DATE OF SUMMARY: APRIL 2001

SUMMARY OF THE MEETING OF THE COMMITTEE ON SAFETY OF MEDICINES SUB-COMMITTEE ON PHARMACOVIGILANCE HELD ON TUESDAY 20 JUNE 2000

PRESENT

Professor M Kendall (Chairman)
Dr K Beard
Professor R Jones
Ms A Lee
Dr M Pirmohamed
Professor K McPherson
Professor P Routledge
Dr S Thomas

Miss S Wark (Principal Assessor)
Dr J Williams (Secretary)
Dr J Raine
Dr P Arlett
Dr N Baber
Dr M Barratt-Johnson
Miss S Bhasin
Mrs C Carty
Dr K Cheng
Mr M David
Dr S Davis
Dr S Dodd
Ms J Eaton
Mr T Green
Dr C Hawkins
Dr M Hudson
Miss L Kerr
Mrs J MacDonald
Dr S Millican
Dr S Morris
Dr O'Mahony
Dr J Pallett
Dr C Parikh
Dr F Rotblat
Dr R Survana
Dr P Tsintis
Dr P Waller
Mrs A Williams
Dr J Woolley

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

1. INTRODUCTORY ITEMS

1.1 Apologies and announcements

1.1.1 Apologies were received from Dr Robin Ferner, Professor Jennifer Hunt, Professor Tom MacDonald, Mrs Leigh Henderson, Dr Edmund Major, Dr Jane Moseley and Mr Jim Slattery.

1.1.2 The Chairman welcomed to the meeting Professor Shenfield of the Adverse Drug Reaction Advisory Committee, Sydney, Australia.

1.1.3 The Chairman also welcomed to the meeting new members of MCA personnel Mr Amer Alghabban, Dr Angela Horsfall, Dr Bridget Jennings and Dr Jane Woolley.

1.1.4 The Chairman informed members that the issues considered at SCOP are confidential and that members should not speak directly to the press but should refer any enquiries to the Chairman, MCA or Press Office. At scientific meetings, they should take care not to give the impression that they speak on behalf of the Committee.

1.1.5 The Chairman also reminded members that at meetings, before each paper is discussed, they must declare any interest in the issues to be considered.

1.2 Minutes of the last meeting

The minutes of the meeting held on 25 April 2000 were agreed as a correct record.

1.3 Feedback from the last meeting

1.3.1. Clozapine and haematological monitoring – ***[see note 1 below]***

1.3.2 Revocation proposal – ***[see note 1 below]***

1.3.3 Quixil – neurotoxic potential

The Committee was informed that, following the consideration of the neurotoxicity of Quixil by SCOP and CSM in April, the Marketing Authorisation for Quixil had been amended. The changes were to Section 4.4 (Special Warnings and Precautions for Use) to include a warning that Quixil must not be used in any situation where it may come into contact with the CNS, dura mater or CSF, and to Section 5.3 (Pre-clinical Safety Data) to include reference to the neurotoxicity seen in the rabbit studies, in accordance with the Committees'advice.

2. CURRENT SAFETY ISSUES

2.1/2.2 Meningitis C (Meningitec and Menjugate): Safety review

2.1.1. The Chairman informed the Committee that item 2.1 and item 2.2 were to be considered together under item 2.1 as both relate to Meningitis C and the proposed recommendations would apply to both.

2.1.2 A Committee member declared a lapsed personal non-specific interest in Wyeth.

2.1.3 The Committee was informed that Meningococcal C disease has a mortality of approximately 10%. The impact of the vaccination programme has been to reduce the incidence of Meningococcal C disease by 75%. Thirteen million doses of vaccine had been supplied by May 2000. Because of the very high uptake of the vaccine, spontaneous reporting of suspected ADRs has been extensive. A number of reports of convulsions or epilepsy have been received in association with the use of Meningitis C vaccine. However, the reporting rate on convulsions is very rare i.e. less than 1 in 10, 000. Alternative causative factors were present in many of the cases.

2.1.4 The Committee considered that the balance of risks and benefits for Meningitis C vaccine was overwhelmingly favourable. However, there were concerns that some of the reported suspected adverse reactions may not be causally related and there may be a lack of good quality reports. A proactive strategy to collect data may be appropriate in vaccine programmes in future.

2.1.5 The Committee reviewed the list of suspected adverse reactions proposed for inclusion in product information. It considered that some of the reported convulsions could have been misdiagnosed faints. In addition, in infants causality of convulsions was difficult to assess because of administration of concomitant vaccines. Despite this, the Committee considered that causal association between Meningitis C vaccine and convulsions could not be excluded and therefore warnings should be added to product information. The Committee recommended that statements questioning the causal association between convulsions and Meningitis c vaccine should not be included in the product information. A further study of a possible association with convulsions with Meningitis C vaccine should be considered.

2.1.6 The Committee recommended that warnings about anaphylaxis should be included in product information. Where there was no recorded previous exposure to Meningitis C vaccine, the appropriate term was anaphylactoid rather than anaphylactic. All other proposed changes to product information were endorsed.

2.1.7 The Committee advised that the Black triangle status should remain for both vaccines despite the extensive exposure gained with the vaccine to date. This would maintain consistency of reporting requirements. A further product was expected to be authorised in the near future and would also carry a Black Triangle.

2.1.8 The Committee advised on communications regarding the safety of Meningitis C vaccine. It was agreed that information should be cascaded via vaccine co-ordinators as well as an article in the *Current Problems in Pharmacovigilance* bulletin and CMO's update. Any communication should be balanced setting the safety profile against the overwhelming benefits of vaccination.

[**Note**: messages from the Chairman of the CSM and the Chairman of the JCVI can be viewed on http://www.mca.gov.uk/mca/csmhome.htm]

2.3 SSRIs and suicidal behaviour

2.3.1 Two Committee members declared non-personal, non-specific interests in Pfizer and one Committee member declared non-specific interests in Pfizer and Lundbeck. Another Committee member declared a personal, specific interest in Pfizer and left the meeting whilst this item was discussed.

2.3.2 The Committee was informed that the issue of Selective Serotonin reuptake Inhibitors (SSRIs) and suicide had been reviewed following recent media activity. Previous reviews of fluoxetine and suicide in the early 1990's had concluded that it was likely that fluoxetine was not causally associated with suicidal ideation, however information on high risk patients was lacking and concern remained.

2.3.3 The Committee was informed that, despite a large body of data collected since the last review, some of it reassuring, it was not possible to rule out an adverse effect in a small population of high risk patients.

2.3.4 The Committee was also asked to consider the relevance of the publication of case reports of suicidal ideation in healthy volunteers given sertraline.

2.3.5 The Committee considered the paper before them and agreed with the conclusions of the assessor. They commented that:

- Data collected since the last review of the issue in 1991 did not raise any new concerns.

- Reporting rates of suicidal behaviour associated with fluoxetine in recent years were reassuringly low.

2.3.6 The Committee agreed that Patient information leaflets (PILs) for the SSRIs should be updated to include a warning that suicidal thoughts may increase in the early stages of treatment. They considered that the following wording, which includes specific mention of suicide and suicidal thoughts, was appropriate for the PIL.

'Occasionally, thoughts of suicide or self-harm may occur or may increase in the first few weeks of treatment with < >. Tell your doctor immediately if you have any distressing thoughts or experiences.'

2.3.7 The Committee also agreed that the outcome of this review should be published in 'Current Problems in Pharmacovigilance' as part of an 'In Focus' article bringing together a number of issues relating to SSRIs.

2.3.8 The committee commented that a further study on GPRD to update that published by Jick et al in 1995 may be of benefit.

[**Note**: the article mentioned in 2.3.7 above appeared in *Current Problems in Pharmacovigilance* in September 2000 – see http://www.mca.gov.uk/mca/csmhome.htm]

2.4 Thromboembolic events and rofecoxib (Vioxx): VIGOR study

2.4.1 A Committee member declared a non-personal, non-specific interest in Merck, Sharp & Dohme.

2.4.2 The Committee was informed of the potential safety signal regarding rofecoxib and cardiovascular thrombo-embolic events, which has arisen following release of the preliminary results of the VIGOR trial (comparing rofecoxib and naproxen), in the treatment of rheumatoid arthritis.

2.4.3 The Committee was informed that the data from other trials did not corroborate this potential safety signal but that data from a low number of spontaneous adverse drug reaction reports was weakly supportive. Evidence from experimental pharmacology, reported in the literature, suggests that protective (antiplatelet) effects of naproxen and harmful (pro-aggregatory) effects of rofecoxib are both biologically plausible.

2.4.4 The Committee was informed that the Marketing Authorisation (MA) Holder's position was that the results of the VIGOR study reflect protection from cardiovascular ischaemia offered by naproxen and do not represent a safety signal for rofecoxib.

2.4.5 In considering the paper, the Committee was in agreement that COX-2 inhibitors lack antiplatelet activity, and that the thrombo-embolic event rates in the VIGOR study were consistent with a protective effect of the non-selective NSAID naproxen and the absence of such an effect with rofecoxib. The Committee considered the possibility of a prothrombotic effect of rofecoxib, noting several factors (dose, inflammatory process), which may be important.

2.4.6 The Committee discussed the need for the addition of new warnings to the Summary of Product Characteristics (SPC) and concluded that the existing statement (included in section 5.1 of the SPC), indicating that rofecoxib does not inhibit platelet function, is adequate and that no regulatory action is required.

2.4.7 The Committee agreed that an article in "Current Problems in Pharmacovigilance" should focus on the safety profile of rofecoxib.

2.5 Fexofenadine (Telfast)

One member declared a non-personal, non-specific interest – ***[see not 1 below***

2.6 Drugs and Driving

No interest were declared – ***[see not 1 below***

2.7 European pharmacovigilance – Post-Licensing issues

The Committee noted this information.

2.8 CPMP Conclusions: May 2000

The Committee noted this information.

3. NEW SIGNALS

3.1 Doxazosin (Cardura): ALLHAT Study

3.1.1 Two Committee members declared non-personal, non-specific interests in Pfizer and another Committee member declared a personal, non-specific interest in Pfizer.

3.1.2 The Committee was informed of the proposal to prepare an assessment report on the safety of doxazosin, in the light of the recent premature termination of the doxazosin arm of the ALLHAT study.

3.1.3 The Committee agreed that an assessment would be appropriate once more analyses of the ALLHAT interim results are available and that the assessment should include evidence on the safety and efficacy of doxazosin from other sources, such as the published literature.

3.2 Olanzapine (Zyprexa) and diabetic ketoacidosis

No interests were declared – ***[see note 1 below]***

3.3 Raloxifene (Evista) and hypertension

3.3.1 No interests were declared.

3.3.2 The Committee was informed that several spontaneous reports of hypertension, some of which were particularly severe, including suspected malignant hypertension have been received in association with raloxifene. The Rapporteur has been made aware of the MCA's concern and will approach the MA holder for a cumulative review of hypertension cases.

3.3.3 The Committee considered this paper and expressed their concern, especially as some of the cases the increases in systolic blood pressure were very marked.

3.4 Palivizumab (Synagis) and sudden death in premature babies

3.4.1 A Committee member declared a non-personal, non-specific interest in Abbott Laboratories.

3.4.2 The committee was informed that the first Periodic Safety Update Report has highlighted a worrying number of deaths in premature babies coincident with palivizumab therapy. This issue is to be considered by the Pharmacovigilance Working Party of the CPMP at its July meeting.

3.4.3 The Committee considered this paper and commented that the mortality and morbidity rate in premature babies is very high compared with infants born at full term. However, it was agreed that further information and a detailed review of this issue was required. It was also agreed that a epidemiological study, with input from an expert paediatrician, may be the most appropriate way to investigate this issue further.

4. LEGAL RECLASSIFICATION – *[see note 2 below]*

4.1 Bezylpenicillin, streptokinase, frusemide, syntometrine, metoclopramide, morphine sulphate (For ambulance paramedics)

4.1.1 No interest were declared.

4.1.2 The Committee considered whether benzylpenicillin (for suspected meningococcal septicaemia), syntometrine (for post partum haemorrhage), morphine sulphate (for pain relief in severe pain), metoclopramide (for nausea and vomiting), frusemide (for acute pulmonary oedema), and streptokinase (for immediate thrombolytic therapy in acute myocardial infarction) are appropriate medicines to be made available for administration by Ambulance Paramedics for the immediate necessary treatment of sick and injured persons.

4.1.3 The Committee recommended that the following drugs should be added to the list of drugs already approved for administration by paramedics in emergency medical situations:

Benzylpenicillin
Frusemide
Syntometrine
Morphine sulphate
Metoclopramide
Streptokinase

4.2 Application for a change in legal reclassification from POM to P

One member declared a non-personal, non-specific interest. The committee considered that the POM order could be amended to allow non-prescription supply. [**Note**: the CSM, at its meeting on 12 July, did not agree the application – ***see note 3 below]***

4.3 Application for a change in legal reclassification from POM to P for Motilium (domperidone maleate)

4.3.1 No interests were declared.

4.3.2 The Committee considered whether domperidone maleate falls within a description or class specified for the purpose of Section 58 of the Medicines Act 1968 by Order made under Section 58(1), as being appropriate for supply on a prescription only basis in accordance with Section 58A(2) of that Act.

4.3.3. The Committee advised that the POM order could be amended to allow non-prescription supply, under the following conditions:

The container or package contains not more than 200 mg of domperidone as domperidone maleate.

4.4 Application for a change in legal reclassification from POM to P for Rhinolast Allergy nasal Spray (azelastine hydrochloride)

4.4.1 No interests were declared.

4.4.2 The Committee considered whether azelastine hydrochloride falls within a description or class specified for the purpose of Section 58 of the Medicines Act 1968 by Order made under Section 58(1), as being appropriate for supply on a prescription only basis in accordance with Section 58A(2) of that Act.

4.4.3 The Committee advised that the POM Order be amended to allow non-prescription supply under the following conditions.

Adults and children 12 years and over:
For the treatment of both seasonal allergic rhinitis and perennial allergic rhinitis.

The other conditions of the POM exemption for Azelastine hydrochloride will remain the same.

The committee commented that medical supervision was required in children under 12 years.

4.5 Application for a change in legal reclassification from POM to P for Alomide Allergy Eye Drops (lodoxamide trometamol)

4.5.1 No interests were declared.

4.5.2 The Committee considered whether lodoxamide trometamol falls within a description or class specified for the purpose of Section 58 of the Medicines Act 1968 by Order made under Section 58(1), as being appropriate for supply on a prescription only basis in accordance with Section 58A(2) of that Act.

4.5.3 The Committee advised that the POM order could be amended allow non-prescription supply, under the following conditions:

For ocular administration at a maximum strength of 0.1%
For the treatment of ocular signs and symptoms of allergic conjunctivitis in adults and children aged 4 years and older

4.6 Application for a change in legal reclassification from POM to P

No interests were declared. The Sub-committee did not recommend a change in the legal status of the product – ***[see note 3 below]***

5. PHARMACOVIGILANCE PROCEDURES

5.1 General Medical council guidelines on confidentiality

5.1.1 The Committee was informed that the General Medical Council (GMC) has adopted guidelines for doctors “Confidentiality:protecting and providing information” which are expected to be issued in August 2000. These Guidelines advise doctors to seek patients’ consent before disclosing personal information, whenever practicable.

The MCA raised its concerns with the GMC about the potential impact of the Guidelines on the reporting of suspected adverse reactions. But the central issue of the requirement for informed consent has not been conceded.

5.1.2 The Committee was invited to comment on the proposal to take steps to anonymise the Yellow Card and issue guidance to doctors in parallel with the GMC guidelines.

5.1.3 The committee expressed concerns over the ability to follow up reports if the Yellow Card was anonymised. Professor shenfield commented that this was not a problem in Australia where the reporting of suspected adverse drug reactions is already anonymised. It was commented that if the patients' practice or hospital number was used it may overcome this potential problem.

5.2 Current ADROIT Statistics

5.2.1 The Committee noted this information.

6. CURRENT PROBLEMS IN PHARMACOVIGILANCE

None.

7. ANY OTHER BUSINESS

None

8. DATE OF THE NEXT MEETING

The Chairman informed the Committee that the date for the next meeting is Tuesday, 26 September 2000 at 2pm.

Note 1:information about this item 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 2: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.

Note3: 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.