside significant morbidity and mortality. Despite the substantial economic and morbidity burden associated with depression, the disorder is often unrecognised and untreated.
- Anxiety disorders often follow a chronic course, and are frequently comorbid with other anxiety disorders or depression. This can significantly affect both patients functionality and quality of life. The lifetime prevalence of any anxiety disorder has been reported as up to 25% (National Co-morbidity Survey) [Kessler, 1994].
- Depression and anxiety are highly comorbid with approximately 66% of depressed patients suffering a comorbid anxiety disorder. The published literature indicates that

the co-morbidity of these psychiatric disorders worsens functional impairment and morbidity and increases suicidal risk.

- Depressive illness and anxiety disorders exist in children and adolescents with similar morbidity and functional impairment to that seen in adults. This can have significant effects on the social and educational development of these patients, for whom there are very few approved treatment options available.
- Depression and anxiety disorders are well documented risk factors for suicide and suicide attempt.

10.2. Summary of Benefits of Paroxetine

10.2.1. Adults

The efficacy of paroxetine in adult patients has been clearly established in depressive illness and anxiety disorders in clinical programmes involving over 24,000 patients. Paroxetine has demonstrated efficacy for depressive illness of all types including mild, moderate and severe depression, depressive illness in the elderly and depressive illness co-morbid with anxiety and physical illness. It has been shown to be effective for the long term treatment of depressive illness and for the prevention of relapse. Efficacy has also been demonstrated in five major anxiety disorders (Obsessive-Compulsive Disorder (OCD), Social Phobia or Social Anxiety Disorder (SAD), Panic Disorder (PD), Post-Traumatic Stress Disorder (PTSD), Generalised Anxiety Disorder (GAD)) and paroxetine is approved for use in all five anxiety disorders and for the prevention of relapse in OCD, SAD, PD and GAD. Taken overall, paroxetine has extensive long-term data across all indications, showing maintenance of effect, producing significant functional improvement relating to work, social and family life in patients with depressive illness and anxiety disorders. Most recently, efficacy in Pre-Menstrual Dysphoric Disorder (PMDD). Although other therapies for the treatment of depressive illness and anxiety disorders are available, notably other SSRIs, none have demonstrated the same breadth of efficacy in both depression and anxiety. In addition, paroxetine has extensive long-term data across all indications, showing maintenance of effect. Again, no other SSRI has demonstrated this to the same extent.

10.2.1.1. Depression

In 6 to 24 week well designed adult clinical trials, paroxetine (10 to 50 mg/day) administered orally was significantly more effective than placebo, similarly as effective as tricyclic antidepressants (TCAs) and similarly as effective as other selective serotonin reuptake inhibitors (SSRIs) and other antidepressants (maprotiline, mianserin, mirtazipine, nefazodone, tianeptine, trazodone, venlafaxine) in the treatment of in- or outpatients with mainly moderate to severe major depressive disorder (MDD) [GSK database; Baldwin, 1996; Poirer, 1999]. Relapse or recurrence one year following the initial response was significantly lower with paroxetine 10 to 50 mg/day than with placebo and similar to that with imipramine 50 to 275 mg/day. The efficacy of paroxetine 10 to 40 mg/day was similar to that of TCAs and fluoxetine 20 to 60 mg/day in 6 to 12 week trials in older patients (≥ 60 years) suffering from MDD. Studies involving

depressed patients comorbid with either dementia, cancer, rheumatoid arthritis, HIV or ischaemic heart disease showed improvement in depressive symptomatology with paroxetine 10 to 40 mg/day to a similar extent to TCAs.

Studies in depression are not always successful. A proportion of placebo-controlled studies with most approved antidepressants have failed to provide statistically significant separation of the antidepressant from placebo. Meta-analysis of all placebo-controlled, randomised, double-blind acute paroxetine studies in patients diagnosed with depression revealed a statistically significant treatment difference in reduction of HAM-D total score from baseline (-2.37, 95% CI: –2.94 to -1.81; p<0.001) (GSK internal report: Lawrinson S, Whately-Smith C. Meta-analysis of placebo-controlled depression studies. 2002). It can therefore be seen that the evidence in support of paroxetine being effective in depression is not solely based on the fact that the majority of placebo-controlled studies are positive. Findings are positive overall. Similar analysis also demonstrates the antidepressant efficacy of paroxetine in patients presenting with depression with anxiety. The treatment difference in reduction of HAM-D from baseline in such patients was estimated as –2.33 (95% CI: -3.07 to –1.59, p<0.001).

10.2.1.2. Anxiety Disorders

Paroxetine has been evaluated and shown to be effective in the treatment of anxiety disorders. In clinical trials, paroxetine 20 to 60 mg/day or 20 to 50 mg/day was more effective than placebo after 8 to 12 weeks treatment of OCD, PD, SAD, PTSD and GAD. Improvement was maintained or relapse was prevented for 24 weeks to 1 year in patients suffering OCD, PD, SAD and GAD. The efficacy of paroxetine was similar to that of other SSRIs and clomipramine in patients suffering OCD and PD and was similar to the efficacy of imipramine but superior to a benzodiazepine in patients suffering GAD [Rocca, 1997].

It should be mentioned that the studies in PTSD allowed patients to be enrolled who had appreciable depressive symptoms, something that was actively discouraged in studies of the other anxiety disorders. There is a high degree of comorbid depression in patients with chronic PTSD and the intention was to study patients as they would present in clinical practice. This raises the possibility that the positive effects of paroxetine in patients with PTSD may have been due to the well-accepted antidepressant effect of the drug. However, patients entering the study with and without a diagnosis of depression were analysed, patients with a baseline Montgomery and Asberg Depression Rating Scale (MADRS) score of >18 and <=18 were compared, the treatment-by-baseline MADRS score interaction in all covariate adjusted efficacy analyses were investigated, and correlation analysis of the change from baseline in Clinician Administered Post-traumatic Stress Disorder Scale-2 (CAPS-2) total score vs the change from baseline in the MADRS total score was performed. These further investigations demonstrated that by no means could all of the improvement in PTSD symptoms be ascribed to a reduction in depressive symptoms and demonstrated that paroxetine produces a significant benefit in the treatment of PTSD over and above its well-known antidepressant effect.

Comorbid symptoms of anxiety often occur in patients suffering depressive illness, exacerbating functional disability. Several studies have explored the reduction of anxiety symptoms by paroxetine in adults suffering depression [Lepine, 2001; Ravindran, 1997]. Efficacy was noted for both the depressive illness and the anxiety symptoms, which were similar to the efficacies of the active comparators [Lepine, 2001; Ravindran, 1997]. Montgomery (2001) performed a meta-analysis on pooled data from 39 depression trials to investigate anxiolytic efficacy (using anxiety items 9 to 11 on the HAMD). There was a statistically significant difference in favour of paroxetine versus TCAs for reduction in anxiety scores, but not between paroxetine and clomipramine, which showed similarity. All these drugs led to improvements in depressive illness [Montgomery, 2001].

Most recently, a clinical trials programme in PMDD has been completed using continuous treatment with a controlled release formulation of paroxetine (paroxetine CR).To date, no application has been made for approval for the use of paroxetine in the treatment of PMDD in Europe. However, the efficacy of 12.5 mg/day and 25 mg/day paroxetine CR (that deliver similar amounts of paroxetine as 10 mg/day and 20 mg/day paroxetine IR, respectively)have been clearly demonstrated in three double-blind placebo-controlled, short-term (3 treatment menstrual cycles), continuous treatment studies with significant efficacy being observed within the first menstrual cycle. The continued efficacy of paroxetine CR was also confirmed in a longer-term (6 menstrual cycles) extension study. The efficacy of short-term, intermittent (luteal phase only) treatment with paroxetine CR has also been demonstrated in one double-blind, placebo-controlled study, and in one other study 20mg paroxetine IR has been shown to be effective when given continuously or intermittently [GSK database].

In addition to showing significant effects on the primary measures of efficacy in the above conditions, paroxetine has been demonstrated to show improvements in quality of life (QoL) and in disability related to depressive illness and anxiety disorders.

In depression studies, rapid improvement in QoL has been demonstrated by the Battelle QoL Questionnaire, demonstrating that 90% of subjects receiving paroxetine or sertraline responded with improved QoL scores by 12 weeks and continued to improve for the 6 month study period [Aberg-Wistedt, 2000]. Holm et al (2000) demonstrated a 50% improvement in QoL scores of responders at 6 weeks, utilising the Quality of Life Enjoyment and Satisfaction (QLESQ) scale, with paroxetine and mirtazepine showing equivalence [Holm, 2000]. Similarly, utilising the Medical Outcomes Study (MOS SF36), paroxetine, fluoxetine and sertraline demonstrated an equivalent improvement in QoL over a 9 month study period [Kroenke, 2001]. Treatment with paroxetine and bupropion SR over a 6 week period were both associated with improvements in quality of life from baseline as demonstrated with the MOS SF-36 and the Quality of Life in Depression Scale (QLDS) in a clinical trial in a depressed geriatric population. [Doraiswamy, 2001].

A variety of scales have also been used in paroxetine anxiety studies, with the Sheehan Disability Scale (SDS) which assesses functional impairment relating to work, social and family life, being used most consistently. In GSK clinical studies, paroxetine produced significantly greater reductions in SDS than placebo at study endpoint for all the anxiety indications in which it was employed (panic disorder, SAD, GAD, PTSD and PMDD).

Published findings include significant improvement in functional impairment for paroxetine compared to placebo in three anxiety studies using the SDS [Baldwin, 2000] and in studies of patients with GAD [Rickels, 2003], [Pollack, 2001], SAD [Liebowitz, 2002], [Lydiard, 2000], [Baldwin, 1999] and [Allgulander, 1999]. As for depression and the above anxiety disorders, paroxetine has also demonstrated improvement in both QoL and disability utilising a variety of instruments in PTSD and OCD [Tenney, 2003; Tucker, 2001].

The evidence to support efficacy of paroxetine in the treatment of depressive illness, panic disorder, OCD, SAD, GAD, PTSD and now PMDD is clear and substantial, in terms of improvement of main symptoms of each disorder, functional impairment, and globally. The efficacy from real-life observational and general clinical practice studies reflects that observed in more rigorous clinical trials [Mackay, 1997; Mackay1999; Inman1993], further corroborating the effectiveness of this pharmacotherapy as a treatment of depressive illness and anxiety disorders.

10.2.2. Children and Adolescents

In clinical programmes involving over 1600 paediatric patients, over 1100 children and adolescents (aged 7-18 years) were treated with paroxetine in GSK paediatric clinical trials. The total exposure to paroxetine was 352.9 patient-years, with 194 patients receiving a daily dose of at least 50 mg, and 197 patients received paroxetine for 6 months or more. Efficacy was assessed principally from 5 acute placebo-controlled studies, 3 in MDD, and one each in OCD and SAD. A long-term relapse prevention study in OCD provided supportive evidence of the efficacy of paroxetine in children with that disorder.

Overall, the results of the GSK clinical trials programme demonstrated that paroxetine is effective in the treatment of children and adolescents suffering from OCD or SAD, producing improvements of clinical relevance.

The improvements in Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) total scores achieved in the paediatric OCD studies compare well with improvements in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) total scores produced by paroxetine in adults with OCD. While there is no clear consensus in the published literature on a minimum change from baseline in CY-BOCS total score considered to be clinically meaningful, the magnitude of the reduction in the CY-BOCS total score at endpoint for patients who received paroxetine was comparable to reductions reported in paediatric OCD trials with sertraline [Geller, 2001; March, 1998; Riddle, 2001]. Sertraline and fluvoxamine are approved for use in paediatric OCD in several European countries. Clinical Global Impression (CGI) of Severity of Illness data illustrate important information on a patient's overall condition. In the OCD study 704, 91.9% of patients in the paroxetine group (and 81.0% on placebo) were either moderately or markedly ill at baseline. By the end of the study this had fallen to 46.9% for paroxetine and 62.0% for placebo, reductions of 45% on paroxetine vs 19% on placebo. In fact at the end of the 10 week study, almost twice as many paroxetine patients (27.1%) were described as being "normal, not at all ill", or only "borderline mentally ill" compared with placebo (14.3%).[Study 704]

The findings from the SAD study 676 are very clear. Improvements in disorder-specific scales, and measures of global improvement, disease severity and functioning were all significantly greater in paroxetine treated patients than in those receiving placebo. The improvement by paroxetine was demonstrated both symptomatically and behaviourally, confirming the clinical relevance of the treatment changes. The magnitude of effect was clinically relevant and in keeping with previous acute adult studies with paroxetine, all of which have been positive. In adults, response rates (based on CGI- Global Improvement scores of 1 or 2 at study endpoint) have ranged from 42.9% to 65.7% in patients receiving paroxetine compared to 23.9% to 30.4% in patients receiving placebo. In study 676, 77.6% of children treated with paroxetine were responders compared with 38.3% treated with placebo.

Looking at changes in disease specific scales, in paroxetine studies in adults, mean baseline Liebowitz Social Anxiety Scale (LSAS) total scores have ranged from 76.9 to 87.6. Mean reductions seen with paroxetine by study endpoint have ranged from 24.5 to 31.4 points, compared with mean reductions of 14.5 to 17.6 with placebo. In study 676, the mean baseline LSAS-CA total scores were 77.6 in the paroxetine group and 77.7 in the placebo group. The mean reductions in LSAS-CA total score at study endpoint were 48.0 points and 24.2 points in the paroxetine and placebo groups, respectively. These changes in disease specific scores are impressive and are put into context by looking at the change in CGI-Severity of Illness status over the course of Study 676. At baseline 83.4% of paroxetine and 83.9% of placebo patients were described as markedly or moderately ill. By the end of the 16 week study, only 24.7% of paroxetine patients were in those categories (compared with 57.2% of placebo patients). In fact at endpoint 47.5% of paroxetine-treated patients were described as "normal, not at all ill" or "borderline mentally ill". The corresponding proportion for placebo patients was 20.7% [Study 676].

The three acute placebo-controlled paediatric depression studies did not provide sufficient evidence to conclude that paroxetine is an effective treatment for major depressive disorder (MDD) in children and adolescents, although post hoc analyses by age group revealed some significant benefit in patients aged ≥ 15 years, but not in younger patients. All three MDD studies demonstrated very high placebo response rates (>50%), which may be due to the short-lived episodes of depression children and adolescents often suffer, with rapid response regardless of treatment arm, enhancing the placebo-effect, making it difficult to discern a treatment effect. Placebo-controlled paroxetine studies in depressed adults have typically reported response rates of 30-40% in placebo treated groups. From a clinical standpoint these studies in children and adolescents are perhaps more appropriately regarded as failed studies, rather than negative studies, because it would be more difficult to achieve statistical separation from placebo under such circumstances. Studies have also failed to demonstrate that TCAs are superior to placebo in the treatment of paediatric MDD although it is generally considered to be similar to adult MDD in terms of clinical presentation, comorbidity and recurrence [Geller, 1999]. Reasons that have been proposed to explain the lack of response of TCAs compared to placebo in this age group have included clinical characteristics (severe, chronic condition), high rate of comorbidity, high rate of placebo response, and small sample size [Birmaher, 1998]. However, positive results have been obtained with the SSRI fluoxetine in a double-blind placebo-controlled study

demonstrating efficacy of treatment in children and adolescents with MDD [Emslie, 1997].

In summary, the paediatric programme of studies with paroxetine has given clear evidence of paroxetine's efficacy as a treatment for children and adolescents with OCD or SAD but not MDD although some benefit was apparent in patients aged ≥ 15 years with MDD. The extents of effect in paediatric patients with OCD or SAD are at least comparable to paroxetine's known efficacy in adults.

10.3. Summary of Risks of Paroxetine

10.3.1. General summary of the tolerability profile of paroxetine

10.3.1.1. Adults

Paroxetine and other SSRIs have shown an improved tolerability profile compared to TCAs, alongside greater safety in overdose. GlaxoSmithKline (GSK) clinical trials have shown that the tolerability profile of paroxetine is consistent irrespective of the indication being treated. The most commonly observed adverse events associated with the use of paroxetine in the clinical trials were: nausea, somnolence, sweating, tremor, asthenia, dry mouth, insomnia, sexual dysfunction, dizziness, constipation, diarrhoea and decreased appetite. These adverse effects are also seen in real-life observational and general clinical practice studies [Mackay, 1997; Mackay,1999; Inman, 1993].

In adult placebo controlled trials for depressive illness and anxiety disorders, a total of 14,289 patients were exposed to paroxetine (n=8481) or placebo (n=5808). In the active controlled trials, a total of 11,491 patients were exposed to either paroxetine (n=6522) or active comparators (n=4969), including TCAs, SSRIs, tetracyclics, benzodiazepines or other drugs. The outcome of the evaluation of possibly suicide-related or self-harm adverse events rejects the possibility that treatment with paroxetine may increase the risk of self-harm and suicidal behaviour in adults. On the contrary available data suggest efficacy of paroxetine in ameliorating baseline suicidal ideation and intent.

Montgomery (2001) included over 3700 patients in a meta-analysis of 39 well designed studies, showing a significantly lower proportion of patients receiving paroxetine (64%) experienced adverse events with an incidence of >1% than those patients receiving a TCA. There was also a trend towards a lower incidence of discontinuation of treatment due to adverse events with paroxetine treatment compared to TCAs [Montgomery, 2001].

The tolerability profile of paroxetine has been compared to other SSRIs in various clinical trials of a variety of indications [Ansseau, 1994; De Wilde, 1993; Gagiano, 1993; Tignol, 1993; Kiev, 1997; Ontiveros, 1997; Fava, 1998; Chouinard, 1999; Aberg-Wistedt, 2000; Fava, 2000]. These studies do not highlight any specific differences between the tolerability profiles of paroxetine against its SSRI comparator. In terms of the overall incidences of adverse events between SSRIs, no significant differences were reported.

10.3.1.2. Children and Adolescents

Assessment of the pooled adverse event data generated in the five acute, paediatric, double-blind, placebo-controlled acute studies revealed an overall safety and tolerability profile that is similar, but with some differences discussed below, to that seen to date in clinical trials (and in clinical practice) with paroxetine in adult patients. There were no deaths and the majority of adverse events occurring with paroxetine therapy were mild or moderate in severity. Furthermore, the adverse event profile for paroxetine in the paediatric population appears to be very similar to that reported for other SSRIs in children and adolescents [Emslie, 1997; Food And Drug Administration, 1997a; Food And Drug Administration, 1997b; Leonard, 1997; Hawkridge, 1998].

A total of 1270 patients comprised the intention-to-treat population in the five acute (8 to 16 week) placebo-controlled clinical trials. Of these, 633 patients received paroxetine and 542 received placebo. One of the studies had an active control arm; 95 patients received imipramine. In the combined acute controlled studies database, the mean daily dose of paroxetine at study endpoint across all indications was 29.4 mg. Although the majority of the patients enrolled were adolescents aged 12-18 years, children (aged 7-11) were also adequately represented because of the size of the overall dataset. Similarly, both genders were also appropriately represented and overall the two treatment groups were comparable with respect to all demographic and baseline characteristics.

In order to identify adverse experiences specific to the paediatric population, adverse event data from the clinical trial database of the adult acute placebo controlled studies of paroxetine in OCD, SAD and MDD were compared with the acute paediatric studies dataset. There were few adverse experiences which were unique to the paediatric paroxetine population relative to experience in adults with the same indications.

The overall adverse event profile during the treatment phase in paediatric patients treated with paroxetine, was generally similar to that seen in the existing extensive paroxetine adult studies database. The three most commonly reported treatment emergent adverse events for patients taking paroxetine in the acute paediatric studies (headache, nausea and somnolence) were also the three most reported adverse events in the adult studies population. The only treatment phase emergent adverse event in the acute paediatric studies population with an incidence ≥ 5.0% in the paroxetine group and ≥ twice that for placebo is decreased appetite, but this also met these criteria in the adult population.

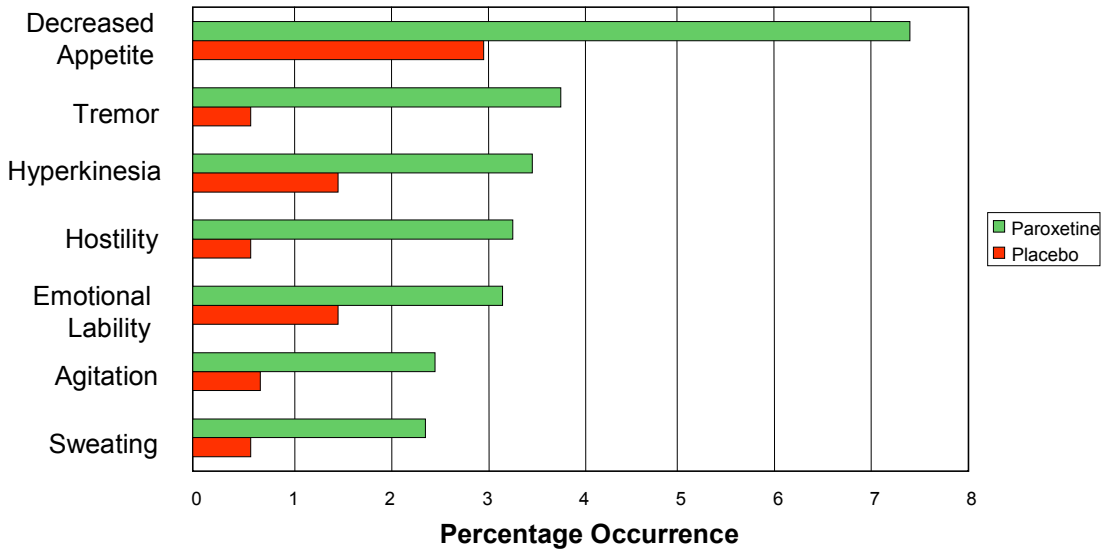
Although the overall paroxetine adverse event profile in paediatric patients was generally similar to that in adult patients, there were some differences when examining some of the less commonly observed adverse events. Six adverse events (in addition to decreased appetite) occurred in the paroxetine group at an incidence ≥ 2% and ≥ twice that for placebo included tremor, hyperkinesia, hostility, emotional lability, agitation and sweating Figure 10.1. Of these, only tremor and sweating also met these criteria in the adult paroxetine trials.

Figure 10.1

Percentage of Paroxetine Patients with Common Treatment Phase Emergent Adverse Events

(>= 2% and at least twice the incidence of Placebo)

Intention-to-Treat Population, Acute Studies Combined, Age Group: Total



A few treatment emergent adverse events (decreased appetite, and also hyperkinesia, hostility, insomnia, nervousness and vomiting) which do not record an incidence ≥ 5% for paroxetine and at least twice that of placebo in the older subset (ages 12-18) of the paediatric combined indication patient population or in adults, met those criteria in the younger (7-11 year old) children. In the older (12-18 year old) subset of the acute paediatric studies population, only somnolence and decreased appetite met these criteria for adverse events. Overall, the paroxetine adverse event profile in older children (12-18 years) proved to be very similar to that which has been reported in adult patients with one exception, emotional lability (which includes crying, mood fluctuations, self-harm, suicidal thoughts and attempted suicide).

In general, the overall incidence of adverse events in paediatric patients with OCD appeared comparable to that in paediatric patients with MDD. Both adverse events that met the criteria of ≥ 5% for paroxetine and at least twice that of placebo in the MDD younger age group population (7-11 years of age), vomiting and insomnia, also met those criteria in the younger OCD patients; and two (somnolence and decreased appetite) of the three adverse events that met the criteria in older (12-18 years) MDD patients also met those criteria in the older OCD patients. However, other adverse events also met the criteria in OCD patients, including some adverse events associated with the nervous system. Hyperkinesia, hostility, agitation, neurosis and asthenia all met the criteria of ≥ 5% for paroxetine and at least twice that of placebo in the OCD younger age group population (7-11 years of age) as well as in the OCD total age group population, but not in the MDD patients (either in the younger subset or in the MDD total age group). Hostility and asthenia also met the criteria in the OCD older age group. Hyperkinesia has

also been reported to be one of the more common adverse events occurring with the use of fluoxetine, sertraline and fluvoxamine in paediatric OCD patients [March, 1998; Geller, 2001; Riddle, 2001].

Overall, adverse events in paediatric patients with SAD were broadly similar to those in patients with MDD and OCD. Adverse events meeting the criteria, incidence ≥ 5% for paroxetine and at least twice that of placebo, in the total age group were insomnia, decreased appetite and vomiting. However, assessment of the adverse events occurring in the age sub-groups is affected by the small numbers in those sub-groups, particularly the younger (7-11 years) group. Nervousness, hyperkinesia, and hostility all met the ≥ 5% for paroxetine and at least twice that of placebo criteria in the SAD younger age group population, but so too did respiratory disorder, otitis media, conjunctivitis, rash and urinary incontinence. Splitting down the adverse event information by age group and by indication is hindered by the small numbers in each sub-group. Nevertheless, it was noted that in both anxiety disorders, hyperkinesia met the criteria of ≥5% and twice placebo in younger children (7-11 years) but not in the older age group.

As with other paroxetine clinical trial programmes, the incidence of serious adverse experiences was low. There were 6.5% patients with serious adverse events in the paroxetine group, and 1.8% in the placebo group. The most common serious events were emotional lability and depression. There were no deaths in the programme.

10.3.2. Summary of the adverse events of special importance

10.3.2.1. Suicidality and self-harm

Most patients who commit suicide show several symptoms of depression, and up to 60% have fully diagnosable affective disorder. It has been estimated that 10-15% of deaths that occur in depressed patients is by suicide [Blair-West, 1997]. Depressive illness is common and suicide risk is high in untreated depressed patients, especially if comorbidity and negative life events are present [Henriksson, 1993; Regier, 1990]. Concurrent depressive illness and anxiety that seem to be aetiologically related and are difficult to separate are typical of suicidal patients [Allgulander, 1994]. Among the anxiety disorders, panic disorder has been specifically studied and data has been presented that associate this anxiety disorder with increased rates of suicide [Coryell, 1982] and suicide attempts [Johnson, 1990]. There is a growing recognition of a range of anxiety disorders that increase the risk of suicidal behaviours when they are present as a comorbid feature of major affective disorders [Angst, 1999; Engstrom, 1999]. It is suggested that the degree of increased suicide risk is related to the severity of the anxiety symptoms, and that anxiety symptoms are sometimes not fully recognised by clinicians in patients with major affective disorder [Fawcett, 1990]. The suicide risk is higher in patients with both anxiety symptoms and affective disorders in comparison to patients who only suffer from affective disorder without anxiety [Fawcett, 1988].

Given the inherent risk of suicidal behaviour in patients suffering depressive illness and anxiety disorders, alongside research suggesting that low serotonin levels may be an

aetiological factor in suicide, debate has continued regarding the effect SSRIs may have on suicidality and aggression in these patients.

10.3.2.2. Paroxetine: effects on suicidality and self-harm

Adults

The use of paroxetine in healthy volunteers should be free of the complications in assessing suicidality and self-harm that are expected in patients with depression or anxiety disorders. A total of 1716 healthy volunteers participated in a total of 90 studies with paroxetine. In these studies no cases of possibly suicide-related events or self-harm were reported.

Data from clinical studies provide evidence that suicidal behaviour is not made worse by paroxetine treatment in adults. Indeed, available data suggest efficacy of paroxetine in ameliorating baseline suicidal ideation and intent.

In adult placebo controlled trials for depressive illness and anxiety disorders, a total of 14,289 patients were exposed to paroxetine (n=8481) or placebo (n=5808). In the active controlled trials, a total of 11,491 patients were exposed to either paroxetine (n=6522) or active comparators (n=4969), including TCAs, SSRIs, tetracyclics, benzodiazepines or other drugs. Evaluation of possibly suicide-related or self-harm adverse events rejects the possibility that treatment with paroxetine may increase the risk of self-harm and suicidal behaviour in adults. In the adult placebo-controlled studies, there was no difference between the treatment groups in the incidence of possibly suicide-related or self-harm events, and in adult actively-controlled studies there was a lower incidence of possibly suicide-related events in the paroxetine treatment group compared to the active comparator group overall. It should be noted that young adults had an increased risk of possibly suicide-related and self harm events irrespective of treatment group. This appears to be heightened among patients treated with antidepressants, although patients treated with paroxetine were at a lower risk compared to those treated with other SSRIs and other classes of antidepressants. The adult placebo-controlled clinical trial data showed a statistically significant treatment benefit with paroxetine compared to placebo in terms of change from baseline in two measures of suicidality (item 3 of the Hamilton Depression Scale (HAM-D) and Item 10 of the MADRS). There was also no evidence of emergent suicidal ideation (based on Item 3 of the HAM-D) in the paroxetine treatment groups compared to the placebo and active comparator groups.

The above data agree with what was already known about paroxetine in this area. No controlled scientific evidence has shown that paroxetine causes suicidal ideation or suicidal behaviour in adults, or that it worsens existing suicidal ideation or behaviour. In fact, there is evidence from controlled clinical trials that paroxetine reduces suicidal ideation and that it also appears to reduce the rate of newly emergent suicidal ideation compared to placebo [Lopez-Ibor, 1993; Montgomery, 1995; Dunner, 1998; Verkes, 1998; Isacsson, 2000; Khan, 2000].

Khan et al (2000), evaluated the US Food and Drug Administration's (FDA) database of all randomised, controlled trials of antidepressants approved for use in the US from 1987-

1997. Among the paroxetine trials, there were 2963 subjects given paroxetine, 1151 given a comparison antidepressant and 554 on placebo. Fewer suicides occurred among subjects given paroxetine (0.5%) than among either subjects on placebo (2.8%) or taking comparator antidepressants (1.4%). Similarly, a lower percentage of subjects taking paroxetine made suicide attempts (4%) when compared to patients on placebo (8.3%) or comparator antidepressants (5.5%) [Khan, 2000].

An observational study conducted by the Drug Safety Research Unit (DSRU) in the UK, evaluated 13,741 patients treated with paroxetine between 1991-2 using the technique of prescription event monitoring (PEM) [Inman, 1993]. The incidence of suicide/parasuicide in the first month of therapy reported for paroxetine was comparable to that observed with other SSRIs and several additional antidepressants. The observed incidence rates expressed as the rate of occurrence per 1000 patient-months treatment were venlafaxine, 5.6; moclobemide, 5.5; fluoxetine, 4.7; nefazadone, 3.9; paroxetine, 3.1; and sertraline, 2.7 [Mackay, 1999].

Children and Adolescents

In the paediatric placebo controlled trials for MDD, OCD and SAD, a total of 1385 patients were exposed to paroxetine (n=738) or placebo (n=647).

There were no completed suicides or deaths within the paediatric clinical trials programme.

There was no conclusive evidence of emergent suicidal ideation (based on Item 3 of the HAM-D) in the paroxetine treatment group compared to the placebo group, and there was no difference between paroxetine and placebo in change from baseline of Item 3 of the HAM-D and Item 10 of the MADRS. However, the incidence of possibly suicide-related and self harm events was greater in paroxetine treated patients than in patients who received placebo, primarily in adolescents with MDD.

The actual number of events observed was small. As many complex factors may have contributed to those cases, and as many of the risk factors for suicidal behaviour in young people cannot be checked for balance between the treatment groups with the data currently available, it cannot be concluded with conviction that the observed differences between treatment groups were attributable to study medication and were not confounded by other factors. However, the excess in such events in adolescents is consistent with the observation in adults that such events may occur at a higher incidence in young adults on antidepressant treatment than on placebo. There was insufficient active comparator data in the paediatric programme to determine whether the effects are specific to paroxetine or are common to other antidepressants.

10.3.2.3. Hostility and aggression

There is no universally accepted definition of aggression and terms relating to hostile and aggressive behaviour [Moyer, 1976; Dorland's Medical Dictionary, 1998; Heiligenstein, 1993]. The aetiology of aggressive behaviour is multifactorial and may involve various neuropsychiatric disorders including depression and anxiety. From a biological point, it has been established that many neurotransmitters, such as serotonin, noradrenaline,

dopamine, acetylcholine and gamma-aminobutyric acid (GABA) have a role to play in the expression of aggression [Silver, 1997]. With regard to the role of serotonin in aggressive behaviour, animal and human studies have reported that lowered levels of serotonergic activity have been associated with increased aggression and impulsivity [Heiligenstein, 1992; Silver, 1997]. Clinical studies of psychiatric patients also suggest that low serotonin activity may be related to psychiatric disorders including hostile and aggressive behaviour [Moyer, 1976].

10.3.2.4. Paroxetine: effects on hostility and aggression

Adults

In adult placebo-controlled clinical studies, involving over 14,000 patients, there was no difference between the incidence of hostility in the paroxetine treatment group compared to placebo.

Only 3 adverse event reports of "hostility" (aggression) were identified within the centrally-databased R&D Phase I studies, including information from over 1700 healthy volunteers, and no evidence of any link between paroxetine and hostility from those studies. Some reports of hostility are expected in such studies given that they can involve confinement for often lengthy periods of time.

Children and Adolescents

In the placebo-controlled studies in children and adolescents, there was a higher incidence of hostility adverse events in patients treated with paroxetine than in those that received placebo. This was mainly seen in patients with OCD and in children under the age of 12 years. It is important to note that the majority of cases of hostility were classed as mild to moderate in severity and did not lead to withdrawal from the study.

These data are in keeping with information available in the product labelling (UK and France) for sertraline, which note that aggression is a potential undesirable effect which may be observed in children.

10.3.3. Withdrawal reactions

Antidepressant withdrawal reactions (also referred to as discontinuation or withdrawal symptoms) were first reported on stopping treatment with the TCA imipramine in the late 1950s [Andersen, 1959; Mann, 1959]. Subsequently, withdrawal reactions were documented as occurring with other TCAs, related compounds and the MAOIs [Kramer, 1961; Le Gassicke, 1965; Santos, 1980; Law, 1981; Mirin, 1981; Bialos, 1982; Nelson, 1983; Weller, 1983; Liskin, 1984; Tyrer, 1984; Roth, 1985; Rothschild, 1985; Geller, 1987; Dilsaver, 1989; Diamond, 1989; Vartzopulos, 1991; Ceccherini-Nelli, 1993; Halle, 1993; Otani, 1994]. Since the emergence of SSRIs and other new antidepressants, all 5 SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline and citalopram) [Rosenbaum, 1998; Einbinder, 1995; Black, 1993; Oehrberg, 1995; Rosenstock, 1996] as well as venlafaxine [Louie, 1996; Fava, 1997; Giakas, 1997] nefazadone [Benazzi, 1998] and mirtazepine [MacCall, 1999] have been reported as causing withdrawal reactions.

The most common symptoms found in SSRI withdrawal reactions include dizziness, nausea, lethargy and headache [Haddad, 1998].

10.3.3.1. Paroxetine: Withdrawal Reactions

Evaluation of clinical trials data demonstrated that the incidence of potential withdrawal adverse events was similar across both adult and paediatric patients. A full analysis of adult and paediatric studies with consistent taper and follow up phases showed that 19.4% of adult paroxetine patients and 9.8% of adult placebo patients reported potential withdrawal events. For paediatric patients these figures were 17.9% paroxetine patients and 8.5% placebo patients.

The most common withdrawal events in adults were: dizziness, headache, nausea, insomnia and anxiety and in paediatrics: nausea, dizziness, nervousness, emotional lability and abdominal pain. The majority of withdrawal events were mild to moderate in nature in both adult (85.4%) and paediatric (93.4%) patients. The majority of withdrawal events resolved within 14 days in both adult (78.5%) and paediatric patients (93.5%), with 1% of adult patients and no paediatric patients restarting paroxetine as a result of a potential withdrawal event.

Age, gender and race were not significant differential risk factors influencing the occurrence of withdrawal events for paroxetine over placebo in either adults or paediatric patients. Indication was not a statistically significant risk factor influencing rates of withdrawal events on paroxetine over placebo in adults. There was a significant treatment by indication interaction in paediatric patients but this should be treated with caution since each indication was represented by only one study and it may be confounded by other effects. There was a possible effect of treatment duration on the incidence of withdrawal events in both adult and paediatric patients. An analysis of the incidence of withdrawal events by treatment duration was potentially confounded by a number of different factors including the effects of indication, fixed study durations and responder rates. However, the treatment by treatment duration interactions were only marginally significant and, in adults, when the effects of a possibly confounding study were excluded, this interaction effect was lost. The relapse prevention studies also showed a potential effect of treatment duration but again this was confounded by a number of factors including lack of placebo control, response rates and the fact that the comparison was drawn between patients undergoing blinded taper versus those knowing that they were stopping medication.

A total of 1716 healthy volunteers participated in a total of 90 studies with paroxetine. All patients underwent abrupt withdrawal of paroxetine with no tapering of dose. Adverse events were then collected 24 hours after the final dose and a follow-up visit occurred usually 10 to 14 days after the last dose. The method of collecting adverse event data made objective evaluation of this data difficult. However, the data available suggests that, with the exception of abnormal dreaming, there do not appear to be any difference in withdrawal adverse events reported between patients and healthy volunteers.

Debate has has occurred regarding the presence of features of dependence in patients experiencing withdrawal reactions. An evaluation of the GSK clinical safety database

was undertaken and 937 reports of alleged addiction or dependence were identified, of which 764 (81.5%) were also present in the dataset of 3,830 reports of withdrawal reactions. A review of these cases found no reports in which the ICD-10 diagnostic criteria for dependence syndrome were met [ICD-10, 1992].

10.4. Overall Benefit-Risk profile of paroxetine

10.4.1. Adults

This Article 31 response clearly shows the benefits of paroxetine in the treatment of depressive illness and anxiety disorders in adults, and recent completion of a paediatric clinical trial programme has demonstrated efficacy in the treatment of OCD and SAD in children and adolescents. Paroxetine has demonstrated in more than 170 adult clinical trials, enrolling over 24,000 patients, in controlled clinical studies a consistent safety and efficacy profile in adults. This has been translated into clinical practice, with an extensive worldwide use for an increasing range of approved indications. Over the past 10 years, there have been over 164 million patient treatments worldwide, improving the mental health of the majority of patients it helps treat. Paroxetine has consistently shown superior efficacy to placebo treatment in clinical trials of depressive illness of all types, including depression comorbid with anxiety and physical illnesses. Paroxetine's anxiolytic effect has consistently and reproducibly been evident in a wide-range of anxiety disorders, leading to its recommendation as a first-line therapy for OCD, PD, SAD, PTSD and GAD. As the only SSRI currently indicated for all five major anxiety disorders, much of the data for the use of SSRIs in the treatment of anxiety disorders are for paroxetine. Given the high degree of psychiatric comorbidity associated with depressive illness, paroxetine is an important therapeutic option for the mental health prescriber.

The main areas of focus of this Article 31 referral are suicidal behaviour, self-harm, hostility and withdrawal reactions.

The available data have been reviewed and do not change the view that paroxetine has a positive benefit-risk balance in all currently approved indications in adults.

Comprehensive evidence has been provided demonstrating that the likelihood of paroxetine increasing the risk of suicidal behaviour, self-harm and hostility related events in adults is remote. In fact there is clear evidence from controlled clinical trials, that paroxetine can reduce suicidal ideation alongside a strong body of opinion suggesting that improved treatment of depressed and anxious patients is one of the most effective ways to reduce suicide rates [Hall, 2003; Isacsson, 2000].

It should be noted that young adults had an increased risk of possibly suicide-related and self harm events irrespective of treatment group. This appears to be heightened among patients treated with antidepressants, although patients treated with paroxetine were at a lower risk compared to those treated with other SSRIs and other classes of antidepressants. The data demonstrated a reduced risk of a possibly suicide-related adverse event on paroxetine than on active comparator across the entire age range of the

active controlled studies. In fact, this advantage of treatment with paroxetine, compared to active controls, is statistically significant in young adulthood.

It is also important to view this adverse event data along side other clinical markers of suicidality such as change in baseline suicidal ideation on treatment. Assessment of this clinical marker demonstrated that patients suffering suicidal ideation at baseline were less likely to experience possibly suicide-related and self-harm adverse events if treated with paroxetine than placebo, indicating an advantage with paroxetine treatment.

With regards to adverse events of hostility, there were no differences in the incidence of on-therapy hostility events between the paroxetine treatment group and the placebo group in adults.

Regarding withdrawal reactions, it was interesting to note that potential withdrawal events were reported by 19% and 10% of adult patients withdrawing from paroxetine and placebo, respectively, that 85% of those events were described as of mild to moderate severity, that 78% resolved within 14 days, and that only 1% of adult patients restarted paroxetine as a result of a potential withdrawal event. It is accepted on the basis of spontaneous reports received that some patients have severe difficulties on withdrawing from paroxetine treatment, but the above data from our clinical studies, particularly the fact that only 1% of patients required to restart paroxetine, give reassurance as to the rarity of truly severe problems.

Overall, new information resulting from this current review of information on paroxetine does not change the view that paroxetine has a clearly positive benefit-risk balance in all currently approved indications in adults.

10.4.2. Children and Adolescents

Safety signals regarding possibly suicide-related and self harm events were observed from the paediatric clinical trials. It should be noted that these are based on small numbers of cases and that the contribution of paroxetine to the overall risk of possibly suicide-related and self-harm adverse events may be confounded by other factors as well as treatment factors. However, in the absence of information to the contrary, such safety signals must be given serious consideration.

Paroxetine has been investigated in paediatric studies in three indications, OCD, SAD and MDD. The efficacy advantage of paroxetine over placebo in paediatric OCD and SAD was considerable, particularly in SAD. Bearing in mind the potential advantages of bringing early relief to children or adolescents with those conditions, the safety signal should not necessarily preclude the use of paroxetine for such patients. However, for children and adolescents with MDD the situation is different. The three paediatric MDD studies all failed to separate paroxetine from placebo overall and so do not provide strong evidence of efficacy in this indication. Post-hoc analyses were performed on the paediatric MDD studies and suggested that patients aged ≥ 15 years derived some benefit from paroxetine treatment. However that age group was also the age group with the strongest signal of possibly suicide-related events. Consequently it must be concluded that the benefit-risk balance is in favour of not treating children and adolescents with

MDD with paroxetine. It should be noted that there is no safety information to suggest that the safety signal seen for possibly suicide-related and self-harm events in paediatric patients with MDD, is not similarly present with other SSRIs.

In children and adolescents, paroxetine was associated with an increased risk of hostility compared to placebo. The additional risk was seen mainly in patients with OCD and in children < 12 years. These data are in keeping with information available in the product labelling (UK and France) for sertraline, which note that aggression is a potential undesirable effect which may be observed in children. However the majority of cases were classed as mild or moderate in severity and did not lead to withdrawal from the study. Consequently they are viewed as having little impact on the overall benefit-risk in children and adolescents, even children with OCD.

Potential withdrawal events were observed in children and adolescents at similar incidences as in adults. There was no suggestion that such events were of greater severity, longer duration or more troublesome than events in adults. Therefore they were not considered to impact assessment of the benefit-risk balance for the use of paroxetine in this population.

10.4.3. Benefit-Risk Conclusions

Review of all available data does not change GSK's view of the benefit-risk balance for paroxetine in adults. We believe paroxetine has a clear positive benefit-risk balance in all currently approved indications in adults.

Paroxetine has been studied in paediatric OCD, SAD and MDD clinical trials, and impressive efficacy has been demonstrated in children and adolescents with OCD or SAD. However, efficacy has not been clearly demonstrated in MDD. Hence in view of a safety signal concerning a possible increase in suicidal behaviour, particularly in adolescents with MDD, the use of paroxetine in children and adolescents with MDD cannot be recommended.

10.5. Risk Reduction Strategies

As discussed above, GSK considers that the benefit/risk balance for paroxetine clearly remains favourable. Therefore, certain options, such as suspension of the product licence or withdrawal of paroxetine from the market, are not justified. However, the company recognises the importance of evaluating and implementing measures that will potentially reduce risks associated with the use of the product. As such, GSK is proposing a comprehensive risk reduction plan comprising a series of complementary measures in the following areas:

- multiple significant modifications to the product information for prescribers and patients
- communication of reinforced medical information to the medical profession
- initiation of new research

- making an oral suspension available

These measures, which are discussed in detail below, will supplement the ongoing close monitoring of the safety of paroxetine conducted by GSK through existing procedures, which include the routine preparation of Periodic Safety Update Reports (PSURs) on a 6-monthly basis.

10.5.1. Modifications to the product information for prescribers and patients

Without doubt, the single most important means of minimising risks associated with drug therapy is the provision of clear, up-to-date information to prescribers through product labelling. Central to GSK's risk reduction strategy for paroxetine, therefore, is a proposal to make extensive revisions to the SmPC, based on current knowledge of the safety profile of the product. These revisions comprise new statements specifically relating to the use of paroxetine in paediatric patients, the risk of disease-related suicidal behaviour in the initial phase of antidepressant therapy, and the potential for withdrawal reactions on discontinuation of paroxetine treatment. The primary features and rationale for these proposed revisions to prescribing information are summarised below, after which the full text of the safety statements is presented.

10.5.1.1. Features of revised labelling relating to the use of paroxetine in paediatric patients

The proposed new statements relating to the use of paroxetine in paediatric patients are intended to enhance, and therefore supercede, the labelling changes previously submitted to EU regulatory authorities as a safety variation in June 2003. The updated statements are centred on a new Warning statement that will be positioned prominently within section 4.4, Special Warnings and Precautions for Use, of the prescribing information. This statement will:

- inform prescribers that paroxetine is not indicated for use in children and adolescents
- warn of the higher reporting rate of suicidal ideation and suicide attempts in paroxetine-treated paediatric patients as compared with placebo-treated patients, particularly in adolescents with Major Depressive Disorder (MDD), in the pooled paediatric clinical trials population
- inform prescribers of the higher reporting rate of hostility (predominantly aggression, oppositional behaviour and anger) in paroxetine-treated paediatric patients as compared with placebo-treated patients, particularly in children with obsessive compulsive disorder (OCD), and especially in younger children less than 12 years of age, in the pooled paediatric clinical trials population
- highlight the lack of proven efficacy in paediatric patients with MDD.

These key messages will be further re-inforced through the proposed inclusion of accompanying statements within sections 4.1 Therapeutic Indications, 4.2 Posology and Method of Administration and 4.8 Undesirable Effects (see below for full text of the statements).

10.5.1.2. Features of revised labelling relating to disease-associated suicidality

With respect to the risks of disease-related suicidal behaviour, approved prescribing information for paroxetine in some EU countries already included a statement within section 4.4, Special Warnings and Precaution for Use, advising that the inherent risk of suicide attempt associated with MDD may persist in the initial phase of antidepressant therapy, until significant remission occurs, and that patients should be closely monitored during this time. However, other treatment indications for which paroxetine is prescribed, including anxiety disorders, have been found to be independently associated with an increased risk of suicide attempt [Kessler, 1999]. Moreover, these conditions can be co-morbid with major depressive disorder, with a resultant increase in the risk of suicide attempt. Therefore, as with MDD, it is prudent to monitor patients with these conditions for suicidal ideation/behaviour in the initial stages of drug therapy. The need for close monitoring is an integral component of patient management when treating individuals with psychiatric disorders, rather than a precaution specifically required for patients receiving therapy with paroxetine. Nevertheless, GSK has concluded that it would be beneficial from a risk reduction perspective to include a Precautionary statement within section 4.4 of paroxetine prescribing information across EU countries reminding prescribers of the need to monitor patients for disease-related suicidal ideation/behaviour in the early stages of therapy.

10.5.1.3. Features of revised labelling relating to withdrawal reactions

With regard to withdrawal reactions, information on these events is provided in approved prescribing information across EU countries, generally within section 4.8, Undesirable Effects. Even though the potential for withdrawal reactions is clearly labelled, it has been alleged that some prescribers may not be advising patients of the potential for such symptoms. GSK recognises that the development of such symptoms in patients who have not been adequately counselled can lead to significant concern in these individuals. Moreover, anecdotal reports suggest that paroxetine therapy is discontinued abruptly in some patients (although approved SmPCs advise against this), whilst others may be subject to a very long period of drug tapering when therapy is no longer deemed to be required. In view of these observations, GSK considers it appropriate to update the information relating to withdrawal reactions by proposing major revisions to three sections of the prescribing information,

- Section 4.2, Posology and Method of Administration, will be amended to include a new statement which
    i. highlights the importance of avoiding abrupt discontinuation of therapy whenever possible,
    ii. describes the dose tapering regimen currently employed in GSK clinical studies of paroxetine, as a guideline to help prescribers design a schedule for discontinuing paroxetine treatment in their patients, and
    iii. provides guidance for physicians on the management of those patients who may experience intolerable symptoms on discontinuation of paroxetine treatment.

- Section 4.4, Special Warnings and Precautions for Use will be revised to include a new Precautionary statement advising prescribers of the potential for withdrawal reactions and recommending that the dose of paroxetine be gradually tapered when discontinuing treatment. This statement will serve to reinforce the importance of prescribers informing patients of the potential for withdrawal reactions.
- Section 4.8, Undesirable Effects, will be updated to include a more detailed description of withdrawal reactions to facilitate counselling of patients. In addition, the expanded statement will repeat the recommendation that gradual discontinuation of paroxetine by dose tapering be carried out, when paroxetine treatment is no longer required.

10.5.1.4. Proposed Labelling Changes

The full text of these proposed new safety statements for inclusion in SmPC information referred to above is provided here:

4.1 Therapeutic Indications

Depression

Children (7-17 years):

Controlled clinical studies failed to demonstrate efficacy and do not support the use of paroxetine in the treatment of children with Major Depressive Disorder (*see 4.4 Special Warnings and Precautions for Use & 4.8 Undesirable Effects*).

4.2 Posology and Method of Administration

Depression

Children (7-17 years):

Controlled clinical studies failed to demonstrate efficacy and do not support the use of paroxetine in the treatment of children with Major Depressive Disorder (*see 4.4 Special Warnings and Precautions for Use & 4.8 Undesirable Effects*).

General Information

DISCONTINUATION OF PAROXETINE

As with other psychoactive medications, abrupt discontinuation should generally be avoided (*see 4.4 Special Warnings and Precautions for Use & 4.8 Undesirable Effects*). The taper phase regimen used in recent clinical trials involved an incremental decrease in the daily dose by 10 mg/day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for one week before treatment was stopped. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

Populations

- **Children (7-17 years)**

The efficacy of paroxetine in children with panic disorder, generalised anxiety disorder or post-traumatic stress disorder has not been investigated. More than 600 children (7-17 years) with Major Depressive Disorder (MDD), obsessive compulsive disorder, or social anxiety disorder have received paroxetine in clinical trials. Controlled clinical studies in depression failed to demonstrate efficacy and do not support the use of paroxetine in the treatment of children with MDD (*see 4.4 Special Warnings and Precautions for Use & 4.8 Undesirable Effects*).

4.4 Special Warnings and Precautions for Use

CHILDREN (7-17 YEARS): Paroxetine is not indicated for use in children and adolescents under the age of 18 years. In a pooled analysis of all paediatric clinical trial data there was a higher rate of reporting of suicidal thoughts and suicide attempts in paroxetine-treated patients versus those treated with placebo, primarily in adolescents with Major Depressive Disorder (MDD). Controlled clinical trials in MDD failed to demonstrate efficacy (*see Adverse Reactions*).

Hostility (predominantly aggression, oppositional behaviour and anger) was also reported more frequently in paroxetine-treated patients, particularly in children with obsessive compulsive disorder, and especially in younger children less than 12 years of age (*see Adverse Reactions*).

SUICIDE/SUICIDAL IDEATION AND PSYCHIATRIC DISORDERS: The possibility of a suicide attempt is an inherent component of major depressive disorder and may persist until significant remission occurs. It is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery. As improvement may not occur during the first few weeks or more of treatment, patients should therefore be closely monitored until such improvement occurs. Other psychiatric conditions for which paroxetine is prescribed can also be associated with an increased risk of suicidal behaviour. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders. Additionally, it is a characteristic of psychiatric disorders that younger patients (i.e. adolescents and young adults), patients with a history of suicidal behaviour or thoughts, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

SYMPTOMS SEEN ON DISCONTINUATION OF PAROXETINE TREATMENT: Some patients may experience symptoms on discontinuation of paroxetine, particularly if treatment is stopped abruptly (*see 4.8 Undesirable*

Effects). It is therefore advised that the dose should be gradually tapered when discontinuing treatment (*see 4.2 Posology and Method of Administration*).

4.8 Undesirable Effects

Symptoms seen on discontinuation of paroxetine treatment:

Common: Dizziness, sensory disturbances, sleep disturbances, anxiety.
Uncommon: Agitation, nausea, sweating.

As with many psychoactive medicines, discontinuation of paroxetine (particularly when abrupt) may lead to symptoms such as dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances, agitation or anxiety, nausea and sweating. In the majority of patients, these events are mild to moderate and are self-limiting. No particular patient group appears to be at higher risk of these symptoms; it is therefore advised that when paroxetine treatment is no longer required, gradual discontinuation by dose tapering be carried out (*see 4.2 Posology and Method of Administration & 4.4 Special Warnings and Precautions for Use*).

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 at least twice that of placebo: decreased appetite, tremor, sweating, hyperkinesia, agitation, hostility (predominantly aggression, oppositional behaviour and anger, particularly in children with obsessive compulsive disorder, and especially in younger children less than 12 years of age), 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 tapering regimen, symptoms reported during the taper phase or upon discontinuation of paroxetine at a frequency of at least 2% of patients and occurred at a rate 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 (*see 4.4 Special Warnings and Precautions for Use*).

10.5.1.5. Patient Information

Having considered the proposed revisions to EU prescribing information, it is also relevant to discuss the information that will be provided to patients. GSK recognises that the provision of clear information to patients, in order that they may understand the potential risks of drug therapy, and identify emergent adverse drug reactions such that they seek early medical advice, is a further means of reducing the levels of concern experienced by patients and the likelihood of serious outcomes. Therefore, as a second risk reduction measure in the category of modifications to product information, GSK will undertake to conduct a Central review of Patient Information Leaflets across the EU to

ensure that safety information, including the important new messages discussed above, are presented in a consistent and clear manner.

10.5.2. Communication of reinforced medical information to the medical profession

In view of the critical importance of prescribing information in reducing risks of drug therapy, GSK will actively inform prescribers of the safety-related changes to the paroxetine prescribing information in all EU markets This will be conducted using the most practicable method at the national level, based on country-specific best practices (eg. a letter to healthcare professionals or update to representatives' detail aids). This step will help to ensure that prescribers base their clinical decision making on the most up-to-date information.

Additionally, GSK will undertake to make available the clinical trial data on self-harm/suicide-related events in paediatric and adult patients through publication in a widely-read, reputable journal, such that prescribers will have full access to the available evidence upon which prescribing information statements have been based. The company will take steps to inform prescribers of the availability of this information, once the data have been published, and will also take the opportunity afforded by meetings with Key Opinion Leaders (KOLs) as a further means of communicating these specific data to the medical community.

10.5.3. Initiation of new research

Notwithstanding the available evidence presented in this document that paroxetine therapy is not associated with the development of self-harm/suicidal behaviour in adult patients, GSK acknowledges the importance of continuing to evaluate this issue in order to provide reassurance to prescribers and patients. Therefore, GSK has begun new research into paroxetine use and the risk of suicide-related events through initiation of an epidemiological study utilising the UK General Practice Research database (GPRD). This study, which is discussed in more detail in the response to question 11 in this document, will compare patients newly prescribed paroxetine, those receiving another SSRI and patients on a non-SSRI antidepressant. The baseline risks for suicidal behaviour will be compared across these cohorts by examining their medical history for risk factors present prior to their antidepressant prescription. These defined cohorts will then be followed forward in time and the incidence of suicidal behaviour in each group will be determined to establish if there is an association between use of paroxetine, or any SSRI, and suicidal behaviour. The results of the study will be communicated to EU regulatory authorities upon its completion and reporting.

10.5.4. Registration of new dosage forms

As a further component of the risk reduction plan specifically relating to withdrawal reactions, GSK will undertake to register and make available an oral suspension (2 mg/ml paroxetine) in all countries across the EU to provide physicians with maximum flexibility in tailoring a tapered regimen for paroxetine discontinuation for those occasional patients

who experience intolerable symptoms on discontinuing paroxetine treatment. (The oral suspension is already marketed in some EU countries but will require regulatory applications or launch in others).

10.6. Summary of risk reduction strategies

To summarise, GSK has carefully considered the evidence provided in this Response Document and concluded that the benefit/risk profile remains clearly favourable and that options such as suspension or withdrawal of paroxetine from the market are therefore not justified.

However, the company has evaluated the additional options provided in the report of CIOMS Working Group IV (Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals) and proposes to implement a comprehensive risk reduction plan comprised of a series of complementary measures involving:

- multiple significant modifications to the product information for prescribers and patients, including the addition of new statements to Section 4.4, Special Warnings and Precautions for Use, relating to paediatric patients, disease-related suicidal behaviour and withdrawal reactions
- active communication of reinforced medical information to the medical profession
- further research to investigate the risk of suicide-related events through initiation of an epidemiological study involving the UK General Practice Research Database (GPRD)
- making available an oral suspension to provide physicians with maximum flexibility in tailoring a tapered regimen for paroxetine discontinuation for individual patients who experience intolerable symptoms on discontinuing paroxetine treatment

In combining these specific activities with the ongoing close surveillance of the safety of paroxetine through existing pharmacovigilance procedures, such as the preparation of Periodic Safety Update Reports (PSURs) on a 6-monthly basis, GSK believes that the benefit/risk balance can be shifted in an even more positive direction.

10.7. Overall Conclusion

The results of this review strongly support the continued inclusion of paroxetine as an important option for clinicians and patients. This comprehensive review confirms that restriction of the use of paroxetine is not warranted and would result in limiting an important treatment option to doctors, which could potentially lead to unfavourable clinical consequences for the patient. The benefit/risk ratio for paroxetine remains clearly favourable across all adult indications. Further, there is a favourable benefit risk ratio in the OCD & SAD indications in children and adolescents although use in children and adolescents with MDD cannot be recommended.

GSK's risk reduction and communications strategies currently underway will be augmented with additional risk reduction measures which may further shift the benefit/risk balance in a positive manner.

10.8. References

Aberg-Wistedt A, Agren H, Ekselius L, et al. Sertraline versus paroxetine in major depression: clinical outcome after six months of continuous therapy. *J Clin Psychopharmacol.* 2000; 20(6): 645-52.

Allgulander C. Suicide and mortality patterns in anxiety neurosis and depressive neurosis. *Arch Gen Psychiat.*1994; 51: 708-712.

Allgulander C. Paroxetine in social anxiety disorder: a randomized placebo-controlled study. Acta Psychiatr Scand 1999;100(3):193-8.

Andersen H, Kristiansen ES. Tofranil treatment of endogenous depressions. *Acta Psychiatr Scand.*1959; 34: 387-97.

Angst J, Angst F, Stassen HH. Suicide risk in patients with major depressive disorder. *J Clin Psychiatry.*1999; 60(suppl 2): 57-62.

Ansseau M, Gabriels A, Loyens J, et al. Controlled comparison of paroxetine and fluvoxamine in major depression. *Human Psychopharm.* 1994; 9(5): 329-36.

Baldwin DS Birtwistle J. Improving impairment and disability in anxiety disorders with paroxetine treatment, *European Neuropsychopharmacology*. 2000; 10(Suppl 3): 351.

Baldwin DS, Hawley CJ, Abed RT, et al. A multicenter double-blind comparison of nefazodone and paroxetine in the treatment of outpatients with moderate-to-severe depression. *J Clin Psychiatry*. 1996; 57(Suppl 2): 46-52.

Baldwin D, Bobes J, Stein DJ et al. Paroxetine in social phobia/social anxiety disorder. Br J Psych 1999;175: 120-124.

Benazzi F, Nefazodone withdrawal symptoms. *Can J Psychiatry*. 1998; 43(2): 194-5.

Bialos D, Giller E, Jatlow P, et al. Recurrence of depression after discontinuation of amitriptyline. *Am J Psychiatry.* 1982; 139(3): 325-9.

Birmaher B, Waterman GS, Ryan ND et al. Randomized, controlled trial of amitriptyline versus placebo for adolescents with "treatment-resistant" major depression. *J Am Acad Child Adolesc Psychiatry*. 1998; 37(5): 527-535.

Black DW, Wesner R, Gabel J. The abrupt discontinuation of fluvoxamine in patients with panic disorder. *J Clin Psychiatry.* 1993; 54(4): 146-9.

Blair-West GW, Mellsop GW, Eyeson-Annan ML. Down-rating lifetime suicide risk in major depression. *Acta Psychiatr Scand.* 1997;95:259-263.

Ceccherini-Nelli A, Bardellini L, Guazzalli M, et al. Antidepressant withdrawal phenomena: prospective findings. *Am J Psychiatry.* 1993; 150(1): 165.

Chouinard G, Saxena B, Belanger M-C, et al. A Canadian multicenter, double-blind study of paroxetine and fluoxetine in major depressive disorder. *J Affect Disord*. 1999; 54(1-2): 39-48.

Coryell W, Noyes R, Clancy J. Excess mortality in panic disorder. A comparison with primary unipolar depression. *Arch Gen Psychiatry*.1982; 39: 701-703.

De Wilde J, Spiers R, Mertens C, et al. A double-blind, comparative, multicentre study comparing paroxetine with fluoxetine in depressed patients. *Acta Psychiatr Scand*. 1993; 87(2): 141-5.

Diamond BI, Borison RL, Katz R, et al. Rebound reactions due to clomipramine. *Psychopharmacol Bull*. 1989; 25(2): 209-12.

Dilsaver SC. Antidepressant withdrawal syndromes: phenomenology and pathophysiology. *Acta Psychiatr Scand*. 1989; 79: 113-7.

Doraiswamy M, Khan ZM, Donahue RMJ, Richard NE. Quality of life in geriatric depression: a comparison of remitters, partial responders and non-responders. *Am J Geriatric Psychiatry* 2001;9:423-428.

Dorland's Medical Dictionary. 28th Edition.1998.W.B Saunders Co.

Dunner D, Kumar R. Paroxetine: a review of clinical experience. *Pharmacopyschiatry.* 1998; 31(3): 89-101.

Einbinder E. Fluoxetine withdrawal? *Am J Psychiatry*. 1995; 152(8): 125.

Emslie GJ, Rush J, Weinberg WA et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry*, 1997; 54: 1031-1037.

Engstrom G, Persson B, Levander S. Temperament traits in male suicide attempts and violent offenders. *Eur Psychiatry.* 1999; 14: 278-283.

Fava M. Depression with Anger Attacks. *J Clin Psychiatry.* 1998; 59(S18): 18-22.

Fava M, Mulroy R, Alpert J, et al. Emergence of adverse effects following discontinuation of treatment with extended-release venlafaxine. *Am J Psychiatry*. 1997; 154(12): 1760-2.

Fava M, Rosenbaum JF, Hoog SL, et al. Fluoxetine versus sertraline and paroxetine in major depression: tolerability and efficacy in anxious depression. *J Affect Disord.* 2000; 59: 119-26.

Fawcett J. Predictors of early suicide: identification and appropriate intervention. *J Clin Psych.* 1988; 49(suppl 10): 7-8.

Fawcett J. Targeting treatment in patients with mixed symptoms of anxiety and depression. *Journal of Clinical Psychiatry.* 1990; 51(Suppl): 40-3.

Food And Drug Administration. Summary Basis of Approval. Fluvoxamine (Luvox®) use in paediatric patients with obsessive-compulsive disorder. 1997a.

Food And Drug Administration. Summary Basis of Approval. Sertraline (Zoloft®) use in paediatric patients with obsessive-compulsive disorder. 1997b.

Gagiano CA. A double blind comparison of paroxetine and fluoxetine in patients with major depression. *Br Clin Res.* 1993; 4: 145-152.

Geller B, Cooper TB, Carr LG. Prospective study of scheduled withdrawal from nortriptyline in children and adolescents. *J Clin Psychopharmacol.* 1987; 7: 252-4.

Geller, B, Reising D, Leonard HL, Riddle MA, Walsh BT. Critical review of tricyclic antidepressant use in children and adolescents. *J Am Acad Child Adolesc Psychiatry*, 1999; 38: 513-516.

Geller DA, Hoog SL, Heiligenstein JH, Ricardi RK, Tamura R, Kluszynski, Jacobson JG. Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: a placebo-controlled clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2001; 40(7): 773-779.

Giakas WJ, Davis SM. Intractable withdrawal from venlafaxine treated with fluoxetine. *Psychiatric Ann.* 1997; 27(2): 85-6.

Haddad P. The SSRI discontinuation syndrome. *J Psychopharmacol.* 1998; 12(3): 305-13.

Hall WD et al. Association between antidepressant prescribing and suicide in Australia, 1991-2000: Trend analysis. *BMJ.* 2003; 326: 1008-12.

Halle MT, Dilsaver SC. Tranylcypromine withdrawal phenomena. *J Psychiatry Neurosci.* 1993; 18(1): 49-50.

Hawkridge SM, Stein DJ. A risk-benefit assessment of pharmacotherapy for anxiety disorders in children and adolescents. *Drug Safety*. 1998; 19(4): 283-297.

Heiligenstein JH, Beasley CM, Potvin JH. Fluoxetine not associated with increased aggression in controlled clinical trials. *Int Clin Psychopharmacol* 1993; 8(4): 277-280

Henriksson M, Aro H, Marttunen M et al. Mental disorders and comorbidity in suicide. *Am J Psychiatry*. 1993; 150: 935-940.

Holm K, Jarvis B, Foster RH. Mitazapine A pharmacoeconomic review of its use in depression: *Pharmacoeconomics.* 2000; 17(5): 515-534.

Inman W, Kubota K, Pearce G et al. PEM Report Number 6. Paroxetine. *Pharmacoepidemiology and Drug Safety*. 1993; 2: 393-422.

Isacsson G. Suicide prevention: A medical breakthrough? *Acta Psychiatr Scand.* 2000; 102: 113-117.

Johnson J, Weissman MM, Klerman GL. Panic disorder, comorbidity and suicide attempts. *Arch Gen Psych*. 1990; 47: 805-8.

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen H-U, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psych* 1994; 51: 8-19.

Kessler RC, Guilhernme B, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Arch Gen Psych.* 1999; 56: 617-626.

Khan A, Warner H, Brown WA. Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials. *Archives of General Psychiatry*.2000;57(4):311-317

Kiev A, Feiger A. A double-blind comparison of fluvoxamine and paroxetine in the treatment of depressed outpatients. *J Clin Psychiatry.* 1997; 58(4): 146-52.

Kramer JC, Klein DF, Fink M. Withdrawal symptoms following discontinuation of imipramine therapy. *Am J Psychiatry*. 1961; 118:549-50.

Kroenke K West SL. Swindle R. Gilsenan A. Eckert GJ. Dolor R. Stang P. Zhou XH. Hays R. Weinberger M. Similar effectiveness of paroxetine, fluoxetine and sertraline in primary care: JAMA 2001: 286(23) 2947 – 2955.

Law W 3rd, Petti TA, Kazdin AE. Withdrawal symptoms after gradual cessation of imipramine in children. *Am J Psychiatry*. 1981; 138: 647-50.

Le Gassicke J, Ashcroft GW, Eccleston D, et al. The clinical state, sleep and amine metabolism of a tranylcypromine ('Parnate') addict. *Br J Psychiatry*. 1965; 111: 357-364.

Leonard HL, March J, Rickler CK, Allen AJ. Pharmacology of the selective serotonin reuptake inhibitors in children and adolescents. *J Am Acad Child Adolesc Psychiatry*, 1997; 36(6): 725-736.

Lepine JP, Altamura C, Ansseau M, et al. Tianeptine and paroxetine in major depressive disorder, with a special focus on the anxious component in depression: An international 6-week double-blind study. *Hum Psychopharmacol*. 2001; 16: 219-27.

Liebowitz MR, Stein MB, Tancer M et al. A randomized double-blind fixed dose comparison of paroxetine and placebo in the treatment of generalized social anxiety disorder J Clin Psych 2002;63:66-74

Liskin B, Roose S, Walsh T. Acute psychosis following phenelzine discontinuation. *J Clin Psychopharmacol*. 1984; 5(1): 46-7.

Lopez-Ibor JJ. Reduced suicidality with paroxetine. *Eur Psychiatry*.1993;8(Suppl 1);17s-19s.

Louie AK, Lannon RA, Kirsch MA, et al. Venlaxfaxine withdrawal reactions. *Am J Psychiatry*. 1996; 153(12): 1652.

Lydiard RB, Bobes J. Therapeutic advances: Paroxetine for the treatment of social anxiety disorder. Depression and Anxiety 2000; 11: 99-104

MacCall C, Callender J. Mirtazapine withdrawal causing hypomania. *Br J Psychiatry* 1999; 175: 390.

Mackay FJ, Dunn NR, Wilton LV, et al. A comparison of fluvoxamine, fluoxetine, sertraline and paroxetine examined by observational cohort studies. *Pharmacoepidemiology and Drug Safety*. 1997; 6: 235-246.

Mackay FR et al. Newer antidepressants: a comparison of tolerability in general practice. *British Journal of General Practice*. 1999; 49: 892-6.

Mann AM, MacPherson A. Clinical experience with imipramine (G22355) in the treatment of depression. *Can Psychiatr Assoc J*. 1959; 4: 38-47.

March JS, Biederman J, Wolkow R, Safferman A, Mardekian J, Cook EH et al. Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. *JAMA*. 1998; 280(20): 1752-1756.

Mirin SM, Schatzberg AF, Creasey DE. Hypomania and mania after withdrawal of tricyclic antidepressants. *Am J Psychiatry*. 1981; 138: 87-89.

Montgomery SA. A meta-analysis of the efficacy and tolerability of paroxetine versus tricyclic antidepressants in the treatment of major depression. *Int Clin Psychopharmacol*. 2001; 16: 169-178.

Montgomery SA, Dunner DL, Dunbar GC. Reduction of suicidal thoughts with paroxetine in comparison with reference antidepressants and placebo. *Eur Neuropsychopharmacol*. 1995; 5: 5-13.

Moyer, KE. The Psychobiology of Aggression. 1976. Harper and Row.

Nelson JC, Schottenfeld RS, Conrad ED. Hypomania after desipramine withdrawal. *Am J Psychiatry*. 1983; 140(5): 624-625.

Oehrberg S, Christiansen PE, Behnke K, et al. Paroxetine in the treatment of panic disorder; A randomised, double-blind, placebo-controlled study. *Br J Psychiatry*. 1995; 167(3): 374-9.

Ontiveros A, Garcia-Barriga C. A double-blind, comparative study of paroxetine and fluoxetine in out-patients with depression. *Br J Clin Res*. 1997; 8: 23-32.

Otani K, Tanaka O, Kaneko S, et al. Mechanisms of the development of trazodone withdrawal symptoms. *Int Clin Psychophamacol*. 1994; 9(2): 131-3.

Poirer M-F, Boyer P. Venlafaxine and paroxetine in treatment-resistant depression: double-blind, randomised comparison. *Br J Psychiatry*. 1999; 175: 12-6.

Pollack MH, Zaninelli R, Goddard A. Paroxetine treatment of Generalized Anxiety Disorder: Results of a placebo-controlled, flexible-dosage trial. J Clin Psychiatry 2001;62(5):350-357.

Ravindran AV, Judge R, Hunter BN, et al. A double-blind, multicenter study in primary care comparing paroxetine and clomipramine in patients with depression and associated anxiety. Paroxetine Study Group. *J Clin Psychiatry*. 1997; 58(3): 1112-8.

Regier D, Burke J, Burke K,. *Comorbidity of affective disorders in the NIMH Epidemiologic Catchment Area Program. In: Maser J, Cloninger R (eds) Comorbidity* of mood and anxiety disorders. Washington DC, USA: American Psychiatric press; 1990: 113-122.

Rickels K, et al. Paroxetine treatment of Generalised Anxiety Disorder: a double blind, placebo controlled study: *Am J Psychiatry*. 2003; 160(4): 749-756.

Riddle MA, Reeve EA, Yaryura-Tobias JA, Yang HM, Claghorn JL, Gaffney G et al. Fluvoxamine for children and adolescents with obsessive-compulsive disorder: a randomized, controlled, multicenter trial. *J Am Acad Child Adolesc Psychiatry*. 2001; 40(2): 222-229.

Rocca P, Fonzo V, Scotta M, et al. Paroxetine efficacy in the treatment of generalised anxiety disorder. *Acta Psychiatr Scand*. 1997; 95(5): 444-50.

Rosenbaum JF, Fava M, Hoog SL, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomised clinical trial. *Biol Psychiatry*.1998;44(2):77-87.

Rosenstock HA. Sertraline withdrawal in two brothers: a case report. *Int Clin Psychopharmacol.* 1996; 11(1): 58-9.

Roth SD. More on psychosis following phenelzine discontinuation. *J Clin Psychopharmacol.* 1985; 5(6): 360-1.

Rothschild AJ. Mania after withdrawal of isocarboxazid. *J Clin Psychopharmacol*. 1985; 5(6): 340-2.

Santos AB, McCurdy L. Delirium after abrupt withdrawal from doxepin: case report. *Am J Psychiatry*.1980;137(2):239-40.

Silver JM, Yudofsky SC. Violence and The Brain. In:Feinberg, TE. and Farah, MJ. Editors: *Behavioural Neurology and Neuropsychology.* McGraw Hill, 1997:711-717.

Tenney NH, Denys DAJP, van Megan HJGM, Glas G, Westenberg HGM: Effects of a pharmacological intervention on quality of life in patients with obsessive-compulsive disorder. *Int Clin Psychopharm*. 2003; 18: 29-33.

Tignol J. A double-blind, randomized, fluoxetine-controlled, multicenter study of paroxetine in the treatment of depression. *J Clin Psychopharmacol*.1993;13(6 Suppl. 2): 18S-22S.

Tucker P, Zaninelli R, Yehuda R, et al. Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry.* 2001; 62(11): 860-8.

Tyrer P. Clinical effects of abrupt withdrawal from tricyclic antidepressants and monoamine oxidase inhibitors after long term treatment. *J Affect Disord*. 1984; 6: 1-7.

Vartzopulos D, Krull F. Dependence on monoamine oxidase inhibitors in high dose. *Br J Psychiatry*. 1991; 158: 856-7.

Verkes RJ, Van der Mast RC, Hengeveld MW, et al. Reduction by Paroxetine of Suicidal Behavior in Patients with Repeated Suicide Attempts But Not Major Depression. *Am J Psychiatry.*1998;155(4):543-547.

Weller Jr RA, McKnelly WV. Case report of withdrawal dyskinesia associated with amoxapine. *Am J Psychiatry*. 1983; 140(11): 1515-6.