Antidepressants and suicidal thoughts and behaviour

Pharmacovigilance Working Party

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1. Introduction

The Pharmacovigilance Working Party has on a number of occasions, examined the possible relationship between suicidal behaviours and the use of Selective Serotonin Reuptake Inhibitors (SSRIs) and other antidepressants.

An Article 31 referral, which concluded in June 2005, resulted in warnings concerning the use of these products in the paediatric population being added to all SPCs for SSRIs and other antidepressants.

In October 2005, following discussion of a review of antidepressant clinical trials conducted by MHRA, class wording concerning the risk of suicidal behaviour in adults (including younger adults) was agreed by the PhVWP for section 4.4 of the SPCs of SSRIs and SNRI (Serotonin and noradrenaline reuptake inhibitor) venlafaxine.

In 2005, the Food and Drug Administration (FDA) in the USA began a comprehensive review of individual antidepressant trials that included adult patients with major depressive disorder (MDD) and other psychiatric disorders, in order to examine the risk of suicidality in adults who are prescribed antidepressants.

Based on this review the FDA's Psychopharmacologic Drugs Advisory Committee agreed that labelling changes were required to inform health care professionals about the potential for an increased risk of suicidality in younger adults (aged 18 to 24) using antidepressants during the initial phases of treatment (generally the first one to two months). The committee additionally agreed that the product labelling should remind health care professionals that the disorders themselves, for which treatment is sought, are the most important cause of suicidality and that antidepressants have beneficial effects in older adults.

This paper provides a summary of the FDA analysis and the PhVWP discussion of these data.

2. FDA review

2.1 Introduction and objectives

As part of this review the FDA has considered data from 372 placebo-controlled trials involving almost 100,000 patients, which examined the use of antidepressants in the adult population. The antidepressants included in this review were the SSRIs and related antidepressants – bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazadone, paroxetine, sertraline and venlafaxine.

The primary objective of the review was to estimate the effect of antidepressants drugs versus placebo on suicidal outcomes in adults in double-blind, randomised, placebo-controlled clinical trials.

The secondary objective was to examine the effect of antidepressants drugs versus placebos on suicidal outcomes in adults in double-blind, randomised, placebo-controlled clinical trials for various subgroups defined by subject-level and trial-level characteristics and indication groups.

The number of patients included in this analysis was similar to that included in the UK/EU review, however, the studies that contributed to these figures differed

between the US and the UK review. For example, neither bupropion (authorised as a smoking cessation therapy in the EU, and in 22 MSs of the EU for the indication major depression (twice daily dose Wellbutrin SR and recently as a once daily dose Wellbutrin XR/ Elontril/Magerion/Voxra)) nor nefazadone (no longer marketed in EU) were included in the UK review.

2.2 Methodology including Statistical Analysis

Identification of trials and suicidal outcomes

The requests to the relevant Marketing Authorisation holders (MAHs) provided instructions for:

i) selection of the trials - completed double-blind, randomised, placebo-controlled trials that included at least 20 patients;

ii) identification of suicidal outcomes – events should be limited to those that occurred during the double-blind phase of treatment or within 1 days of stopping randomised treatment; identification of possible suicide-related adverse events (PSRAEs) was based on text strings searches of all preferred terms, all verbatim terms and any comment fields. The identified events were then classified by experts according to the method developed by the Columbia University group for the classification of the paediatric suicidality data. Unlike the classification of the paediatric suicidality data that was done by the Columbia University expert team, the adults classification was done by experts that could be company employed.

The identified PSRAEs were classified into one of 9 categories – category 1 completed suicide, category 2 suicide attempt, category 3 preparatory acts towards imminent suicidal behaviour, category 4 suicidal ideation, category 5 self-injurious behaviour intent unknown, category 6 not enough information (fatal), category 7 self-injurious behaviour no suicidal intent, category 8 other: accident; psychiatric; medical, category 9 not enough information (nonfatal). Note: Events 7 and 8 were not considered as a PSRAE in the assignment of event code.

The FDA review only considered events which were on treatment or occurred within 1 day of stopping treatment; for trials with a taper period the end of the trial was set to the beginning of the taper period.

Primary endpoints

The primary endpoint was the presence of any of the four events: completed suicide, suicide attempt, preparatory acts towards imminent suicidal behaviour, and suicidal ideation. These events were collectively referred to as “Suicidal Behaviour and Ideation”. The endpoint defined by the first three events was referred to as “Suicidal Behaviour” and the endpoint defined by the fourth event was referred to as “Suicidal Ideation”; these were considered as secondary endpoints.

The primary analysis was performed on the Psychiatric indications cumulative indication group, which represents the union of major depressive disorder, other depression disorders, and other psychiatric disorders. A secondary analysis considered other groups of indications.

Statistical Analysis

The primary analysis consisted of estimating the odds ratio for subjects in the active arms versus the subjects in the placebo arms. The analysis was performed across all drugs and trials, but was stratified by individual trials. A stratified estimate allows the

rates of events for individual trials to differ. Therefore, data from trials with differing durations and intensities of events may be combined.

The primary method chosen for estimation of the odds ratio was the “exact method”. The FDA states that this method is valid with low event rates and small number of subjects per trial. The exact method is based on trial-level summaries and assumes that each trial is independent. It makes use of trials that have events in both arms and also those with events in only one arm but not those with no events in either arm. A common odds ratio across the trials of all drugs and also a common odds ratio across the trials or each drug were estimated. Odds ratios for individual trials were estimated using the exact method, as well.

The difference in study exposure between the treatment groups was evaluated. The mean within-trial treatment group difference was -1.1 days, indicating slightly less exposure in the active arm. As such a small mean difference in exposure was observed, the odds ratio was based on subjects and not subject years.

In addition to the common odds ratio estimation, a common risk difference was estimated using a generalization to risk differences of the Mantel-Haenszel odds ratio method. Use of a risk difference approach means that data from all trials including those with no events can be analyzed.

Sub groups based on subject-level (age, gender, race) and trial-level (drug type (SSRI vs Other), trial location (North America vs Other locations) and trial setting (In Patient and combined in- and out-patients vs Out-Patient)) characteristics were analysed. The analysis of the subgroups was performed with the primary indication group (Psychiatric Indications), endpoint (Suicidal Behaviour and Ideation) and analysis method (odds ratio in active vs placebo arms).

The percentage of subjects with any event of completed suicide, attempted suicide, preparatory suicidal acts or suicidal ideation is provided below. The most common events in all indication and treatment groups were suicidal ideation and suicidal attempts. When broken down according to indications group, not surprisingly the events rates were highest in the MDD indication group followed by the Other Psychiatric disorders group. There is no statistically significant difference between the percentage of events in placebo and the active arm for any of the indication groups and within these for any of the PSRAEs.

Table 13: Cumulative Suicidal Behavior and Ideation Events by Indication Group and Treatment Group.

		Treatment Group		
Indication Group	Event	Placebo % (n/N)	Test Drug % (n/N)	Active Control % (n/N)
Depression Indications	Completed suicide	0.01% (1/16591)	0.02% (4/24668)	0.01% (1/8561)
	Completed or attempted suicide	0.20% (33/16591)	0.21% (52/24668)	0.21% (18/8561)
	Suicidal behavior	0.21% (35/16591)	0.22% (54/24668)	0.26% (22/8561)
	Suicidal behavior and ideation	0.80% (132/16591)	0.69% (171/24668)	0.69% (59/8561)
Psychiatric Indications	Completed suicide	0.01% (2/27164)	0.01% (5/39729)	0.01% (1/10489)
	Completed or attempted suicide	0.17% (46/27164)	0.19% (76/39729)	0.18% (19/10489)
	Suicidal behavior	0.18% (49/27164)	0.20% (79/39729)	0.22% (23/10489)
	Suicidal behavior and ideation	0.72% (196/27164)	0.62% (248/39729)	0.62% (65/10489)
Psychiatric and Behavioral Indications	Completed suicide	0.01% (2/32382)	0.01% (5/47873)	0.01% (1/10922)
	Completed or attempted suicide	0.14% (46/32382)	0.16% (77/47873)	0.17% (19/10922)
	Suicidal behavior	0.15% (49/32382)	0.17% (80/47873)	0.21% (23/10922)
	Suicidal behavior and ideation	0.61% (199/32382)	0.53% (254/47873)	0.60% (65/10922)
All Indications	Completed suicide	0.01% (2/35904)	0.01% (5/52960)	0.01% (1/10975)
	Completed or attempted suicide	0.13% (46/35904)	0.15% (77/52960)	0.17% (19/10975)
	Suicidal behavior	0.14% (49/35904)	0.15% (80/52960)	0.21% (23/10975)
	Suicidal behavior and ideation	0.57% (203/35904)	0.49% (260/52960)	0.59% (65/10975)

Table 14: Suicidal Behavior and Ideation Events by Drug (Psychiatric Indications).

		Treatment Group		
Event	Drug	Placebo % (n/N)	Test Drug % (n/N)	Active Control % (n/N)
Suicidal behavior and ideation	Bupropion	0.22% (4/1800)	0.26% (7/2659)	0.45% (4/881)
	Citalopram	0.54% (4/744)	1.04% (20/1928)	0.00% (0/98)
	Duloxetine	1.23% (18/1460)	1.07% (25/2327)	0.36% (3/835)
	Escitalopram	0.14% (3/2189)	0.23% (6/2567)	0.27% (3/1096)
	Fluoxetine	1.86% (53/2857)	1.21% (58/4783)	0.69% (3/434)
	Fluvoxamine	0.71% (13/1828)	1.01% (22/2187)	0.99% (8/805)
	Mirtazapine	0.93% (6/644)	0.79% (8/1016)	0.22% (1/452)
	Nefazodone	0.79% (14/1781)	0.42% (12/2836)	0.68% (4/592)
	Paroxetine	0.49% (28/5763)	0.53% (46/8728)	1.13% (17/1506)
	Sertraline	0.53% (23/4330)	0.29% (15/5234)	0.49% (5/1013)
	Venlafaxine	0.80% (30/3768)	0.53% (29/5464)	0.61% (17/2777)
	All Drugs	0.72% (196/27164)	0.62% (248/39729)	0.62% (65/10489)

Figure 1 shows the odds ratio estimates of the active drug versus placebo for each drug substance and overall for events of suicidal behaviour and ideation using data from clinical trials for the Psychiatric indication (this includes indications of major depressive disorder, other depression disorders, and other psychiatric disorders). The overall odds ratio estimate is less than one. For bupropion, citalopram, escitalopram and fluvoxamine there is a trend towards an increased risk of suicidal behaviour with that for citalopram being most marked but does not reach statistical significance for any of these drugs. A similar pattern is seen when risk differences is examined. There was no evidence for heterogeneity between drugs.

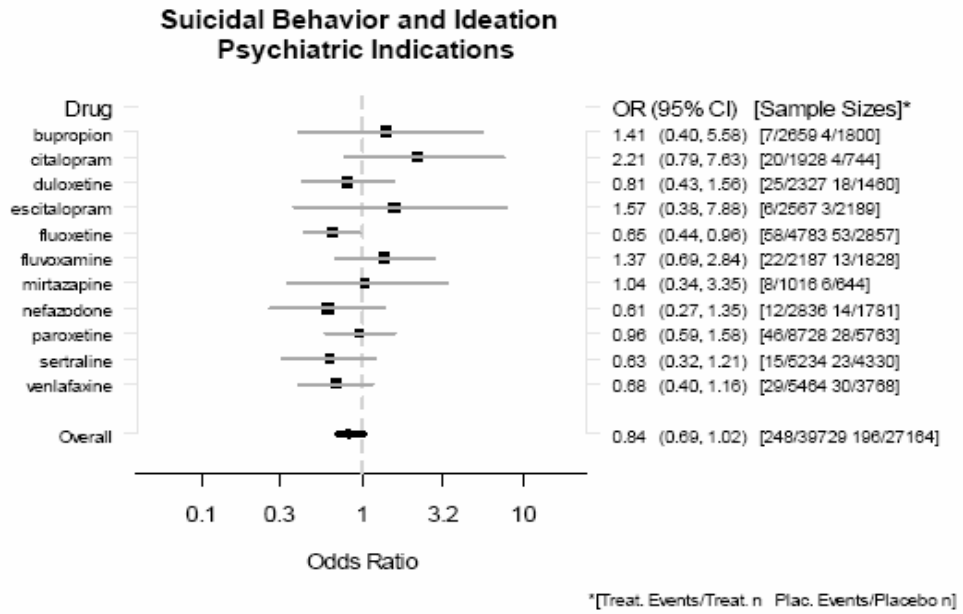

Figure 1: Odds Ratios by Drug for Suicidal Behavior and Ideation (Psychiatric Indications).

Figures 2 and 3 below show the odds ratio estimates of the test drug versus placebo by age group, including paediatric data. These data suggested that in the 18-24 age group there was a trend towards an increased risk of suicidal behaviour and ideation. Of note is that for the 18-24 age group the odds ratio estimate for suicidal behaviour (OR 2.31, 95% CI 1.02 – 5.64) was higher than the estimate for suicidal ideation (OR 1.11, 95%CI 0.55-2.32) and the odds ratio estimate for the former just reached statistical significance. These data were not broken down further according to drug substance.

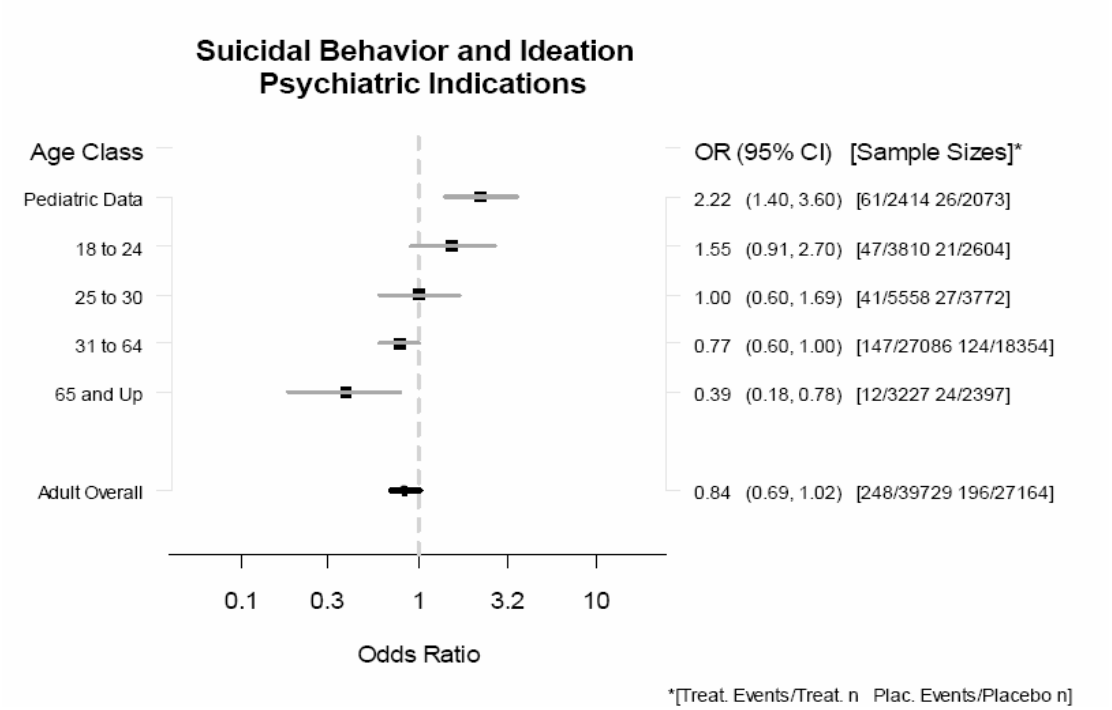

Figure 2: Odds Ratio by Age Group for Suicidal Behaviour and Ideation (Psychiatric Indications)

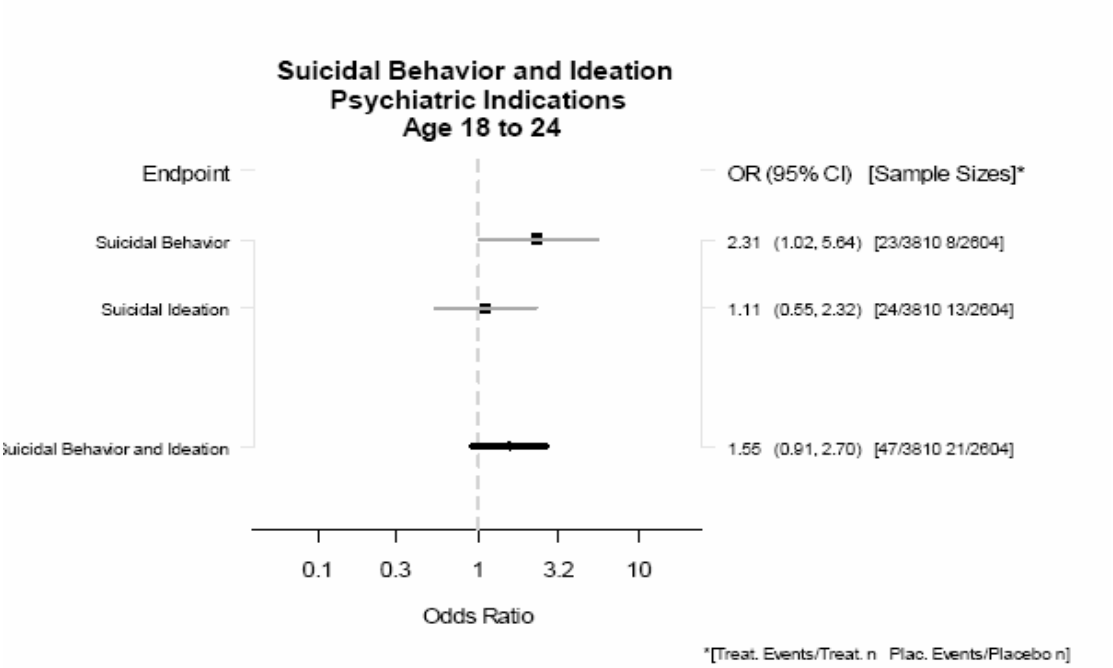

Figure 3: Odds Ratios by outcome for the 18-24 Age Group (Psychiatric indications)

There was no notable difference between the odds ratio for suicidal behaviour and ideation between genders or races.

The FDA also examined the risk of suicidality by drug class for subjects under age 25. The results are presented in Figures 4 and 5 below. For all drug classes there appear to be a trend towards an increased risk, which appeared slightly more marked for all drug classes when suicidal behaviour alone is examined.

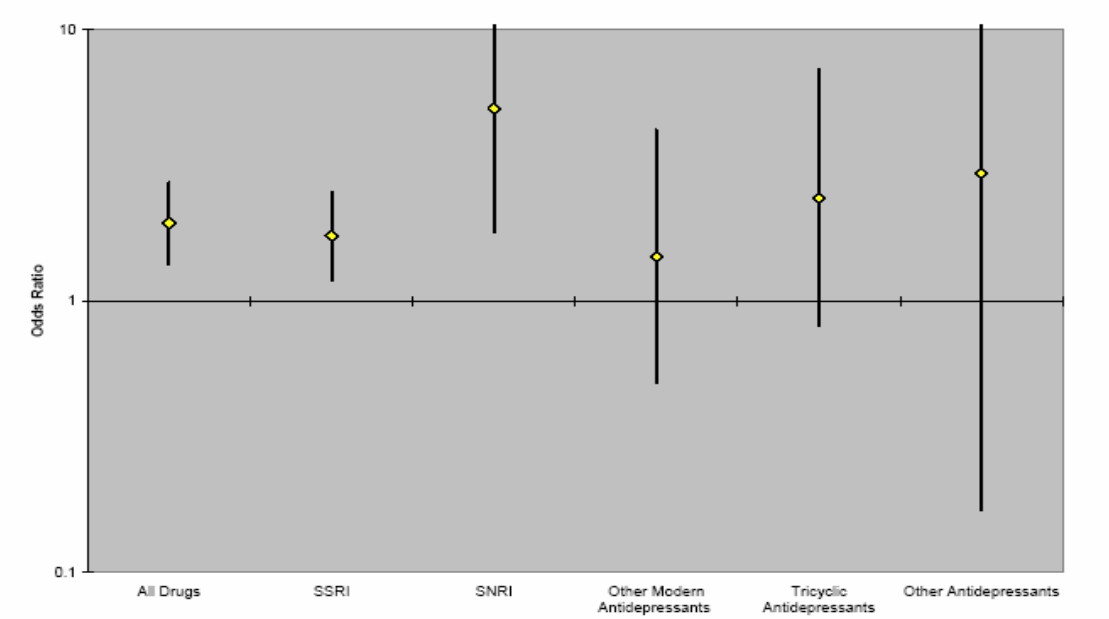

Figure 4: Suicidality Odds Ratio for Active Drug relative to Placebo – Ideation or Worse- Subjects under age 25 with Psychiatric Disorders – by Drug Class

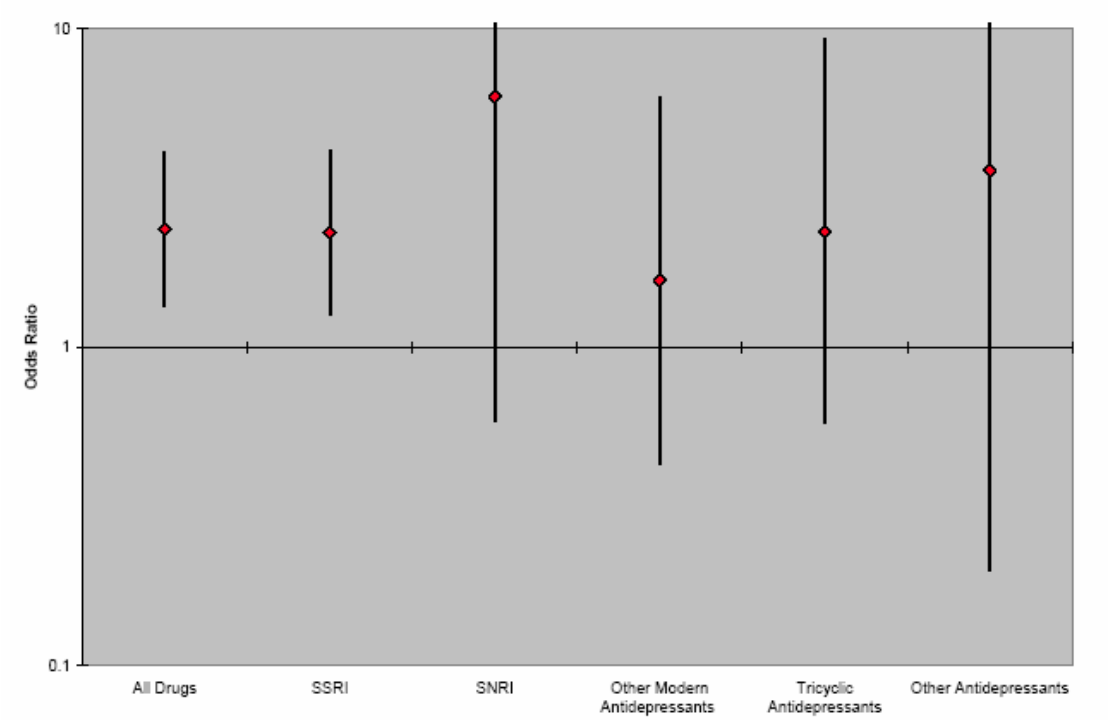

Figure 5: Suicidal behaviour Risk for Active Drug relative to Placebo – Preparation or Worse- Subjects under age 25 with Psychiatric Disorders – By Drug Class

Generally the findings of the FDA review were similar to that of the UK/EU review in that the available data did not suggest overall that treatment with the SSRIs and

related antidepressants was associated with an increased risk of suicidal behaviour and ideation but that there was a trend towards an increased risk of suicidal behaviour and ideation in the younger age groups.

2.4 FDA Conclusions

The FDA concluded that overall there was no evidence to support that use of SSRIs and related antidepressants in patients with MDD or other psychiatric disorders leads to an increased risk of suicidal behaviour and ideation. This was based on the odds ratio estimate of suicidal behaviour and ideation of 0.84 (95% CI 0.69-1.02) for the active group versus the placebo group and a risk difference of -0.001 (95% CI -0.002 to 0.000).

The FDA concluded that there appeared to be an age effect in the results of their analysis. Younger age groups had higher odds ratio estimates than older age groups. The youngest age group considered (18-24 age group) had an odds ratio estimate of 1.55 (95% CI: 0.91, 2.70). They also comment that the magnitude of increase in risk approaches that seen in the paediatric population. Other subgroups based on gender, race, trial location or treatment setting did not show notable differences in the odds ratio estimates.

With regard to any differences among drugs, the FDA did not consider that there was any marked difference between the drugs.

The conclusions from the FDA Psychopharmacological Drug Advisory Committee (PDAC) meeting of December 2006 included agreement that the analyses presented were sufficient to draw conclusions and make recommendations. The PDAC unanimously agreed with the following FDA conclusions:

- The previous finding of increased short-term risk for suicidality with antidepressant treatment in paediatric patients appears to extend into younger adults (up to age 25).
- Beyond age 30, antidepressants begin to show a protective effect for suicidality, and this is most pronounced beyond age 65.

The PDAC voted 6:2 to include the above concepts as an extension to the existing black box warning and also advised that labelling needs to address the 25-30 age group. The PDAC stressed the need for balanced labelling that conveyed the benefit of antidepressant treatment, the potential risk of untreated depression, and did not discourage patients from seeking treatment.

The wording developed for the product labelling by the FDA on the basis of this advice is at Annex 1.

3.0 Conclusions and recommendations

Overall the conclusions reached by the FDA in its review were consistent with that of the UK/EU review. Both reviews concluded that young adults may be at an increased risk of suicidal behaviour when treated with antidepressants. The FDA discussions on an explanatory hypothesis highlighted that even in older adults the possibility that in SSRIs may increase risk of suicidal behaviour cannot be ruled out.

The FDA review also provided evidence to suggest that there is no substantial real difference in risk of suicidal thoughts/behaviour across classes or types of antidepressant. In particular the analysis of the available data that examined the risk in young adults supported the possibility of an increased risk of suicidal thoughts/behaviour for young adults with all antidepressant classes.

The PhVWP considered these data and concluded that the EU class wording in summaries of product characteristics for SSRIs and other antidepressants which was agreed in 2005 should be updated to more fully reflect current evidence regarding potential risk for suicidal behaviours with antidepressants. The PhVWP also concluded that the agreed class wording should be applied to all antidepressants. Patient information leaflets should be updated to provide more comprehensive and helpful information for patients taking these medicines. The agreed wording for summaries of product characteristics and patient information leaflets is provided at Annex 2.

Annex 1

Revisions to Product Labeling

[These changes should be made to the box warning at the beginning of the package insert.]

DRUG NAME

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Insert established name] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Insert Drug Name] is not approved for use in pediatric patients. [The previous sentence would be replaced with the sentence, below, for the following drugs: Prozac: Prozac is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD). Zoloft: Zoloft is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). Fluvoxamine: Fluvoxamine is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD).] (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

[The following changes should be made to the current language under the **WARNINGS-Clinical Worsening and Suicide Risk** section.]

WARNINGS-Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs

(SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children,adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table [add table number].

Table [add table number]	
Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Drug-Related Increases
<18	14 additional cases
18-24	5 additional cases
	Drug-Related Decreases
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hosti aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and ma have been reported in adult and pediatric patients being treated with antidepressants major depressive disorder as well as for other indications, both psychiatric nonpsychiatric. Although a causal link between the emergence of such symptoms either the worsening of depression and/or the emergence of suicidal impulses has been established, there is concern that such symptoms may represent precursor emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including poss discontinuing the medication, in patients whose depression is persistently worse, or are experiencing emergent suicidality or symptoms that might be precursors to worse depression or suicidality, especially if these symptoms are severe, abrupt in onset were not part of the patient's presenting symptoms.

[The labeling for the following drugs with discontinuation language would include next paragraph: Celexa, Cymbalta, Effexor, Fluvoxamine, Lexapro, Paxil, Pex Prozac, Sarafem, Symbyax, and Zoloft.]

If the decision has been made to discontinue treatment, medication should be taperec rapidly as is feasible, but with recognition that abrupt discontinuation can be associ with certain symptoms (see PRECAUTIONS and DOSAGE A ADMINISTRATION—Discontinuation of Treatment with [Insert established name]. a description of the risks of discontinuation of [Insert established name]).

Families and caregivers of patients being treated with antidepressants for ma depressive disorder or other indications, both psychiatric and nonpsychiat should be alerted about the need to monitor patients for the emergence of agitat irritability, unusual changes in behavior, and the other symptoms described ab as well as the emergence of suicidality, and to report such symptoms immediatel health care providers. Such monitoring should include daily observation by fam and caregivers. Prescriptions for [Insert Drug Name] should be written for the sma quantity of tablets consistent with good patient management, in order to reduce the ris overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be initial presentation of bipolar disorder. It is generally believed (though not establishe controlled trials) that treating such an episode with an antidepressant alone may incr the likelihood of precipitation of a mixed/manic episode in patients at risk for bip disorder. Whether any of the symptoms described above represent such a conversio unknown. However, prior to initiating treatment with an antidepressant, patients depressive symptoms should be adequately screened to determine if they are at risk bipolar disorder; such screening should include a detailed psychiatric history, includi family history of suicide, bipolar disorder, and depression. It should be noted that [In Drug Name] is not approved for use in treating bipolar depression. [The prev sentence would be replaced for the following drugs: Seroquel: It should be noted

Annex 2

PhVWP core SPC wording for all antidepressants

SUICIDAL THOUGHTS/BEHAVIOUR

I Section 4.4 - Special Warnings and Special Precautions for Use

Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which <name of antidepressant> is prescribed can also be associated with an increased risk of suicide-related events. 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. ***[Please note: This paragraph only needs to be included in the SPCs for medicinal products which have additional indications to a depression indication]***

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Section 4.8
Where reports of suicidal thoughts or behaviour have been reported with a particular product, this should be reflected in section 4.8

Where a table of adverse drug reactions (ADRs) is included in this section, suicidal ideation and suicidal behaviour should be included in this table – frequency not known and include the following as a footnote:

“Cases of suicidal ideation and suicidal behaviours have been reported during <*drug substance*> therapy or early after treatment discontinuation (see section 4.4).”

Where no table of ADRs is included the above text should be inserted in this section.

Revised wording for the Patient Information Leaflet

Thoughts of suicide and worsening of your depression or anxiety disorder

If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.

You may be more likely to think like this:

- If you have previously had thoughts about killing or harming yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, **contact your doctor or go to a hospital straight away.**

You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.