

**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 WEDNESDAY 25 AUGUST 2004 AT 10AM IN CR1 AT MARKET TOWERS.**

**Members Present**

Professor Ian Weller (Chairman)	Professor of Sexually Transmitted Diseases & Director of Centre of Sexual Health & HIV Research, Royal Free & University College Medical School
Professor Deborah Ashby	Professor of Medical Statistics, Queen Mary, University of London
Dr Jonathan Chick	Consultant Psychiatrist, Alcohol Problems Service, Royal Edinburgh Hospital & part time Senior Lecturer at Edinburgh University
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 & Honorary 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
Ms Sarah Wark	Unit Manager, Pharmacovigilance Group
Dr Julie Williams	Scientific Assessor, Pharmacovigilance Group
Dr Simon Day	Statistics Unit Manager, Licensing Division
Mr David Brown	Statistician, Licensing Division
Dr Lesley Wise	Statistician/Epidemiologist, Pharmacovigilance Group
Dr Carlos Martinez	Head of Research, GPRD
Dr Simon Amyes	Post Licensing Division (item 3)

**Observers**

Professor Alasdair Breckenridge	Chairman, MHRA
Mr Jeremy Mean	Senior Policy Manager, Post Licensing Division
Ms Claire Davies	Scientific Assessor, Post Licensing Division

**Others**

Professor Karen Facey	Consultant
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**Invited Experts**

Ms Rachel Burbeck	National Collaborating Centre for Mental Health
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## **1.0 INTRODUCTION**

- 1.1 The Chairman welcomed members of the Group and thanked them for coming to the meeting.
- 1.2 The Chairman welcomed to the meeting Professor Alasdair Breckenridge, Chairman of the MHRA, and Ms Rachel Burbeck from the National Collaborating Centre for Mental Health.
- 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. APOLOGIES AND ANNOUNCEMENTS**

- 2.1 Apologies were received from Professors Chambers, Drummond and Ebmeier.

## **3. MINUTES OF MEETING OF 23 JULY**

- 3.1 The minutes of the meeting on 23 July 2004 were agreed as a correct record.

## **4. DECLARATION OF INTERESTS**

- 4.1 The Group confirmed that their interests remained unchanged.

## **5.0 MATTERS ARISING**

### **5.1 Meta-analysis of paroxetine adult clinical trial data.**

- 5.1.1 The Group was reminded that at the April meeting it had recommended that a formal meta-analysis of the paroxetine adult clinical trial data should be carried out. The Group was informed that further data had been sought from the MAH in order to perform this meta-analysis.

### **5.2 Fluoxetine toxicity study**

- 5.2.1 The Group was informed that CSM considered further interim results from the juvenile rat toxicity studies involving fluoxetine at its meeting on 29 July 2004 and that CSM will consider the final report as soon as it is available. The Group will be kept updated on this issue.

### **5.3 Communications surrounding article 31 referral for paroxetine**

- 5.3.1 The Group was reminded that during the meeting of 23 July it had considered a draft article conveying the key prescribing advice arising from the European review of paroxetine for inclusion in the drug safety bulletin, Current Problems in Pharmacovigilance. A revised version was provided which, where possible, had taken the Group's comments into account. The Group was informed that it had not been possible to include comments relating to

prescribing practice except where these recommendations were evidence based.

5.3.2 The Group endorsed the tabled version of the draft article.

#### **5.4 Draft Seroxat Patient Information Leaflet (PIL)**

5.4.1 The Group was provided with an update on the progress of GSK's User testing of the Seroxat PIL. The Group was informed that further independent user testing of the Seroxat PIL was to be conducted via a Focus Group, chaired by Professor Mary Chambers, to be held on 7 September 2004. Once agreed a further draft of the Seroxat PIL would be provided to the Expert Working Group.

#### **5.5 Risk:Benefit review of venlafaxine**

5.5.1. The Group was reminded that due to concerns that venlafaxine may be more toxic in overdose it had recommended that a full review of the balance of risks and benefits of venlafaxine should be conducted. The Group was informed that members of the secretariat have met with the Marketing Authorisation Holder to discuss these concerns and inform them of this risk:benefit review, which would be considered by the Group at its October meeting.

### **6.0 PAPERS**

#### **6.1 FINAL REPORT OF GPRD STUDY AND REGULATORY IMPLICATIONS**

6.1.1 The Group was provided with the final draft of the report of the MHRA General Practice Research Database study and informed of the following key findings:

- the overall findings are reassuring in suggesting that SSRIs, as a class, are unlikely to be worse than TCAs in respect of either non-fatal self-harm (NFSH) or suicide in adults;
- SSRIs appear to be associated with an increased risk of NFSH compared with TCAs in under 19s although this finding requires caution in interpretation;
- comparisons within drug classes do not allow firm conclusions on differential risks with individual products, although the odds ratios (OR) for NFSH in under 19s for paroxetine is significantly higher than that for sertraline.

6.1.2 The Group's advice was sought on:

- whether the GPRD study has any immediate implications for the current regulatory position on the use of SSRIs as a class or individual products;
- What is the strength of the evidence from this study on the risk of paroxetine compared with other agents;
- Is further study of the risk of paroxetine versus other SSRIs warranted.

- 6.1.3 Some members of the Group expressed concern that the final report placed too much emphasis on the higher risk of NFSH in young people treated with paroxetine compared with other SSRIs. The Group was informed that this issue had been considered in great detail by the Steering Group and agreed that the current approach of mentioning the higher risk but carefully qualifying these findings in the text was considered the most appropriate.
- 6.1.4 The Group was asked if they were content that the text of the manuscript draft does not specifically mention in the results section the data on the risk of NFSH in relation to selected specific antidepressants by age in young people (Table 7 of the paper). The Group commented that the difference between the risk of NFSH and completed suicide between the selected specific antidepressants was not statistically significant and the OR had wide confidence intervals. The Group advised that the inclusion of these data in the table allowed readers to see the results, but did not consider that they warranted specific mention in the results section.
- 6.1.5 The Group considered that inclusion of absolute rates of NFSH in association with SSRI treatment may not be helpful. It was agreed that absolute rates would be subject to a degree of uncertainty and that it may be advisable that any mention of absolute rates was restricted to the discussion section and be surrounded by appropriate caveats. It was agreed that outside the meeting the Steering Group should give further consideration on how best to address this concern.
- 6.1.6 The Group commented that the covering paper accompanying the draft manuscript states that the MHRA study, taken together with the Jick study, found that the risk of suicidal behaviour may increase in the early stages of treatment with an antidepressant. The Group pointed out that, in contrast with the Jick study, the MHRA study had not been designed to detect such an effect.
- 6.1.7 With regard to the regulatory implications of these data, the Group advised that these data supported the action that had already been taken to restrict the use of SSRIs in children and adolescents but did not raise any further safety concerns that warranted immediate UK regulatory action. However, it was considered that they were extremely pertinent to the ongoing Article 31 referral procedure and that they should be submitted urgently for consideration by the Committee for Medicinal Products for Human Use (CHMP) prior to Final European Commission Decision. The Group also supported the suggestion that the results of the study be shared with the FDA in a way that would not jeopardise future publication. The MHRA reminded the Group that the study had been commissioned by the Licensing Authority for regulatory purposes and that the Licensing Authority would have a view on future publication/presentation.

- 6.1.8 No specific recommendations were made with regard to further study of the risk of paroxetine versus other SSRIs.

## **6.2 ANALYSIS OF DOSE RESPONSE DATA FOR SSRIs**

- 6.2.6 The Group was provided with an statistical analysis of the dose response data submitted by the Marketing Authorisations Holders for Cipralax (escitalopram), Cipramil (citalopram), Faverin (Fluvoxamine), Lustral (sertraline), Prozac (fluoxetine) and Zispin (mirtazapine). The Group was informed that before firm conclusions could be made it was necessary to seek further information/clarification from the relevant Marketing Authorisation Holders and complete the ongoing analysis of usage databases to obtain a profile of the starting and maintenance doses of each product used in practice. The Group was informed that the full statistical analyses of all products, the usage data and the regulatory implications would be discussed at its October meeting.
- 6.2.2 The Group noted this information and agreed that it was important to obtain all relevant data before considering the regulatory implications.

## **6.3 NICE GUIDELINES ON THE TREATMENT OF POST-TRAUMATIC STRESS DISORDER (PTSD) AND ANXIETY**

- 6.3.1 The Group's comments were sought on a draft of the NICE guideline on the treatment of PTSD, which is in the 1st consultation phase, and a draft of the NICE guideline on the Management of Anxiety, which is in the 2nd phase of the consultation process.
- 6.3.2 The Group had the following general comments in relation to both guidelines:
- The information about the possibility of withdrawal reactions should include more detailed information about the nature of these reactions and should be consistent across all the NICE guidelines;
  - the guidelines should contain consistent detailed information on monitoring of patients.
- 6.3.3 The Group had the following comments on the PTSD guideline:
- The statement that it is not possible to determine whether there is a clinically important difference between paroxetine and placebo is not consistent with the advice of CSM or the CHMP which considered that based on the available data paroxetine was efficacious in the treatment of PTSD;
  - although it was not possible to complete a meta-analysis on setraline due to lack of data it is of concern that it is not recommended as it has been granted a licence for the treatment of PTSD in women.
- 6.3.4 The Group had the following comments on the Anxiety guideline

- the recommendations that where antidepressants are used it may sometimes be necessary to use doses at the upper end of the dosage range is not consistent with the CSM advice for paroxetine that 20 mg is the recommended daily dose in adults for the treatment of social anxiety disorder (SAD) and generalised anxiety disorder (GAD). There is no evidence from clinical trials that increasing the dose above the recommended dose increases efficacy in the treatment of SAD and GAD;
- the guideline needs to clearly reflect the difficulty in the diagnosis of anxiety versus depression and the relevance of close observation for emergence of suicidal behaviour in this population .

6.3.5 It was agreed that the secretariat would feed these comments into NICE on behalf of the Group.

6.3.6 Dr Rachel Burbeck presented the NICE recommendations for practical implications of ‘close monitoring’ which had been tabled. The Group welcomed the suggestion but considered that the following aspects should be addressed:

- There should be some examples of timing of visits that would be considered ‘appropriate and regular’.
- Prescribers should be encouraged to actively question patients about suicidal thoughts and other adverse effects at visits.
- Some consideration should be given to recommending an open channel of communication (for example by telephone) for the patient to use should they experience adverse effects of concern.

It was agreed that Dr Taylor, on behalf of the Group, should take forward further discussion with Rachel Burbeck.

6.3.5 Dr Burbeck informed the Group that the November deadline for publication of the NICE Depression Guideline meant that the Guideline would have to be finalised by 22 September. The Chairman responded that the Group’s work would not be complete before that date and asked that there was liaison between MHRA and NICE to ensure that any key new information from ongoing assessment was transmitted to NICE.

## **7.0 CURRENT LITERATURE**

7.1 The Group was provided with a recently published paper entitled ‘Are selective serotonin re-uptake inhibitors associated with an increased risk of self-harm by antidepressant overdose?’ and an article from Pulse magazine entitled ‘SSRIs: Where are we now?’. The latter had been commissioned by Pulse and had been written, with the agreement of the Chair and the secretariat, by Dr Ross Taylor.

7.2 The Group noted this information.

## **8.0 ORAL UPDATES**

### **8.1 Update on patient representation**

9.1.1 The Group was informed that the appointment of Hilary Hawking as a lay member to the Group is being progressed.

8.1.2 The Group noted this information.

### **8.2 Update on FDA Paediatric Advisory Committee Meeting**

8.2.1 The Group was provided with an update on the ongoing review by the FDA of the safety and efficacy of the SSRIs and related antidepressant in the treatment of children and adolescents. The Group was also informed that the next meeting of the Paediatric Advisory Committee was scheduled for 13/14<sup>th</sup> September and that a member of the secretariat would be attending the Advisory Committee meeting and would feed back to the Group at its October meeting.

8.2.2 The Group noted this information and commented that it would be advisable for the results of the GPRD study to be communicated to the FDA in appropriate form.

## **9.0 ANY OTHER BUSINESS**

9.1 The Chairman informed the Group that the next meeting would be held at 10am on 1st October 2004.

9.2 The Group was informed that the secretariat had just received the report of the GPRD study conducted by GSK and that an assessment report of this study would be considered at its next meeting.

**MHRA**  
**August 2004**