

CSM/SSRIsWG/04/9th MEETING

COMMITTEE ON SAFETY OF MEDICINES

EXPERT GROUP ON SAFETY OF SSRIs

MINUTES OF THE MEETING OF THE CSM EXPERT GROUP ON THE SAFETY OF SSRIS HELD ON FRIDAY 27 FEBRUARY 2004 AT 10AM IN CR1 AT MARKET TOWERS.

Members Present

Professor Ian Weller (Chairman)	Professor of Genitourinary Medicine & Head of Department of Sexually Transmitted Diseases, Royal Free & University College London Medical School
Professor Deborah Ashby	Professor of Medical Statistics, Queen Mary, University of London
Mr Richard Brook	Chief Executive of Mind
Dr Jonathan Chick	Consultant Psychiatrist, Alcohol Problems Service, Royal Edinburgh Hospital & part time Senior Lecturer at Edinburgh University
Professor Klaus Ebmeier	Professor of Psychiatry, University of Edinburgh
Professor David Gunnell	Professor of Epidemiology, Department of Social Medicine, Bristol University
Dr Elizabeta Mukaetova-Ladinska	Consultant Psychiatrist Newcastle General Hospital & Senior Lecturer in Old Age Psychiatry, Newcastle University
Dr Ross Taylor	Senior Lecturer in General Practice, University of Aberdeen & General Medical Practitioner Principal, Grampian Health Board

Professional staff of MHRA

Dr June Raine	Director, Post Licensing Division
Ms Sarah Wark	Unit Manager, Pharmacovigilance Group
Dr Julia Dunne	Specialist in Paediatrics, Pharmacovigilance Group
Dr Simon Day	Statistics Unit Manager, Licensing Division
Dr David Brown	Statistician, Licensing Division
Dr Julie Williams	Scientific Assessor, Pharmacovigilance Group
Dr Lesley Wise	Statistician/Epidemiologist, Pharmacovigilance Group
Dr Frances Rotblat	CPMP Delegate, Post Licensing Division
Ms Claire Davies	Scientific Assessor, Pharmacovigilance Group
Dr Carlos Martinez	Head of Research, GPRD

Others

Dr Karen Facey	Consultant
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Observers

Dr Jane Moseley	Pharmacoepidemiology Team Leader, Pharmacovigilance Group
Dr Camilla Parikh	Medical Assessor, Pharmacovigilance Group
Dr Martina Riegl	Medical Assessor, Post-Licensing Division

1.0 INTRODUCTION

- 1.1 The Chairman welcomed members of the Group and thanked them for coming to the meeting.
- 1.2 The Chairman introduced Dr Karen Facey to the meeting and explained that she is an external consultant statistician contracted to MHRA who is reviewing the paroxetine clinical trial data submitted to the MHRA by GSK.
- 1.3 The Chairman informed members that the issues considered by the Expert Working Group are confidential and that members should not speak directly to the press but should refer any enquiries to the Chairman, MHRA or Press Office. At scientific meetings, they should take care not to give the impression that they speak on behalf of the Group.

2.0 APOLOGIES AND ANNOUNCEMENTS

- 2.1 Apologies were received from Drs York and Zwi.

3.0 MINUTES OF MEETING OF 25 NOVEMBER

- 3.1 The Group was informed that the minutes of the meeting on 30 January 2004 would be circulated following the meeting and that any written comments should in the first instance be provided to the secretariat and these minutes would be formally agreed at the meeting on 31 March 2004.

4.0 DECLARATION OF INTERESTS

- 4.1 The Group confirmed that their interests were as declared at the meeting of 30 January 2004.

5.0 PAPERS

5.1 GPRD study

- 5.1.1 The Group was reminded that during the presentation on this study at the meeting on 30 January 2004, the Group raised a number of points for clarification. In order to address these comments further analysis is required and the following work is ongoing
 - Validating cause of death for documented suicides and establishing cause of death for those with no documented cause, from death certification information from the Office for National Statistics;
 - Ensuring that events that occur on the day of first prescription (i.e. indication for treatment) are not included as outcome events;
 - Establishing the level of evidence for heterogeneity between groups.

- 5.1.2 The Group was informed that the preliminary data have not shown anything that would change current prescribing advice.
- 5.1.3 The epidemiology and statistical experts of the Group who have been closely involved in advising on the study design and methods of analysis commented that this is a necessary delay to ensure confidence in the validity of the results obtained.
- 5.1.4 The Group noted this information.

5.2 Paroxetine referral – Assessment of MAH’s response to the list of outstanding issues

- 5.2.1 The Group was reminded that as a result the Article 31 referral for paroxetine, initiated by the UK, the Marketing Authorisation holder (MAH) for paroxetine has been asked to respond to a list of questions regarding the safety and efficacy of paroxetine. The assessment on the initial submissions from the MAHs was considered by the CPMP at its meeting in November 2003. At this meeting a list of outstanding issues to be addressed by the MAH was adopted. The key concerns of the UK relating to the dose, safety in the paediatric population and the risk of suicidal behaviour and self-harm, and withdrawal reactions were included. The Group was informed that the MAHs have now responded to the list of outstanding issues and the paper before the Group assessed this response.

Suicide, suicidal thoughts and self-harm

- 5.2.2 The Group was informed that the MAH has conducted further analysis of their clinical trials data to examine:
 - i) the risk of suicidal behaviour in the first two and four weeks of treatment;
 - ii) the risk according to baseline suicidal risk on study entry;
 - iii) the risk according to previous paroxetine or other SSRI exposure;
 - iv) and to provide a stratified analysis by dose.
- 5.2.3 The Group considered that these additional analyses did not suggest that there was an increased risk of suicide, suicidal thoughts and self-harm in older adults treated with paroxetine, but raised concern about the possibility of an increased risk in young adults. The Group expressed concern that reports of suicide and suicidal thoughts had been combined as suicide-related events and that these should be analysed separately as suicide, suicidal thoughts and self-harm.
- 5.2.4 The Group commented that this was contrary to the data from clinical trials where paroxetine was compared with an active comparator. In these studies the incidence of suicide-related events in young adults treated with paroxetine was lower than that in the active comparator group, but this was not sufficiently reassuring given that this may indicate that the problem may be

worse with other active comparators. The Group commented that it would be important to obtain data on efficacy of paroxetine in young adults.

- 5.2.5 The Group advised, that overall, these additional data did not rule out the possibility that there may be an increased risk in younger adults (i.e. less than 30 years of age) and that this should be reflected in the product information.
- 5.2.6 The Group was reminded that in the original submission provided by the MAH some studies had been excluded from the analyses and therefore the MAH was asked to provide information on these studies and the number of patients involved. The studies which the MAH excluded from their analysis of clinical trials are those not included in the central research and development aggregated database. This comprises 22 studies involving 3740 patients. Almost one half of these studies (10 studies involving 1706 patients) were those which were performed for the Japanese development programme.
- 5.2.7 The Group advised that the MAH should be requested to provide a summary of the safety data from these studies, particularly the data relating to suicide, suicidal thoughts and self-harm. Information on the type of trial, duration of the studies, age of patients included and the inclusion and exclusion criteria with respect to suicide should also be provided.

Withdrawal reactions

- 5.2.8 The Group was informed that the MAH had been asked to provide further information on the severity of withdrawal reactions, the type of corrective therapy administered and whether tapering took place. Furthermore, in the original submission, the MAH conducted a review of these clinical trial data to examine possible risk factors for withdrawal reactions. In this analysis the MAH decided to exclude events that were possibly confounded by concomitant psychotropic medication and events of emotional lability occurring after treatment was stopped. As requested, the MAH has repeated this analysis including these events. The MAH has also as requested examined the possibility that there may be an increased risk of withdrawal in patients treated for anxiety disorders and following longer duration of treatment, which had been suggested from the initial analyses.
- 5.2.10 The Group considered that the additional data provided and the further analyses conducted did not raise any new concerns about the nature or incidence of withdrawal reactions that occur on stopping paroxetine.
- 5.2.11 With regard to the additional analyses of risk factors and examination of the effect of duration of treatment, indication and responder status, the Group commented that due to the confounding between study duration and indication these additional analyses do not allow firm conclusions to be drawn from these data. The Group advised that further studies were needed in this respect, however, whilst these studies were being conducted the product information should be amended to reflect the available data which suggests that patients treated for anxiety disorders and those treated for a longer duration may

potentially be at an increased risk of withdrawal reaction on stopping paroxetine.

Risk:Benefit in the paediatric population

5.2.12 The Group was informed that as requested, the MAH has provided further information and further analyses of paediatric clinical trial data. This included i) a stratified analysis by age band, ii) examination of whether increase in suicidality is coupled with deterioration of other symptoms of depression, iii) incidence of suicide-related events according to whether they occurred on treatment or during the taper or follow-up phase, iv) information on nature and severity of the suicide-related events and v) a sub-group analysis according to pubertal status.

5.2.13 The Group advised that these additional analyses do not alter its previous conclusion that the balance of risks and benefits in children and adolescents for the treatment of major depressive disorder is negative and that use should remain contraindicated in this population.

Risk:Benefit of doses above 20mg

5.2.14 The Group was informed that as requested the MAH has provided a justification for the use of paroxetine at doses above 20mg for each of the indications and discussion of the balance of risks and benefits of paroxetine at these doses.

5.2.15 The Group advised that these data support the following dosage recommendations

- OCD – recommended dose of 40mg with titration as necessary up to 60mg;
- Panic disorder – recommended dose of 40mg. Titration above this dose is not supported by the data;
- Depression, SAD, GAD and PTSD – recommended dose of 20mg. Titration above this dose is not supported by the data.

and that the SPCs for the 20mg and 30mg tablet formulations and the oral suspension should be amended accordingly.

5.2.16 The Group expressed concern that the lack of additional efficacy above 20mg in the depression, SAD, GAD and PTSD indications had not been identified in the original applications submitted to the MHRA. The Group considered that this raised concerns about the initial assessment of these applications and commented that this may have implications for the dosage recommendations for other older licensed medicines and that this issue should be considered by the secretariat.

5.2.17 The Group considered whether there was an increase in adverse events with increasing dose. The Group considered that there were data in the dose finding

studies to suggest an increase in the more common adverse events as dose increased, however these studies were not sufficiently large to identify rare adverse events such as suicidal behaviour.

Risk:Benefit in the elderly population

5.2.18 The Group was informed that in order to review the balance of risks and benefits of paroxetine in patients over the age of 65 years the MAH has analysed data from placebo-controlled and active comparator- controlled clinical trials.

5.2.19 The Group noted that paroxetine has moderate efficacy in the treatment of depression in patients over the age of 65 years. Whilst it was considered that the overall risk and benefits analysis was positive in favour of paroxetine, the Group highlighted a number of potential concerns. These were regarding the anticholinergic adverse effects of paroxetine; co-morbidity (hypertension, hypothyroidism) and an apparent increase in anticholinergic adverse events associated with paroxetine; and the issue of gastro-intestinal bleeding with paroxetine and other SSRIs which was not discussed in the MAHs report. It was also commented that elderly patients with dementia may be more likely to develop anticholinergic adverse events although this was not presented in the MAHs report. It was agreed that these were important areas that should be further investigated by the MAH

Proposals for risk reduction measures and SPC changes

5.2.20 The Group considered the MAH's proposals for risk reduction measures and SPC and advised that:

- The MAH should be requested to introduce a scored 10mg tablet formulation;
- Educational material should be prepared for prescribers and patients to ensure that they are fully aware of the need for gradual dose titration upon withdrawal from paroxetine;
- A warning about the risk of akathisia and its presenting signs should be added to section 4.4 of the SPC together with advice that in the event of the patients developing akathisia increasing the dose is unhelpful ;
- A warning about the possibility of an increased risk of suicidal thoughts and self-harm in young adults (less than 30 years of age) should be added to section 4.4 of the SPC;
- The warnings about the risk of withdrawal reactions should reflect the incidence of these reactions and that they may occur more frequently in association with paroxetine than with other SSRIs and in patients who are treated for anxiety disorders and those treated for a longer duration.

Public Health Implication of revised dosage recommendations

5.2.21 The Group discussed the public health implications of the revised dosage recommendations and whether there was a need for urgent communication. The majority of the Group advised that revision of the current dosage recommendations was an important public health issue, but did not consider that the need for communication on this issue was so urgent that it would warrant pre-empting the ongoing European referral process. The Group felt that EU consensus would be the ideal as inconsistent messages and disagreement among regulators would cause confusion. It was agreed that it was also important to have a comprehensive communication strategy. The Group would reconsider the need for communication at its March meeting following consideration by CSM on 10 March 2004 and following the CPMP consideration on 24 March 2004.

5.2.22 Mr Brook did not agree with the majority decision. He considered that the proposal for revised dosage recommendation was an important issue and that this information should be placed in the public domain promptly as he believed that a significant number of patients were currently receiving inappropriate doses. He also expressed concern that if CPMP did not agree to the revised dosage recommendations that this would limit the regulatory action that could be taken in the UK.

6. CURRENT LITERATURE

6.1 The Group was provided with a recently published paper entitled 'Antidepressants and public health in Iceland'.

6.2 The Group noted the findings of this study that increasing prescribing rates of antidepressants, including SSRIs in Iceland have had no impact on national suicide rates. The Group commented that the bulk of the published literature suggest that increasing prescribing of antidepressants are associated with a decrease in national suicide rates.

7.0 ORAL UPDATES

7.1 Feedback from FDA public health advisory panel

7.1.1 The Group was provided with a news article from the British Medical Journal which gave an overview of the proceedings at the FDA public health advisory meeting to discuss the safety of antidepressants in treatment of childhood depression. The Group noted this information.

7.2 CPMP adoption of report of Ad Hoc Expert meeting with Child Psychiatrists

- 7.2.1 The Group was provided with the report of the European Ad Hoc Expert meeting with child psychiatrists that was adopted at the February CPMP meeting. The Group noted this information.

8.0 UPDATED WORKPLAN

- 8.1 The Group was provided with an update of the proposed plan for completion of the work of the Group. The proposed workplan outlined the main bodies of work completed to date and those still to be completed, identifying where there is a potential for further interim advice from the Group or release of a report from the Group on a specific portion of work.
- 8.2 With regard to the paediatric use of SSRIs the Group was informed that the immediate regulatory action has taken place, although feedback from the Group and from external professionals has indicated that further details of the consideration by the Group and the interpretation of the advice would be useful. It is therefore proposed that a detailed report of this work be prepared for consideration by the Group at the March meeting.
- 8.3 The Group was informed that the next key body of work for completion will be the evaluation of the risks and benefits of paroxetine. The Group was informed that its recommendation will be considered by CSM on 10 March 2004 and its advice and the advice of CSM will inform the UK position at the March CPMP meeting where this issue is scheduled for further discussion.
- 8.4 With regard to the ongoing GPRD study the Group was informed that the results will be discussed as soon as they are available and that the final reports would be released as soon as any regulatory implications of the results have been determined and implemented.
- 8.5 In relation to the adult data for the other SSRIs, the Group was informed that the key questions raised by the paroxetine evaluation and the GPRD study in relation to the risks and benefits in adults will be posed to the Marketing Authorisation holders (MAHs) for other SSRIs. A draft list of questions was provided as a tabled paper and the Group was asked to feedback any comments they may have on this draft list to the secretariat following the meeting. The relevant MAHs will then be asked to respond to these questions by the end of March 2004, which will allow consideration of the data in May 2004.
- 8.6 The Group noted this information and questioned whether the final report of the Group would be available, as has previously been stated publicly, in Summer 2004 and whether the focus of this report would be paroxetine or all SSRIs. The Group was informed that the deadline for completion of the report to which the secretariat is working is Summer 2004 and that this report will consider the safety of all SSRIs.

9.0 ANY OTHER BUSINESS

- 9.1 The Chairman informed the Group of a meeting with representatives of the group developing the NICE guideline on the identification and management of depression children that he and members of the secretariat had attended. The Group noted this information and that one of the members of the NICE group had been asked to attend the Group's next meeting to present their findings.
- 9.2 The Chairman informed the Group that the next meeting would be held at 10am on 31 March 2004.

MHRA
March 2004