

DATE OF SUMMARY: APRIL 2001

**SUMMARY OF THE MEETING OF THE COMMITTEE ON SAFETY OF MEDICINES
HELD ON THURSDAY 26 MARCH 1998**

Committee Members:

Present

Professor M D Rawlins (Chairman)
Professor A M Breckenridge (Vice-Chairman)
Dr K Costeloe
Professor J H Darbyshire
Professor G W Duff
Professor S J Eykyn
Professor E C Gordon-Smith
Professor H S Jacobs
Dr B J Kirby
Dr S Kumar
Professor M J S Langman
Dr A V P Mackay
Professor J M Midgley
Professor B K Park
Professor B L Pentecost
Professor J C Petrie
Professor L L Smith

Apology

Mrs E Kay

Mr L Whitbread (*Secretary*)

Mr E Hazell (*Assistant Secretary*)

Training

Dr P Bridges MCA/L
Dr A Caldwell MCA/L
Mr R Jamieson MCA/L
Dr D Moul MCA/PL
Miss D Mthimkhulu MCA/L
Dr T Pepper MCA/L

Others:

Miss S Bhasin MCA/PL (PAG)
Dr J Dunne MCA/L
Dr A Eyre-Brook MCA/L
Mr C Gardner SoL C5
Dr R Hart MCA/PL
Dr D Jefferys (Director of Licensing)
Dr P Raptopoulos MCA/L

Professional Staff of MCA

- Principal Assessors

Dr A Nicholson (New Drugs)
Dr F Rotblat (Biologicals)
Dr S Wood (Director, Post Licensing)

Licensing Division

Dr M Ali
Mr T Berridge
Dr P Collett
Dr J Cook
Dr R Dickinson
Dr S Eisen
Dr K Facey
Dr G Haase
Professor J Lewis
Dr D Rogers
Dr R Shah
Dr J Sims
Mr J Slattery
Dr C Steele
Mr H Stemplewski
Dr M Thatcher
Dr J Warren

Post-Licensing Division

Dr M Crawley
Dr I Douglas
Professor S Evans
Ms K Foy
Dr S Millican
Dr J Steen
Dr P Waller
Ms S Wark

Dr S S Singh MCA/L
Dr L Tsang MCA/L
Dr D Wooding MCA/L

NOTE: MCA STAFF MAY BE PRESENT FOR ALL OR PART OF THE MEETING OR FOR SPECIFIC AGENDA ITEMS

1. **Announcements and Apologies**

- 1.1 The Chairman reminded the Committee that the papers and proceedings were confidential and should not be disclosed. Members were also reminded to declare their personal specific, personal non-specific, non-personal specific and non-personal non-specific interests in the agenda items.
- 1.2 Apologies were received from Mrs Kay for the day, and from Professors Pentecost and Petrie for the afternoon.
- 1.3 The Chairman reminded members of the 'en college' meeting on 30 April, which would be preceded by a Committee dinner on 29 April.
- 1.4 The Chairman informed the Committee that the meeting scheduled for 11 March had been cancelled because a company involved wished to present new data which neither the MCA or Committee had seen before. He therefore had no alternative but to defer the hearing to a later date so that the data could be assessed in the usual way.

2. **Minutes of the Meeting held on 26th February 1998**

The minutes were agreed and signed by the Chairman as a true record of the proceedings.

3. **Matters Arising from the Minutes**

None.

4. **Consideration of the Applications - New Products**

The Committee considered five applications. In addition, the Committee were also made aware of two applications received via the European centralised licensing system. Details as follows

Application 1: members had no interests to declare. [**Note:** this application, which was received via the European centralised licensing system, was subsequently withdrawn – *[see note 1 below]*]

Application 2: one member declared a non-personal non-specific interest, but this did not debar them from taking part in the proceedings. [**Note:** this application, which was received via the European centralised licensing system, was subsequently withdrawn – *[see note 1 below]*]

Applications 3 and 4 were subsequently withdrawn – *[see note 1 below]*

Regulatory action has been completed by the date of this summary and Marketing Authorisations granted to the fifth and sixth applications as follows:

MA 06745/0087-8:	STAMARIL YELLOW FEVER VACCINE (Live Yellow Fever Virus Vaccine):	PASTEUR MERIEUX
------------------	---	--------------------

Professor Gordon-Smith declared a non-personal non-specific interest, but this did not debar him from taking part in the proceedings.

Regulatory action has been not been completed by the date of this summary on the seventh application. One member declared a personal non-specific interest and left the room. One member declared a non-personal non-specific interest, but this did not debar them from taking part in the proceedings - *[see note 2 below]*.

5. **Legal Status** *[see note 3 below]*

The Committee considered three applications and advised as follows:

Applications 1 and 2: members had no interests to declare – the CSM did not support the applications for a change to the legal classification of the products. *[see note 4 below]*

Third application: One member declared a personal non-specific interest and left the room for this item. The CSM did not support the application for a change to the product’s legal classification. *[see note 4 below]*

6. **Pre-Hearing** *[see note 5 below]*

Members had no interests to declare in the one application considered. The Committee recommended the grant of a Marketing Authorisation to:

MA 10555/0008:	PARIET (Rabeprazole Sodium)	EISAI
----------------	-----------------------------------	-------

6. **Hearing**

The Committee recommended a marketing authorisation be granted in respect of:

MA 11723/0246:	TICLID TABLETS (Ticlopidine Hydrochloride):	SANOFI WINTHROP
----------------	---	-----------------

Professor Langman declared a non-personal non-specific interest, but this did not debar him from taking part in the proceedings.

7. **Withdrawal Reactions Associated with SSRIs and Related Antidepressants**

7.1 Members declared interests as follows:

- E. Lilly: Professor Jacobs declared a personal non-specific interest and left the room. Professor Petrie declared a non-personal non-specific interest, but this did not debar him from taking part in the proceedings.
- Smithkline Beecham: Professor Breckenridge declared a personal non-specific interest, but at the request of the Chairman contributed freely to the discussion and left the room for the decision. Professors Darbyshire, Langman, Midgley, Park and Petrie declared non-personal non-specific interests, but this did not debar them from taking part in the proceedings.
- Pfizer: Professors Duff, Park, Petrie and Smith declared non-personal non-specific interests, but this did not debar them from taking part in the proceedings.
- Bristol Myers Squibb: Professors Darbyshire, Duff and Petrie declared non-personal non-specific interests, but this did not debar them from taking part in the proceedings.
- Wyeth: Professor Smith declared a personal non-specific interest and answered questions from the Chairman and left the room for the decision.

The Committee noted that Dr Mackay had been approached recently by a representative of one of the manufacturers regarding the issue, but that he had declined to enter into any discussions.

- 7.2 The Committee were informed that a review of data on withdrawal reactions associated with the SSRIs and the related antidepressants nefazodone and venlafaxine had been carried out to investigate the nature of withdrawal reactions and to assess any evidence that these drugs are associated with features of dependence. This was done in the light of the publication of 'The Antidepressant Web' by Charles Medawar¹ in which the author likens these drugs to benzodiazepines in their ability to cause dependence.

- 7.2.1 The conclusions of the review were that withdrawal reactions occur with all SSRIs and related antidepressants, although to different extents for each drug. In the main these reactions are mild and self-limiting, although more severe reactions have been reported. No strong evidence from any source, had been identified to suggest that the SSRIs and related antidepressants cause features of dependence other than withdrawal symptoms.

¹ Director of Social Audit Ltd

- 7.2.2 The Committee's attention was drawn to the assessor's conclusions, the first 4 points of which relate to specific changes to product information. The Committee were informed that Lilly (MA holders for Prozac) had expressed concern at the use of the term 'withdrawal reaction' when referring to symptoms occurring on withdrawal of treatment due to the fact that the term 'withdrawal' has a specific meaning and implies that the drug is addictive. Lilly had suggested the use of the term 'discontinuation reactions'.
- 7.2.3 The Committee were informed that the paper had been reviewed by the Sub-Committee on Pharmacovigilance who agreed with the listed conclusions adding that the CSM and further experts should be consulted prior to publication of an article in 'Current Problems in Pharmacovigilance'. [Note: see article in *Current Problems in Pharmacovigilance*, September 2000 - <http://www.mca.gov.uk/mca/csmhome.htm>]
- 7.3 The Committee agreed that the review had revealed no evidence of dependence associated with the SSRIs and related antidepressants. They agreed that withdrawal reactions with the SSRIs and related antidepressants appear to be a class effect, however it was clear that different drugs caused these reactions to different extents.
- 7.3.1 The Committee commented that withdrawal reactions did not appear to be restricted to a particular group of patients but occurred in patients treated for any indication. They noted that to date, studies had not been carried out of an appropriate design to allow an estimation of frequency of withdrawal reactions.
- 7.3.2 The Committee were asked whether they thought that withdrawal reactions with these drugs had public health implications. The Committee considered that there was no evidence to suggest that this was so.
- 7.3.3 The Committee were asked whether they thought that a change in terminology from withdrawal reactions to 'discontinuation reactions' would be appropriate as suggested by Lilly. It was agreed that it would be inappropriate to change medical terminology in this way.
- 7.3.4 The Committee were asked whether they thought that there were similarities between withdrawal reactions with the SSRIs and the situation with benzodiazepines. They commented that dose escalation and drug seeking behaviour were evident in association with benzodiazepines but that these features were not evident in patients taking SSRIs.
- 7.4 The Committee recommended the following:

- 7.4.1 The product information for fluoxetine, citalopram and nefazodone should contain a general statement about the risk of symptoms on withdrawal such as the following:

'Withdrawal reactions have been reported in association with selective serotonin reuptake inhibitors (SSRIs). Common symptoms include dizziness and nausea. Abrupt discontinuation of treatment with SSRIs should be avoided.'

This general statement should be tailored to take into account different classes and properties of each drug.

- 7.4.2 A reassuring statement should be added to the SPC and PIL along the lines of the following:

'The majority of symptoms experienced on withdrawal of SSRIs are non-serious and self-limiting.'

The PIL should contain the following additional advice:

'If you experience severe symptoms, contact your doctor '.

- 7.4.3 The current warning in the product information for sertraline should be expanded to include information on the symptoms to be expected on withdrawal.

- 7.4.4 The statement *'symptomatic treatment is seldom warranted'* should be removed from the paroxetine SPC.

- 7.4.5 Reference to withdrawal reactions being *'rare'* should be removed from the product information for fluvoxamine and sertraline.

- 7.4.6 Reports of withdrawal reactions associated with the SSRIs and related antidepressants should continue to be carefully monitored for signs of dependence and the follow up procedure for Yellow Card reports for all SSRIs and related antidepressants should be continued.

- 7.4.7 An article in 'Current Problems in Pharmacovigilance' should be published summarising this review and reminding doctors about the risk of withdrawal reactions with SSRIs and other antidepressants. [**Note:** see article in *Current Problems in Pharmacovigilance*, September 2000 - <http://www.mca.gov.uk/mca/csmhome.htm>]

- 7.4.8 The possibility for specific targeted investigation of the frequency and severity of withdrawal reactions, and of dependence should be discussed with the MA holders.

- 7.5 The Committee complimented the assessors on a very good report.

8. **Clozapine & Gastro-Intestinal Obstruction**

8.1 Professor Park declared a non-personal non-specific interest, but this did not debar him from taking part in the proceedings.

8.2 The Committee considered the paper and recommended that the Product Literature (SPC, PIL and NSF) should include a precaution suggesting that patients should be encouraged to maintain a reasonable level of physical activity and should also adopt preventative measures such as a high fibre diet or supplements. Suggested wording is as follows:

"Constipation may occur, possibly due to the anticholinergic properties of the drug. This is usually mild, but can on occasions be more severe, and sometimes fatal complications have been reported, including gastrointestinal obstructions and paralytic ileus. Preventative measures should be taken. The importance of recognising and treating constipation is also emphasised. The effects of other psychotropic drugs may exacerbate the situation".

8.3 The Committee also recommended the Clozaril Patient Monitoring Service (CPMS) should be asked to run a feature on this problem in their regular newsletter and that an article in *Current Problems in Pharmacovigilance* would also be useful in highlighting the problem and its prevention. [Note: – see article in *Current Problems in Pharmacovigilance*, volume 25, March 1999 - <http://www.mca.gov.uk/mca/csmhome.htm>]

9. **Alendronate and Severe Upper Gastro-Intestinal Adverse Reactions**

9.1 Professor Langman declared a personal non-specific interest, answered questions from members and left the room for the decision.

9.2 The Committee considered the paper and endorsed the recommendations regarding concerns over this issue given that severe oesophageal reactions are still occurring despite warnings in the SPC and PIL and recommended as follows:

- i. Further analysis of the available studies is required to determine whether it is possible to predict a patient population who may be at particular risk.
- ii. In addition, the overall risk:benefit of alendronate needs to be addressed particularly in relation to oesophageal reactions.
- iii. The warning in the SPC needs to be strengthened stating that these reactions may still occur, in spite of compliance with dosing instructions.
- iv. An article in *Current Problems in Pharmacovigilance* is required to remind prescribers of the risk of potential oesophageal reactions and, the need for detailed advice to patients on the side-effects and the importance of strictly adhering to dosing instructions at the time of prescribing. [Note: an article appeared in August 1998 – see volume 24 on <http://www.mca.gov.uk/mca/csmhome.htm>]

- v. In addition, concern was expressed that the cause of the oesophageal problems may be due to the pill becoming lodged and discussions centred around the possible need for a change in formulation. This should be discussed with the Marketing Authorisation holders.

10. **Hormone Replacement Therapy and Reproductive Cancers and Cardiovascular Disease: Proposed Remit and Membership of Working Party:**

The Committee endorsed both the remit and its membership but suggested that a gynaecological expert was included.

11. **MMR Vaccine:**

The Committee noted that the Committee/MCA have set up an expert working group under the Chairmanship of Professor Langman and this group will be evaluating cases principally of autism thought by parents to be associated with MMR Vaccine received by the MCA through the solicitors, Dawbarns. The work is ongoing and the group will report to the Committee later this year.

12. **Annual Report 1997 - for written comments**

Members were asked to send their written comments to the Secretary by 31 March 1998.

13. **Adroit Statistics**

The Committee noted a 20% increase so far this year.

14. **Essential Similarity**

This item was withdrawn from the agenda.

15. **Any Other Business**

None.

16. **Date and Time of Next Meeting**

The next meeting will take place on **Wednesday 15th April 1998 at 10.00 a.m.**

note 1: information is being withheld on the grounds that this application was withdrawn before regulatory action was complete and therefore details of that application should remain confidential (exemption 13 of the Code of Practice on Access to Government Information)

note 2: information about these applications is being withheld on the grounds that this advice remains confidential as at the date of this summary and publication would be premature while regulatory action continues. The advice will be published in due course. Exemption 10 of the Code of Practice on Access to Government Information applies

note 3: for information - proposals to change the legal classification of medicines, as recommended by CSM, are subject to wide consultation and the approval of Ministers. This process generally takes six months. Any changes come into force on the effective date in the relevant Statutory Instrument.

note 4: the CSM did not support the application(s) for a change in the product(s) legal classification. Further information is being withheld at this stage under exemption 13 (third party's commercial confidences) of the Code of Practice on Access to Government Information.

note 5: for information - at a pre hearing the CSM considers the company's written data and decides whether or not its concerns have been addressed by that data. If not, the company is invited to attend the Committee the following month to present its data orally.