

COMMITTEE ON SAFETY OF MEDICINES**EXPERT GROUP ON SAFETY OF SSRI****MINUTES OF THE MEETING OF THE CSM EXPERT GROUP ON THE SAFETY OF SSRIS HELD ON FRIDAY 1 OCTOBER 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 Klaus Ebmeier	Professor of Psychiatry, University of Edinburgh
Professor David Gunnell	Professor of Epidemiology, Department of Social Medicine, Bristol University
Ms Hilary Hawking	Service User representative
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
Mr Jeremy Mean	Senior Policy Manager, Post Licensing Division
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 Julia Dunne	CHMP delegate
Dr Frances Rotblat	Co-opted CHMP delegate
Dr Camilla Parikh	Medical Assessor, Pharmacovigilance Group
Dr Michael McKenna	Medical Assessor, Post Licensing Division
Dr Jonathan Sisson	Medical Assessor, Post Licensing Division
Dr Martina Riegl	Medical Assessor, Post Licensing Division
Dr Sue Morgna	Medical Assessor, Post Licensing Division
Dr Bill Richardson	Medical Assessor, Pharmacovigilance Group
Ms Claire Davies	Scientific Assessor, Pharmacovigilance Group

Observers

Mr Mark Loughrey	Pharmacovigilance Scientist (item 4.2 only)
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Others

Professor Karen Facey	Consultant
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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 welcomed to the meeting Ms Hilary Hawking as the new lay member to the Group. Ms Hawking is currently working as a Clinical Governance User representative for South West London & St Georges' Mental Health NHS Trust. She also is a trustee for a mental health advocacy project in Kensington and Chelsea and is part of the user reference group for the London development 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 Professor Drummond and Drs Mukaetova-Ladinska and Taylor.

3. MINUTES OF MEETING OF 25 AUGUST

- 3.1 The minutes of the meeting on 25 August 2004 were agreed as a correct record.

4. DECLARATION OF INTERESTS

- 4.1 Professor Ebmeier declared a new non-personal, non-specific interest in Denflect Pharma. (lecture fee)

5.0 MATTERS ARISING

5.1 Meta-analysis of paroxetine adult clinical trial data.

- 5.1.1 The Group was the further data had been received from the MAH in order to perform this meta-analysis and that the secretariat would discuss with Professor Gunnell how best to proceed the analysis.

5.2 Recommendations for close monitoring

- 5.2.1 The Group was reminded that the last meeting it was agreed that Drs Burbeck and Taylor should liaise over the NICE recommendations for practical implications of 'close monitoring'. The Group reviewed a draft proposal for guidance on this issue. The Group agreed that this should be revisited at the next meeting.

6.0 PAPERS

6.1 Review of dose recommendations, withdrawal reactions and suicidal behaviour

- 6.1.1 The Group considered assessments of dose recommendations, withdrawal reactions and suicidal behaviour for citalopram/escitalopram, fluvoxamine, fluoxetine, mirtazapine and sertraline.
- 6.1.2 The Group advised that further information was required for fluvoxamine, fluoxetine, and mirtazapine before conclusions and recommendations could be made, particularly in relation to suicidal behaviour. A subgroup meeting was held following the plenary meeting to define the exact data/analyses to be sought for each product. It was agreed that the further data would be urgently sought from the companies concerned and that this issue would be revisited at the next meeting.
- 6.1.3 The Group advised that, unless data warranted product-specific warnings, the warnings in the SPC should be made consistent across products.

6.2 Risk:Benefit evaluation of venlafaxine

- 6.2.1 The Group considered the benefits and risks of treatment with venlafaxine with regard to which regulatory options would prevent or minimise the risk of harm associated with the use of venlafaxine.
- 6.2.2 The Group considered that venlafaxine should not be used in primary care and that initiation of treatment should be restricted to specialist care and under specialist supervision. The Working Group considered that there was modest evidence to support the use of venlafaxine in the treatment of patients with severe depression/melancholia although the optimum dose had not been established.
- 6.2.3 The Group considered that the safety concerns relating to cardiotoxicity and seizure in overdose and withdrawal reactions were such that the risk benefit balance of venlafaxine was called into question. The Working Group discussed whether suspension or revocation of the marketing authorisation would be appropriate, however they considered that venlafaxine could be an important therapeutic alternative in some patients. The Working Group advised that the balance of risks and benefits of venlafaxine could only be considered favourable in a restricted indication under specialist supervision.
- 6.2.4 The Group advised that further clinical trial data may be required to define the exact population which would benefit most from venlafaxine treatment. The Group was informed that the CSM would review this issue at their next meeting.

6.3 Assessment of GSK's GPRD study

- 6.3.1 The Group was provided with an assessment of the GSK GPRD study.

6.3.2 The Group noted that despite different study designs and populations, the results of the GSK GPRD study were consistent with that of the MHRA study in particular with respect to the increased risk of suicidal events in patients aged 18 and under on SSRIs compared to other antidepressants and paroxetine compared to other SSRIs.

6.4 Final report of GPRD study commissioned by MHRA

6.4.1 The Group noted the final report of this GPRD study. The Group recommended that this it was important that this study was published as soon as possible. The Group was informed that the Agency was working towards a co-ordinated publication of the final report of the review and the GPRD study.

6.5 Fluoxetine – TAD study

6.5.1 The Group was provided with the recently published Treatment for Adolescents with Depression Study (TADS) which was published in JAMA (Vol 292, No 7). This study compared fluoxetine alone, placebo alone, cognitive behavioural therapy (CBT) alone and CBT with fluoxetine. Fluoxetine+CBT was statistically significantly superior to placebo ($p=.001$). The differences between fluoxetine alone and placebo, and CBT alone and placebo, did not reach statistical significance. The safety results indicated a statistically significant elevated risk for harm-related events in the 2 fluoxetine-containing arms, the odds ratios for suicide-related events showed a similar pattern but did not reach statistical significance since numbers were small. The Group was asked for its advice on the implications of this study for the risks and benefits of fluoxetine in children and adolescents.

6.5.2 The Group advised that the study was limited by the lack of a CBT + placebo arm. The Group advised that the study overall did not alter previous conclusions in relation to efficacy of fluoxetine in MDD in under 18s. The Group advised that the safety findings should be considered carefully during the assessment variation.

7.0 ORAL UPDATES

7.1 Update on Article 31 referral for paroxetine

7.1.1 The Group was informed that draft European Commission Decision for paroxetine had been received and that as is usual practice Member States have 30 days in which to comment. This draft decision does not take into account the results of the either the GPRD study commissioned by the MHRA or the GSK GPRD study. It is important that these data are considered before a final decision is reached and the Agency is exploring ways to achieve this.

7.1.2 The Group noted this information.

7.2 Update on FDA Paediatric Advisory Committee Meeting

7.2.1 The Group was provided with feedback on the meeting of the Paediatric Advisory Committee was scheduled for 13/14th September and the copies of the FDA's assessment reports on the possibly suicide-related events from the paediatric placebo-controlled trials that were considered at that meeting.

7.2.2 The Group noted this information.

7.3 Fluoxetine – paediatric variation

7.3.1 The Group was informed that CSM will be considering the final results from the juvenile rat toxicity studies involving fluoxetine in October 2004 and the Group will be informed of CSM's advice.

7.3.2 The Group noted this information

7.4 Update on communications including final report

7.4.1 The Group was informed that the secretariat has begun working on the various chapters of the final report. A draft version will be provided for the Group's comments at the next meeting.

7.4.2 The Group noted this information

8.0 ANY OTHER BUSINESS

8.1 Concerns were raised that for some SSRIs the section of the overdose section of the SPC is not consistent with the recommendations on the management of overdose in the NICE guideline. The Group advised that the overdose section for the SPCs for all SSRIs and related antidepressants should contain up to date, authoritative information.

8.2 The Chairman informed the Group that the next meeting would be held at 10am on 9th November 2004.

MHRA
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