

## CSM/SSRIsWG/04/10th MEETING

### COMMITTEE ON SAFETY OF MEDICINES

#### EXPERT WORKING GROUP ON SAFETY OF SSRIs

#### MINUTES OF THE MEETING OF THE CSM EXPERT GROUP ON THE SAFETY OF SSRIs HELD ON WEDNESDAY 31 MARCH 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
Professor Mary Chambers	Professor of Mental Health, University of Ulster
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 Ann York	Consultant & Honoray Senior Lecturer in Child & Adolescent Psychiatry, Child & Family Consultation Centre, Richmond Hospital
Dr Morris Zwi	Consultant Child & Adolescent Psychiatry, Child & Family Consultation Centre, Richmond Hospital

#### Professional staff of MHRA

Professor Kent Woods	Chief Executive
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
Dr Stephan Rietbrock	Researcher, GPRD

#### Others

Dr Karen Facey	Consultant
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#### Observers

Mr Jeremy Mean	Policy Group Manager, Post Licensing Division
Dr Jane Moseley	Pharmacoepidemiology Team Leader, Pharmacovigilance Group
Dr Camilla Parikh	Medical Assessor, Pharmacovigilance Group
Dr Bill Richardson	Medical Assessor, Pharmacovigilance Group

## **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 Professor Kent Woods, Chief Executive of the MHRA, to the meeting. Professor Woods expressed his thanks to the Group for its continuing work on this very important issue.
- 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 Professor Drummond and Drs Taylor and Jezzard.

## **3. MINUTES OF MEETING OF 30 JANUARY and 27 FEBRUARY**

- 3.1 The minutes of meeting on 30 January and 27 February 2004 were agreed as a correct record.

## **4. DECLARATION OF INTERESTS**

- 4.1 Professors Ashby and Weller declared new non-personal, non-specific interests in GlaxoSmithKline, this did not debar them from taking part in the proceedings. The other members of the Group confirmed that their interests were as declared at the meeting of 27 February 2004.

## **5 PAPERS**

### **5.1 GPRD study**

- 5.1.1 The Group was presented the results of an initial analysis of the GPRD study. As validation of the cases of completed suicide is still ongoing the presentation focussed on the initial findings in relation to the risk of self-harm.
- 5.1.2 The Group considered that it was essential to ensure confidence in the validity of the results obtained. The Group commented that before any firm conclusions could be made with regard to the risk of self-harm between groups of antidepressants and across the SSRI classes it was crucial that the following additional information was obtained and further analyses were conducted:

- (i) The possibility of removing patients identified through free text search of patients prescribed antidepressants, or an analysis with an identifier which differentiates between patients with a specific Read code for depression and those identified by free text.
- (ii) The possibility of including a marker for severity of depression.
- (iii) Examine heterogeneity between and within treatment groups.
- (iv) Treat age as a continuous variable.
- (v) Consider reasons for TCA prescribing (particularly relevant for patients identified through searching free text)

5.1.3 The Group was informed of a recent New Zealand Health Technology Assessment report, which examines the risk of suicide with the different classes of antidepressants. The Group asked that these data should be provided at its next meeting.

5.1 The Chairman thanked the members of the Group and the secretariat for their continuing work on this study.

## **5.2 Draft outline of paediatric report**

5.2.1 The Group was reminded that, at its meeting in February it was proposed that a detailed report of the work in relation to paediatric use of SSRIs be prepared for consideration at the next meeting. Work on this report is ongoing but the Group was provided with an outline detailing the proposed areas to be covered in this report. The Group was asked to provide written comments on this outline to the secretariat.

## **5.3 Critique of the report of Ad Hoc Expert meeting with Child Psychiatrists**

5.3.1 The Group was reminded of the report of the European Ad Hoc Expert meeting with child psychiatrists that was adopted at the February CPMP meeting. The Group was provided with a critique of that meeting report.

5.3.2 The Group considered that this critique raised some valid points, many of which had been expressed during the meeting.

5.3.3 The Group noted that the primary purpose of the meeting had been to inform European guidelines for treatment of psychiatric disorders in children and the consideration of the paroxetine clinical trial data in children and adolescents had formed only part of that meeting. The Group advised that the secretariat should consider how the critique could inform the ongoing referral procedure.

## **5.4 Study comparing the effects of paroxetine and maprotiline in depression**

5.4.1 The Group was informed of the results of a study comparing the effects of paroxetine and maprotiline in depression. The initial doses were 20mg/day paroxetine or 100mg/day maprotiline. After three weeks, patients who were

responding well were continued on the same dose. Patients who were not classed as 'responders' were re-randomised so that their dose was either maintained, or increased to 40mg/day paroxetine or 150mg/day maprotiline.

- 5.4.2 This study report was submitted by GSK in the autumn of 2003 upon the MHRA's request for copies of GSK's paroxetine study reports. As part of the review of all of these study reports, principally reviewing the adverse event data, this study was considered and its importance regarding dose and dose titration was noted.
- 5.4.3 The Group was informed that in the study report the MAH had made the following statement in relation to this study: 'In assessing the effect of increasing the daily paroxetine dose from 20mg to 40mg, in patients who did not show an early response to treatment, there was no evidence that this gave any advantage in the final efficacy outcome, supporting the contention that 20mg daily dose is the optimum dose.'
- 5.4.4 The Group commented that the approach taken in this study to re-randomise patients who had not responded following three weeks of treatment did not reflect normal clinical practice. It is usual to wait until about 6 weeks before considering any dose increase, as it is recognised that the patient's condition may continue to improve up to 7 weeks after starting treatment.
- 5.4.5 The Group advised that although this study had some limitations it is a more appropriate design to address the question of whether there is any additional efficacy at doses of paroxetine above 20mg and the conclusions of the MAH seems fully justified by the design and analysis of the study. The Group recommended that this study be included in the referral process.

## **6. CURRENT LITERATURE**

- 6.1 The Group was provided with a recently published paper entitled 'Death and dependence: current controversies over the SSRIs' and a pre-publication copy of a paper by Professors Ashby and Gunnell entitled 'Antidepressants and suicide: what is the balance of benefit and risk'.
- 6.2.1 The Group noted this information.

## **7.0 ORAL UPDATES**

### **7.1 Public communication of reminder of dosage recommendations for paroxetine**

- 7.1.1 The Group was informed that following its meeting on 27 February 2004 the CSM considered the paper assessing the data submitted by the MA holder in response to the outstanding questions relating to the ongoing European Article

31 referral. Alongside this paper the CSM also considered data from a primary care database which estimated that 17,000 patients were being started on paroxetine at a daily dose greater than 20mg in primary care. These data had not been available at the time of the Group's meeting in February.

- 7.1.2 In the light of these prescribing data suggesting that a significant proportion of patients are started at higher than the recommended dosage and given the likely timescale of the ongoing European referral, CSM advised that communication reminding health professionals of the recommended dosage in each of the licensed indications, and outlining the lack of clinical trial data to support titration above the recommended dosages, was warranted at this stage. CSM advised that this communication should be accompanied by a summary of the relevant clinical trial data.

## **7.2 Feedback from CPMP discussion of paroxetine Article 31 referral**

- 7.2.1 The Group was informed that MAHs response to the list of outstanding issues for the European referral for paroxetine was considered at the March meeting of the CPMP. At this meeting it was agreed the following key outstanding issues were agreed:

- i) the balance of risks and benefits in children and adolescents;
- ii) the balance of risks and benefits in young adults, particularly the risk of suicide, suicidal thoughts and self-harm;
- iii) the balance of risks and benefits of paroxetine in the treatment of PTSD;
- iv) the additional efficacy of doses of paroxetine greater than 20mg in all indications;
- v) the need for an oral suspension and a scored 10mg tablets to facilitate down titration and minimise the risk of withdrawal reactions.

- 7.2.2 The Group was informed that the companies have been invited to attend a hearing to address these issues. It is anticipated that the CPMP will reach an opinion following the company hearing(s).

- 7.2.3 In relation to the need for the oral suspension, the Group commented that this was a useful formulation in the elderly and that it was important that this formulation be retained.

## **7.3 FDA Talk paper**

- 7.3.1 The Group was informed of an FDA Talk Paper that had been issued on 22 March 2004. This Talk Paper advised that all patients should be carefully monitored for worsening depression and suicidal thinking, which can occur in the early stage of treatment. It also advised that patients should be observed for certain behaviours associated with these drugs, including anxiety, agitation, insomnia, irritability and akathisia.

7.3.2 These interim actions by the FDA follow recommendations made by the FDA's Psychopharmacologic Drugs and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committees, which met on 2 February 2004. The Group was informed that this was a preliminary communication and that the FDA had not made any conclusions in terms of the causal relationship between these antidepressant drugs and suicide.

7.3.3 The Group was also informed of a request, which had been made to the FDA by the Committee on Energy and Commerce in relation to the FDA's ongoing review of the safety and efficacy of antidepressants in the paediatric and adolescent population.

7.3.4 The Group noted this information.

#### **7.4 Further correspondence from Mr Aldred**

7.4.1 The Group was informed that following the advice issued by CSM on 11 March 2004 a letter has been received from Mr Aldred whose mathematical model to estimate patient numbers from DoH prescription data has previously been presented to the Group. In his letter Mr Aldred expressed concerns about the estimate of 17,000 patients starting paroxetine on a daily dose greater than 20mg in primary care, used in this communication. He comments that the number of patients prescribed paroxetine has declined in the last 2 years and therefore feels that the figure for 2003 is misleading. On a more general point he also expressed concerns that risk:benefit assessments are misleading as he considers that benefit and harm cannot occur in the same patient.

7.4.2 The Group was informed that the figure was obtained from a primary care database and was intended to inform current prescribing practice and therefore the MHRA considered it is entirely appropriate that figures for 2003 should be used rather than figures for previous years as Mr Aldred suggests.

7.4.3 In relation to Mr Aldred concerns about risk and benefit, the Group was informed that risk:benefit assessments are conducted according to internationally agreed CIOMS IV criteria. Also given that it is overall impact on public health impact which needs to be evaluated, the balance of risks and benefits are assessed at a population level and that individual risk benefit decisions in relation to drugs were the responsibility of the prescriber in conjunction with the patient.

7.4.4 The Group was informed that the MHRA would reply to Mr Aldred.

#### **7.5 Meeting with paediatric NICE Working Group**

7.5.1 The Group was provided with a note of the meeting with the Group working on the NICE guideline on the identification and management of depression children. The Group was also informed that at this meeting the NICE group had raised a number of questions and it had been agreed that these would be

submitted in writing to the MHRA. The MHRA has since written to the NICE group reminding them of this.

7.5.2 The Group noted this information.

## **7.6 Meeting with Representatives from Faculty of Child and Adolescent Psychiatrists**

7.6.2 The Group was provided with a note of the meeting with Representatives from Faculty of Child and Adolescent Psychiatrists.

7.6.3 The Group noted this information.

## **7.7 Patient representation**

7.7.1 The Chairman informed the Group that Mr Richard Brook had resigned as a member of the Group. The Chairman acknowledged the extremely valuable contribution that Mr Brook had made to the work of the Group.

7.7.2 The Chairman informed the Group of the media interest in Mr Brook's resignation. The Chairman considered that it was important that the Group was provided with a copy of these articles at its next meeting.

7.7.3 The Chairman informed the Group that the appointment of another patient representative was being progressed and that the secretariat had written to the following patients organisation to ask for nominees: Depression Alliance, Manic Depression Fellowship, Rethink and SANE. As is usual practice, the appointment of another member to the Group will be considered by CSM.

## **8. ANY OTHER BUSINESS**

8.1 The Chairman informed the Group that the next meeting would be held at 10am on 28 April 2004 and that meeting had been organised for 26<sup>th</sup> May and 30<sup>th</sup> June. It was agreed that these dates would be emailed out to members after the meeting and if these dates caused particular problems for any of the members they should inform the secretariat.

8.2 The Chairman informed the Group that Dr Craig Whittington from the NICE group on the identification and management of depression in children would be presenting their data to at the Group's meeting in April.

**MHRA  
March 2004**