

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 23 JULY 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 Mary Chambers	Chief Nurse and Professor of Mental Health Nursing at South West London & St Georges' Mental Health NHS Trust
Professor David Gunnell	Professor of Epidemiology, Department of Social Medicine, Bristol 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

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 Lesley Wise	Statistician/Epidemiologist, Pharmacovigilance Group
Dr Stephan Rietbrock	Researcher, GPRD

Observers

Dr Jane Moseley	Pharmacoepidemiology Team Leader, Pharmacovigilance Group
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Invited Experts

Mr Stephen Pilling	Co-Director, National Collaborating Centre for Mental Health
Ms Rachel Burbeck	National Collaborating Centre for Mental Health

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 the meeting that Mr Stephen Pilling and Ms Rachel Burbeck from the National Collaborating Centre for Mental Health would be attending the meeting as observers.
- 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 Drummond and Ebmeier and Drs Mukaetova-Ladinska, Zwi and Higgitt.

3. MINUTES OF MEETING OF 28 APRIL and 26 MAY

- 3.1 The minutes of the meeting on 28 April and 26 May were agreed as a correct record of these meeting subject to the correction of a typographical error in section 6.2.2 of the minutes of the meeting of 28 April.

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. The Group was informed that the secretariat is considering the best way to take this forward and will seek the further data required from the MAH in order to perform this meta-analysis.

5.2 Fluoxetine toxicity study

- 5.2.1 The Group was informed that CSM will be considering further interim results from the juvenile rat toxicity studies involving fluoxetine at its meeting on 29 July 2004. The final report is expected in late August at which point these data will be considered by CSM and its Paediatric Expert Working Group.

6.0 PAPERS

6.1 COMMUNICATIONS SURROUNDING ARTICLE 31 REFERRAL FOR PAROXETINE

- 6.1.1 The Group was informed that the final European Commission Decision on the outcome of the referral for paroxetine containing products is due in early to mid September. At the time of the release of the Commission Decision, the MHRA proposes to add to its website a short document highlighting the important changes in prescribing information brought about by the referral and back this up with key clinical trial data. The comments of the Group on a draft of these documents were sought.
- 6.1.2 The Group advised several editorial changes to the drafts. In relation to the warnings about withdrawal reactions it was agreed that the information about potential severity and duration should be clearly stated in the main body of the report.
- 6.1.3 The Group advised several changes to improve the clarity of the recommendations surrounding young adults. The group wished to communicate that the available data in young adults over 18 years are not sufficient to confirm or refute a negative balance of risks and benefits in some young adults, and therefore this population should be monitored closely. In the overall conclusions it should be clarified that the balance of risks and benefits in the adult population are considered to be favourable.
- 6.1.4 The Group was invited to provide any further comments they may have on these drafts in writing to the secretariat.
- 6.1.5 The Group was also asked to consider the need for an article conveying the key prescribing advice arising from the European review to be included in the next edition of Current Problems in Pharmacovigilance. The Group advised editorial changes. The Group considered that further thought should be given to what is meant in practice by the term ‘close monitoring’.
- 6.1.6 The Group expressed concerns about the appropriate the timing of such an article and asked that this should be further considered by the secretariat. In the meantime, the article would be redrafted taking into accounts the Group’s comments and recirculated to the Group for further comments.

6.2 DRAFT SEROXAT PATIENT INFORMATION LEAFLET

- 6.2.1 The Group was informed that the Seroxat Patient Information Leaflet (PIL) will form a key component of any communications around the time of European Commission Decision in relation to the Article 31 referral for paroxetine.
- 6.2.2 Upon request GSK has submitted an amended version of the Seroxat PIL that reflects the changes to the product information for prescribers recommended

by the recommended by the Committee for Medicinal Products for Human Use. GSK has also outlined its plans to user test this leaflet using a company called Consumption. The Group was informed that the MHRA was also planning to have users independently test the leaflet and commitments had been given to various stakeholders that their comments would be sought.

- 6.2.3 The Group was informed that GSK was provided with initial feedback on the draft Seroxat PIL during a meeting held between the MHRA and GSK on 15 July 2004. In light of these discussions GSK has provided a further draft which takes these comments into account. The Group had the following comments about the content and format of the revised draft Seroxat PIL:

Headline section

The proposal to include key information as bullet points as a headline section at the front of the PIL was supported. However, in the current draft this section was considered to include some repetition and to have too many bullet points, some of which are overly long.

Section entitled ‘What is Seroxat and what is it used for’

The first paragraph in this section is misleading as some patients will recover from an episode of depressive illness without pharmacotherapy. Further consideration should be given to the message being conveyed in this paragraph.

Section entitled ‘Before you take Seroxat’

Bullet point three should read ‘You have previously had an allergic reaction to paroxetine’.

Section entitled ‘Pregnancy and breastfeeding’

The wording around time to onset of symptoms in the neonate should read ‘These symptoms usually occur during the first 24 hours after birth.’

Subsection entitled ‘What if you miss a dose’

The Group considered this section should be cross-referenced to the subsection ‘Possible side effects when stopping treatment’. In relation to the current advice on what to do if a dose is missed, it was agreed that the key message to be conveyed is not to take a double dose the next day, however, if an early morning dose was missed, it would be appropriate to take it later that day within a specified time window. The MAH should be requested to propose an appropriate time window.

Section entitled ‘When you stop taking Seroxat’

The Group considered this section should be cross-referenced to the subsection ‘Possible side effects when stopping treatment’.

Section entitled ‘Possible side effects whilst on treatment’

The proposal to place serious side effects at the start of this section was supported, but the Group recognised the importance of seeking patient input on the most helpful way of presenting information, including that on frequencies of side effects, in this section.

Subsection entitled ‘Possible side effects when stopping treatment’

The reference to sugar pills should be removed from this section, as it does not add to patients’ understanding and can cause confusion. The reference to the possibility of severe and prolonged withdrawal reactions should be clearly stated in the first paragraph of this subsection.

The fourth sentence of the second paragraph should be amended to read ‘Your doctor may decide that it easier for you to take Seroxat liquid or change to fluoxetine during the time that you are coming off your medicine.’

The statement ‘If you do get side effects, it does not mean that you will not be able to stop Seroxat’ could be reworded to remove the double negative.

6.3 FURTHER ADVICE ON DOSE CHANGES

- 6.3.1 The Group was reminded of the concerns expressed at the July 2003 meeting by Mr Medawar and Dr Herxheimer about the association between changes in drug concentration and occurrence of suicidal behaviour.
- 6.3.2 In light of recommendations in the FDA Public Health Advisory of 22 March 2004 and further arguments of Mr Medawar and Dr Herxheimer, the Group considered the evidence supporting suicidal behaviour in temporal association with dose changes of SSRIs. The Group advised that it was plausible that suicidal behaviour may worsen around the time of dose changes, either due to changes of the course of the underlying disease or due to side effects of the drug. However the Group commented that the available controlled data did not provide evidence to support such a link.
- 6.3.3 The Group advised that this issue would be difficult to study further in a controlled manner and that as a precaution, patients should be closely monitored for any side effects around the time of dose changes.

6.4 UPDATED WORKPLAN

- 6.4.1 The Group was informed that the main body of work to be done is the review of the adult data on SSRIs and related antidepressants, other than paroxetine. The adult data for the other SSRIs is being broken down for assessment purposes into three categories – dose, suicidal behaviour and withdrawal reactions - and will be considered at the August and October meetings.
- 6.4.2 The Group noted this information and commented on the need for further review of the balance of risks and benefits of venlafaxine given the concerns that it may potentially be more toxic in overdose than the SSRIs. The Group was informed that the secretariat were scheduled to meet with the Marketing Authorisation Holder to discuss these concerns and would feed back to the Group at its next meeting.

7.0 CURRENT LITERATURE

- 7.1 The Group was provided with recently published papers entitled 'Repetition of deliberate self-harm and subsequent suicide risk: long-term follow-up study of 11,583 patients' and 'Antidepressants and the risk of suicidal behaviour'.
- 7.1.2 The Group noted this information.

8.0 GPRD STUDY BY HERSHEL JICK

- 8.1 Results from the recent JAMA publication by Jick et al on 'Antidepressants and the risk of Suicidal Behavior' using the UK GPRD were presented and discussed.
- 8.1.2 A presentation of the similarities and differences between the design and population of this study and the MHRA study was provided to the group and was noted.
- 8.1.3 The introduction, methods, tables and figures of the MHRA GPRD study draft manuscript were provided to the Group, and the main findings discussed. The similarity in results between the MHRA study and the Jick study was noted, including the possibility of an increased risk in those under 19 years of age. The completed draft manuscript should be submitted to the Group at the meeting on 25th August 2004.

9.0 ORAL UPDATES

9.1 Update on patient representation

- 9.1.1 The Group was informed that Professor Mary Chambers has proposed Hilary Hawking, a member from the hospital patient group at St Georges. It was also agreed that Dr Chick should also pursue the possible lead he had from the Royal College of Psychiatrists Patient and Carers Group. As is usual practice, the appointment of a new member(s) to the Expert Working would be subject to CSM approval.
- 9.1.2 The Group also recommended pursuing the possibility of engaging a Focus Group to consider particular aspects including the wording of Seroxat PIL.

9.2 Update on media coverage

- 9.2.1 The Group was provided with a selection of articles on SSRIs from newspapers in the past month.
- 9.2.2 The Group noted this information.

10.0 UPDATE ON GPRD STUDY

10.1 This item was considered under item 8.0 above.

11.0 ANY OTHER BUSINESS

11.1 The Chairman informed the Group that the next meeting would be held at 10am on 25 August 2004.

**MHRA
July 2004**