

CSM/SSRIsWG/04/8th 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 30 JANUARY 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
Professor Mary Chambers	Professor of Mental Health, University of Ulster
Professor Colin Drummond	Professor of Addiction Psychiatry, St George's Hospital Medical School, London
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
Dr Ann York	Consultant & Honoray Senior Lecturer in Child & Adolescent Psychiatry, Child & Family Consultation Centre, Richmond Hospital
Dr Morris Zwi	Consultant Child & Adolescent Psychiatrist, South West London & St George's Mental Health NHS Trust

Professional staff of MHRA

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

Department of Health

Observers

Dr Jane Moseley	Pharmacoepidemiology Team Leader, Pharmacovigilance Group
Dr Jan Petracek	Head of Pharmacovigilance, Czech Regulatory Authority

1.0 INTRODUCTION

- 1.1 The Chairman welcomed members of the Group and thanked them for coming to the meeting
- 1.2 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. APOLOGIES AND ANNOUNCEMENTS

- 2.1 Apologies were received from Dr Chick.

3. MINUTES OF MEETING OF 25 NOVEMBER

- 3.1 The minutes of meeting on 25 November 2003 were agreed as a correct record, subject to amendment to accurately reflect Dr Mukaetova-Ladinska's professional address and to amend typographical errors in section 5.2.2.

4. DECLARATION OF INTERESTS

- 4.1 The Group confirmed that their interests were as declared at the meeting of 25 November 2003.

5. MATTERS ARISING

5.1 Study designs for fluoxetine and paroxetine in trials for children and adolescents

- 5.1.1 The Group was reminded of its consideration of a paper comparing the study designs for the fluoxetine and paroxetine trials in children and adolescents of at the meeting of 25 November 2003. Having reviewed this paper, the Group recommended that further examination of these data, particularly regarding severity of depression and the concomitant use of diazepam during these studies, should be conducted and that this exercise should be repeated for the other SSRIs
- 5.1.2 The Group was informed that letters have been sent to the relevant Marketing Authorisation holders to request the additional information. With regard to the severity of depression, upon review of the data it is apparent that there is a common endpoint in three of the five trials and that the values are not markedly different. There is limited concomitant use of diazepam in these studies.

5.1.3 The Group noted this information.

5.2 Pharmacology of the SSRIs

5.2.1 The Chairman informed the Group that the secretariat has contacted Professor Pirmohamed to ask him to include the additional information agreed at the meeting on 25 November 2003 to his report on the pharmacology of SSRIs.

5.2.2 The Group commented that mirtazapine should also be added to this report.

5.3 Fluoxetine – feedback from CSM

5.3.1 The Group was provided with feedback on the progress following the consideration by CSM of the assessment of the safety and efficacy of fluoxetine in the paediatric population

5.3.2 The Group noted this information.

6.0 PAPERS

6.1 Update on paediatric use of SSRIs & feedback from European Ad Hoc Expert meeting of child psychiatrists

6.1.1 The Group was informed that a meeting of a European Ad Hoc Expert meeting of child psychiatrists had been held on 14 January 2004 and that this meeting had been attended by members of the secretariat and Drs York and Zwi. The report of the European Ad Hoc Expert meeting of child psychiatrists would be considered at the February CPMP meeting and that this report would be provided to members of the Group at its next meeting.

6.1.2 With regard to the use of paroxetine in children and adolescents, the key conclusions of the European Group were that:

i) the difference in general safety profile of paroxetine in the paediatric and adult population may reflect that children are more susceptible to side effects compared with adults;

ii) it was unlikely that paroxetine and fluoxetine were different in terms of efficacy and that these findings may be due to chance or may reflect limitations of the studies;

iii) the addition of warnings in the product information about the increased risk of suicidal thoughts and self-harm in children and adolescents treated with paroxetine for MDD rather than a contraindication was considered appropriate;

- 6.1.3 The Group was informed that there appeared to differing definitions of what is meant by contraindications across Member States and it was agreed that further consideration of the definition of this term may be required.
- 6.1.4 The Group expressed concern that this European Group had not considered all the available data and questioned whether a class referral of all SSRIs was necessary to ensure that all available data were considered at a European level. The Group was informed that the European group had considered all the available data with respect to paroxetine and had been provided with a copy of the UK's assessment report considered at the Group's October meeting. With regard to the other SSRIs the need for a formal referral to CPMP for the whole class was being kept under close review.
- 6.1.5 The Group was also provided with a copy of a letter from Professor Sue Bailey, Chair of the Faculty of Child & Adolescent Psychiatry, expressing her and her colleagues' comments, queries and concerns about the recent CSM recommendations about the use of SSRIs in children and adolescents under 18 years of age. The Group was informed that a meeting between Professors Bailey and Weller and members of the secretariat has been organised to discuss these issues and that it would be helpful if Drs York and Zwi were willing to attend this meeting.

6.2 Proposal for evaluation of fluoxetine clinical trial data submitted by Dr Healy

- 6.2.1 The Group was reminded that during Dr Healy's presentation at the June meeting and in subsequent correspondence with the Chairman he has mentioned data from fluoxetine clinical trials that he has access to, which illustrate his concerns about:
- i) Miscoding of suicidal acts as failure to respond to treatment rather than adverse effects;
 - ii) Miscoding of suicidal act as emotional lability;
 - iii) Discontinuation of patients from studies for primary adverse effects such as nausea when in fact there has been a suicidal act;
 - iv) Investigators being permitted to lower the dose of treatment at signs of agitation;
 - v) Failure to follow-up patients who dropped out of the studies.
- 6.2.2 The Group was informed that Dr Healy has now submitted these clinical trial data to the MHRA. The data comprise a total of 362 patient records from 6 studies involving fluoxetine conducted by Eli Lilly.
- 6.2.3 The Group was informed of a proposal to enter the key information includes treatment administered, HAM-D data and selected information from the self-report questionnaires into an Excel spreadsheet. It is anticipated that extraction of this information will allow trends over time to be investigated and will also enable us to evaluate the evidence in support of Dr Healy's concerns, though it is unlikely that statistical analyses of these data will be possible.

- 6.2.4 The Group endorsed this proposal, but recommended that additional information including the duration of treatment rather than visit number should be extracted from these reports and that these data should be examined to determine whether the issues Dr Healy has raised occur more frequently on fluoxetine compared with placebo. It was also recommended that further information on the protocols of these studies and clarification on how Dr Healy considers these data will inform the ongoing work of the Group should be sought.

6.3 SSRI and Suicidal behaviour – Update of evidence

- 6.3.1 The Group considered an updated assessment of spontaneous reporting data and the published literature concerning SRIs and suicide, aggression and akathisia.
- 6.3.2 The Group commented that it would be helpful if ‘suicidal ideation’ is distinguished from ‘suicidal behaviour/acts’ in the analyses of spontaneous data. It was commented that a small number of cases of suicide associated with the SRIs could be drug related although the group recognised the limitations of the spontaneous data and published literature presented in determining causality.
- 6.3.3 Additional published literature articles of relevance that were not included in the report were suggested and it was agreed that members of the Group should inform the secretariat of any other articles which they consider should be included in this review. The Group advised that further analyses of the spontaneous data at this time would not provide any further information of value.
- 6.3.4 It was noted that the paper is to form part of the Expert Working Group’s final report.

6.4 GPRD Study

- 6.4.1 The Group was presented with an overview of the progress and analysis to date of the GPRD study. The Group was informed that to be confident about the results of this study it is crucial that its design and analysis control appropriately for age, sex and duration of illness.
- 6.4.2 The Group expressed concern that all cases of suicide may not be included, i.e. if the patient goes to Accident & Emergency and GP is not made aware of this by hospital doctor. It was explained that as well as information entered in key fields by the GP the free text areas of the database are also searched and this should enable identification of hospital discharge letters.
- 6.4.3 The Group commented that there was an obvious peak in suicidal thoughts in 10 year old girls. It was explained that this peak represented a single case and

that due to the small numbers within different age bands this should be interpreted with caution.

- 6.4.4 The Group questioned what criteria were used to determine severity of depression and the validity of this diagnosis. It was explained that diagnoses are entered into GPRD as Read codes, therefore the severity of depression will not be according to DSM criteria. However, this study will represent general practice use and that the number and type of antidepressants used may act as a marker for severity of depression.
- 6.4.5 The Group questioned the power of the study given that only 100 cases of suicide had been identified and whether new episodes in patients with a previous history should be included. It was agreed that it was inadvisable to expand the study to include this group as this may result in important information about the risk of suicide being overlooked and that endpoints of non-fatal self-harm also being examined.
- 6.4.6 The Group commented that it would be important to obtain information on what proportion of patients in GPRD that have ever been prescribed any SSRI are included in the study.
- 6.4.7 The Group was informed that the aim was to provide the results of this study at the meeting on 27th February.

6.5 Evaluation of the safety and efficacy of mirtazapine in children and adolescents

- 6.5.1 The Group considered an evaluation of the safety and efficacy of mirtazapine in children and adolescents. The Group was informed that a trial which contains two separately analysed placebo-controlled studies do not support the efficacy of mirtazapine in major depressive disorder (MDD). There is no evidence of an increased risk of suicide-related events in the paediatric population receiving mirtazapine compared with placebo.
- 6.5.2 The Group advised that based on the available data:
 - (i) there is no evidence of an increased risk of suicidal thoughts and suicidal behaviour in children and adolescents treated with mirtazapine for MDD;
 - (ii) the SPC should be amended to include statements about the clinical trials which have failed to demonstrate the efficacy of mirtazapine in the management of MDD in children and adolescents, and that the safety and efficacy of mirtazapine in paediatric depression cannot be extrapolated from adult data .

6.6 NICE – Depression guideline – 2nd draft consultation

- 6.6.1 The Group was provided with the chapters of further draft of the NICE guideline on the management of depression in primary and secondary care, which relate to pharmacological interventions in the management of depression. The Group was informed that this guideline is now in the 2nd phase of the consultation process and NICE has asked that any comments on this revised draft be provided by close of business on 30 January 2004.
- 6.6.2 The Group commented that the NICE guideline refers to discontinuation reactions whereas the Group defines these as withdrawal reactions and that ideally common terminology should be employed.
- 6.6.3 The Group also recommended that further information should be sought from NICE on:
- i) why children and adolescents are specifically mentioned in the section on withdrawal and not anywhere else in these chapters;
 - ii) what is the evidence base for the use on benzodiazepines in the treatment of side effects occurring on withdrawal;
 - iii) its view on combination therapy.

7 CURRENT LITERATURE

- 7.1 The Group was provided with a recently published paper entitled ‘Antidepressant-related deaths and antidepressant prescriptions in England and Wales, 1998-2000’.
- 7.2 The Group noted this information and commented that the conclusion that tricyclic antidepressants are more toxic than SSRIs in overdose was well recognised and that this paper did not raise any new safety concerns.

8. ORAL UPDATES

8.1 Feedback from further meeting with Mr Aldred

- 8.1.1 The Group was provided with minutes of a meeting between Mr Graham Aldred, Dr David Healy, Dr David Gunnell and members of the secretariat held at Market Towers on 8 January 2004 to further discuss the issues raised at an earlier meeting with Mr Aldred. The Group was informed that Mr Aldred has submitted two further papers for consideration by the Group. The first of these provides the results of a wide range of experiments to both develop the IMR model and to investigate its sensitivity. The second outlines a new model, the baseline suicide rate (BSR) model.
- 8.1.2 The Group considered that Mr Aldred’s BSR model is not sufficiently sophisticated to provide the accuracy of information required and that a

randomised clinical trial would be the best way to obtain this information. The Group agreed that it was important that the dialogue between the MHRA and Mr Aldred continues and that the concerns of the Group are fed back to Mr Aldred

8.2 Feedback from meeting with the Online Seroxat Support Group

8.2.1 The Group was provided with minutes of a meetings held between members of the Online Seroxat Support Group and members of the secretariat. The Group noted this information.

9. UPDATED WORKPLAN

9.1 The Group was provided with an update of the proposed plan for completion of the work of the Group.

9.2 The Group expressed disappointment about the lack of detail in this workplan and concern about the timescales for completion of the SSRI review and the subsequent delay in the publication of the report of the group. It was agreed that a more considered paper should be provided for the next meeting which would outline the proposed timescales for completion of work and consider whether the need to release new advice, where appropriate, in advance of the final report of the Group.

9.3 The Group commented that it would be useful if an overview of the ongoing European referral for paroxetine and what constraints if any this European procedure may place on the ongoing work of the Group was presented at the February meeting.

10. ANY OTHER BUSINESS

10.1 The Chairman informed the Group that the next meeting would be held at 10am on 27 February 2004.

MHRA
January 2004