MINUTES OF THE FOURTEENTH MEETING OF THE MEDICINES CLASSIFICATION COMMITTEE HELD IN MEETING ROOM GO6 ON THE GROUND FLOOR OF THE MINISTRY OF HEALTH BUILDING, 133 MOLESWORTH STREET WELLINGTON ON WEDNESDAY 2 NOVEMBER 1994

Present

Dr S Martindale (Chair)
Mr R Griffith
Dr M Herbert
Dr J Wilcox
Ms U Egan
Mr G Caves
Mrs C Smith (Secretary)

In Attendance

Dr G R Boyd (till noon)
Miss A Surman (for liquid ibuprofen)
Mr M Rowland (afternoon session)
Dr S Jessamine (for oral contraceptives)

1 WELCOME

The meeting opened at 10:35 am. Dr Martindale welcomed members to the fourteenth meeting of the Medicines Classification Committee.

2 APOLOGIES

There were no apologies.

3 CONFIRMATION OF THE MINUTES OF THE THIRTEENTH MEETING

The minutes of the thirteenth meeting were confirmed by the committee and signed by the chairperson.

4 MATTERS ARISING

i Legislation review update

Dr Martindale summarised the action to date in the review of the medicines legislation. She explained that the three-month consultation period had been completed and that during that time there had been a number of public meetings, meetings with interest groups and focus workshops. There had been a good response with some 800 individual submissions and about 8500 form letters from people mainly concerned that access to complementary medicines might be restricted. There was also some concern from individual pharmacists about the proposal to ban advertising of restricted medicines and a number had signed a draft circular letter prepared by one of the pharmaceutical companies. With regard to classification, Dr Martindale said there had been a mixed response from pharmacists over the proposal to place restricted medicines into the prescription category and give pharmacists prescribing rights for these medicines. Support for the proposal had come from the Guild and Society rather than from individual pharmacists. She added that there had been very little comment on the composition of the Classification Committee.

The next step was to report back to Government by the end of November. Dr Martindale promised a further update at the next meeting.

ii Prescribing Rights Discussion Paper

Members noted that the completed Prescribing Rights discussion paper prepared by Professor John Shaw contained no major changes from the draft which they had read earlier. They noted that although the paper provided a considerable amount of information, it stopped short of making specific recommendations.

Two major concerns were noted by the committee. The first centred around the problems of bringing prescribers other than medical practitioners up to a suitable standard of training for prescribing and the cost of implementing this. It was felt that the increased cost could be passed on to consumers and thus provide a barrier to consumer accessibility. There was also discussion about how the classification committee proposed under the new legislation would seek the expertise to assess the training requirements and standards of other would-be prescribers. Dr Boyd explained that this was catered for in the proposed new legislation where the structure of the committee would allow for co-opted members with the required expertise.

The second area of concern was that of medico/legal liability especially of those prescribers with limited training in pharmacology. Members also recognised that there would be a distinction between an OTC medicine recommended by a prescriber and one actually prescribed and wondered about where responsibility would lie in the former case.

As members did not feel sufficiently well-prepared to contribute to a committee submission at that point in time, Dr Martindale suggested that individual members should send in their own responses through the secretary if they wished before the closing date at the end of November. Therapeutics Section would also have input to any policy recommendations made to the Minister following the analysis of submissions.

iii Classification Impact Study

Dr Martindale said that the draft report of the study commissioned by Therapeutics to assess the impact of the reclassification of selected medicines had been received by the Ministry but that the Ministry had not yet had a chance to examine it in depth. She thought that the number of consumers surveyed in the study had been quite small but that the information obtained might still be of value. She briefly outlined the method used to select consumer participants which was designed to preserve consumer privacy. She added that the Proprietary Medicines Association of Australia had shown an interest in making use of the design of the NZ survey to undertake their own study.

iv Review of MCC

Dr Martindale told the committee that the Therapeutics Section had commissioned a review of three Ministerial advisory committees by Health Research and Analytical Services. She said that although the report of the review had been provided mainly for the information of the committee, their comment would be welcome. She pointed out that members of the other committees reveiwed had been given the opportunity to comment and that ultimately the Ministry would decide on which, if any, of the recommendations would be actioned. She also pointed out that some of the recommendations could be actioned only through a change to the existing legislation.

The committee discussed the recommendations contained in the conclusion of the report.

- *That the terms of reference be enlarged to ensure the scope and function of the committee are clearly stated by including when a medicine should be referred to the MCC*

  Committee members had no comment on this recommendation. Dr Boyd pointed out that it was not clear from the present terms of reference exactly what the committee should do. Dr Martindale added that there was no requirement in the legislation at present to classify a medicine but that this would not remain with the introduction of product licensing.

- *That the legislation be changed to ensure that the MCC is no longer chaired by a Ministry representative*
  Members were happy with the chair being provided by the Ministry. They thought that it would be difficult to find a chairperson from outside the Ministry who was impartial and had sufficient knowledge to cope with the position in a competent manner. They acknowledged that members of professions might be tempted to "protect their patches". Dr Boyd explained that it was now Ministry policy not to have advisory committees chaired by Ministry personnel. It was noted that a change of legislation would be required to implement this recommendation. That change was included in the proposed new legislation.

- *That Therapeutics should have the authority to vet the nominees to the MCC to ensure that those with the appropriate expertise are nominated*
  Dr Martindale pointed out that under the present system nominees of the professional bodies were accepted on the basis of their membership of the body. There was no selection system. A change of legislation would be required to alter this. That change was proposed in the new legislation where committee members would be appointed for their particular areas of expertise.

- *That there is scope to open the meetings to allow experts to attend meetings and contribute to discussions*
  The committee considered that it was already open to accepting outside expert opinion when required. It was noted that written expert advice had been sought by the secretary on a number of occasions and that a speaker had been invited to attend a meeting but had been unable to attend. It was also noted that Therapeutics staff now provided reports for all major classification issues. Dr Boyd pointed out that classification changes often resulted in large financial consequences for pharmaceutical companies. Members agreed that it would be reasonable for companies to be allowed to present their views but that they should not be party to the deliberations of the committee.

- *That further thought should be given as to how to involve consumer input in the deliberations of the MCC*
  It was noted that there was no statutory provision at present for the inclusion of a consumer representative. Members felt that the selection of a suitable representative would not be easy. Dr Martindale explained that the concept was working well in Australia with their restructured committee. She said that a consumer representative would not necessarily need to have technical expertise but would have an interest in ensuring that the policies and procedures under which the committee operated were transparent, fair and reasonable and that committee procedures were followed. Dr Martindale commented that it would be possible to incorporate a consumer representative as an observer at meetings. It would also be possible to consult with the Consumers Institute on such matters as the preparation of guidelines and seek its interest in involvement with the terms of reference and operation of the new committee.

- *That an annual report should be produced*
  The committee felt the need for an annual report was not pressing, that interest would be limited and would come mainly from the pharmaceutical industry. Members thought that any annual report should be very short and agreed that one or two paragraphs in the Therapeutics Bulletin would be adequate.

- *That agenda and minutes should be circulated back to PHARMAC*
  Members were unanimous in their agreement that there should be no closer links with PHARMAC. They agreed that classification issues should remain separate from funding issues. The secretary explained that PHARMAC currently received the same information as the other bodies on the MCC mailing list about proposed classification changes and agenda items.

- *That a two tier process for implementing classification changes be implemented*
  Mr Griffith commented that events had overtaken the recommendation to operate on a two-tier system. He said that improved secretarial resources and the provision of expert advice from the Therapeutics Section made the recommendation unnecessary. The committee agreed with this observation.

- *That the MCC should be prepared to advertise widely what is on the MCC agenda so all those who are interested can contribute to the debate at the earliest possible stage*
  There was considerable discussion on how widely MCC should advertise agenda material. It was noted that wider notification would slow down the work of the committee considerably. The secretary pointed out that some initial screening process would be necessary as very few of the medicines submitted for reclassification at recent meetings had proved suitable for reclassification. Without screening much paperwork could be involved dealing with objections to submissions which were "non-starters" anyway. It was noted that any announcement to consider a medicine for reclassification was regarded by the media and general public as a signal that the Ministry thought the medicine suitable for reclassification.
  Dr Martindale outlined the British and Australian systems where prior notification occurred.
  Members questioned whether or not all medicines in a therapeutic group should be considered before individual medicines were reclassified. This would avoid piecemeal reclassifications which might not be consistent. They recognised that this overview might not be appropriate for all submissions but were unable to determine how submissions could be defined as "significant". Dr Martindale suggested that administrative guidelines could be produced within the Ministry to deal with this. She suggested draft guidelines be sent to members for comment before the next meeting.
  Dr Boyd suggested that a review of the terms of reference of the committee should also be drafted along with guidelines about the way in which the committee should operate in line with the changes discussed in this agenda item.

Recommendation
That the above comments be forwarded to Therapeutics for consideration with other feedback generated from the survey of Ministerial advisory committees.

That draft guidelines be drawn up by the Therapeutics Section to describe details of the terms of reference of the committee, the manner in which the committee should operate, the way medicines should be selected for reclassification and the ways in which appropriate agenda items might be widely advertised in advance.

That the involvement of consumer input should be investigated.

That the guidelines should be drawn up with a view to being incorporated into one overall document to cover all aspects of the operations of the committee.

v Liquid ibuprofen

Ms Surman spoke to the Therapeutics Section report that she had prepared. She explained that this item followed on from the previous meeting which had dealt only with the juvenile preparation for children between 12 months and 12 years. A change from prescription to restricted medicine had been recommended. The previous meeting had not dealt with the use of liquid ibuprofen for adults, for children under 12 months of age and for the higher doses required for the treatment of juvenile rheumatoid arthritis. The proposed reclassification of the juvenile preparation only would present classification inconsistencies and scheduling difficulties.

Ms Surman pointed out that the indications for Brufen and Nurofen Junior were similar except for the treatment of juvenile rheumatoid arthritis. She also pointed out that the adult indications for Brufen were the same as those for ibuprofen 200mg tablets. She said that the company did not want to market ibuprofen liquid OTC for adults. It had no intention of marketing Nurofen Junior for rheumatoid arthritis and the dosages on the labels were insufficient for this indication. The company had added extra warnings to the label against use in hypovolaemic children and would probably add more warnings if required. The new labelling was supplied.

The committee was concerned that the label reference to the contraindication for children was based on weight rather than age, as children as young as 4 months could have reached this weight. They agreed that the medicine would not be suitable for OTC sale for children under 12 months of age regardless of weight.

They were also concerned at the advice to reduce the child's dose in the case of high temperature or dehydration through diarrhoea and/or vomiting. Members felt strongly that this medicine should be contraindicated in such cases.

The medicine was compared with paracetamol and it was acknowledged that there was no evidence to suggest that ibuprofen was more hazardous than paracetamol.

Members agreed that the medicine was likely to be used in a safer way if supplied by a pharmacist.

It was agreed that as the warnings and lower age-limit which the committee required for OTC sale could not be enforced through the classification schedule, the sale as a restricted medicine would need to be limited to sale in original, approved OTC packs. Guidelines would be needed by the Therapeutics team for the evaluation of liquid ibuprofen to ensure that OTC consent was obtained only for packs labelled in compliance with committee recommendations.

The Therapeutics Section would finalise details of what was to be contained on labels. The MCC framework for the guidelines for approval for sale as restricted medicine should be used by evaluators when assessing presentations for OTC sale.

Recommendation

That ibuprofen in liquid form be classified as a restricted medicine when:

- *sold in the manufacturer's original pack which has the consent of the Minister for sale as a restricted medicine*
- *in pack sizes of not more than 200 millilitres*
- *in strengths of 100 milligrams or less per 5 millilitres*
- *contraindicated for use for children under 12 months of age*
- *contraindicated for use in children with a temperature higher than 37.7 degrees C*
- *contraindicated for use in children suffering dehydration through diarrhoea and/or vomiting.*
- *juvenile rheumatoid arthritis is not included as an indication*

5 SUBMISSIONS FOR RECLASSIFICATION

i Prochlorperazine (Buccastem, Reckitt & Colman)

Mr Griffith spoke to the report he had prepared. He commented that the company submission was fairly ill-defined in that the company had no proposal to limit the indications for OTC sale. The product measured up reasonably when assessed according to the criteria on the classification checklist, and Mr Griffith felt that an OTC classification could be justifiable for specific indications and limited pack sizes. He pointed out that the medicine was ineffective in the control of nausea caused by motion sickness but that he would support reclassification for use in the treatment of nausea associated with migraine.

Dr Wilcox said that he had not changed his position since the discussions at the 1992 meeting. He felt that it was more appropriate to treat the migraine rather than the resultant nausea. He was also concerned about observed side-effects and that the medicine was known to cause some sedation.

Ms Egan pointed out that any need in the market was already filled by Paramax which was aimed at dealing with both the migraine and the associated nausea.

Members decided that a recommendation should be deferred. They agreed that overall they might be in favour of supporting restricted medicine status for a small pack size of up to 10 tablets and for nausea associated with migraine only. However, before a recommendation could be made they would like to obtain the view of the Medical Assessor from the Centre for Adverse Reactions Monitoring in Dunedin on whether he was satisfied that any adverse effects had not proved sufficient to warrant concern. They would also like more specific information from the company concerning proposed pack size, labelling and indications. The committee would not support motion sickness as an indication.

The committee broke for lunch at 12:35pm.

The two items concerning oral contraception were discussed at the end of the agenda

ii Oral Contraceptives

Dr Martindale explained that in this initial discussion the committee was required to look solely at the safety issues related to the use of oral contraceptives in order to determine whether they felt the safety of these medicines warranted further investigation as a group of medicines to which wider access could possibly be granted. She added that wide consultation and investigation of a number of other issues would be needed before any recommendation could be made. She said that the Ministry had undertaken an extensive literature search on safety-related literature and that members had been provided with the resulting key papers and abstracts together with a summary of these prepared by Dr Stewart Jessamine.

Dr Jessamine then explained his research methods using EMBA database and outlined the content of his summary.

It was noted that:

The oral contraceptive pill has been studied extensively since its first introduction in the 1960s. It has been estimated that in the 35 years since it was first made available the OCP has been taken by up to 3 billion women. It is estimated that about 25-30% of women aged 16-45 years are currently using the OCP for contraception, ie. approx 50 million women worldwide. In the USA alone it is estimated that 10-15 million women currently use the OCP.

The extensive use of the OCP has been paralleled by scientific examination of the risks and benefits associated with their use. Without doubt the OCP is the most investigated and reported upon medicine ever developed. Despite the enormous amount of safety data generated by 35 years of use several studies have reported that up to 75% of women have significant concerns about the safety of the OCP. These largely unfounded safety concerns are probably reflected in the poor compliance rates for pill use and the discontinuation rate of 50% within 1 year. In the papers reviewed the average duration of use of the OCP for women aged 15-45 years is reported as only 49 months.

Risks associated with use of the Oral Contraceptive Pill

It is important to remember that a great deal of the early work which linked use of the OCP to increased risks of cardiovascular disease and other conditions was performed on older patients who were using high dose OCPs containing >50 mcg of ethinyloestrodiol. Review of this data combined with meta-analysis of more recent data using lower dose pills has clarified the situation concerning safety. A further important consideration is to view risks associated with the use of the OCP against the risks associated with pregnancy. In the USA 1-2% of all deaths in women aged 15-44 years are related to pregnancy, with ectopic pregnancy contributing the most to this mortality and therapeutically induced abortion the least.
These risks are put in perspective in a recent paper written by Tyrer which stated that in the USA the risks of death associated with the use of the OCP only exceeds that of pregnancy in women aged >35 yrs who smoke more than 25 cigarettes per day.

Coagulation disorders

The oestrogen contained in the OCP has been demonstrated to have effects on the coagulation system at several points in the clotting pathway increasing the production of several clotting factors. Oestrogen exerts has negative effects at several points in the anti-coagulant system, such as decreasing antithrombin III and increasing platelet aggregation through effects on prostacyclin production. These oestrogenic effects on coagulation produce a dose dependant increase in the risk of thromboembolism and thrombosis.

Cerebral thromboembolism

The Lidegaard paper examined the risk of developing cerebral thromboembolism in women using the OCP. The trial demonstrated that at the time of the event 36% of patients were using the OCP against a background rate of 16% OCP use in the control group. The calculated odds ratio was 2.8 X the control group for women on doses of the OCP containing >50ug oestrogen but only 1.8 for OCP containing 30-40ug oestrogen. The odds ratio did not change with increasing age or duration of pill use, however the odds ratio was increased by a further 50% by smoking, which was independent of OCP use or age, ie odds ratio for non OCP users who smoked was 1.5 against non smoking non OCP use controls. Whilst this study suggests that decreasing the dose of oestrogen decreases the risks of thromboembolism there are several methodological problems associated with this type of study, not least being that women at high risk of embolism have been excluded by physicians prior to prescription. Other confounding factors include the inability to easily separate haemorrhagic strokes from thrombotic and difficulties with age matching the differing OCP using populations within the study. The significance of the results of this type of study are also questioned by comparison of the study results with the incidence and mortality results for cerebral thromboembolism before and after the introduction of the OCP. The incidence of embolic stroke does not exceed that of men and has not increased following introduction of the OCP. The Lidegaard paper concludes that the relative risk of cerebral thromboembolism does not change with increasing age, the absolute risk, which is multiplied, increases nearly exponentially with age. For a 20

year old women the absolute risk for this condition is approx 2/100,000/year increases to 4/100,000/year for a 30-40 ug OCP to 6/100,000/year for a 50ug OCP *respectively, whereas a women of 40 years increases her risk by about a factor of 10.*

Cardiovascular Disease
The La Vecchia paper presents a pharmacoepidemiological overview of the relationships between OCP use, cancer and vascular disease. The paper documents the results of several large cohort type studies which demonstrated that use of the OCP is associated with an increase in the risk of developing vascular disease. Review of these studies suggest that the negative effects of the OCP are possibly restricted only to current users and that OCP use is an independent risk factor from all other risk factors. The relative risk associated with OCP use appears similar in all age groups, however the absolute risk increases with age and in the presence of other risk factors. The independent risk factors for vascular disease are multiplicative with Grimes reporting that the RCGP study demonstrated that current users who were non smokers had no increased risk of infarction, smokers of <15 day had a 3 fold increase in risk and smokers >15 day had a 21 fold increase. The most important risk factors appear to be age and smoking.

La Vecchia concludes that avoidance of the OCP in women at high risk of heart disease (including smoking) who are >35 years of age would avoid most of the increased risk of cardiovascular disease. The authors of this paper point out that the lack of epidemiological data on the newer OCP formulations is in part due to the decreased prevalence of vascular disease for these preparations but also due to the widespread acceptance of this type of exclusion criteria for prescription of the OCP. Indeed they argue that it is selective prescribing which has decreased the incidence of cardiovascular disease rather than the use of low dose formulations.

Once again it appears that the increase in mortality and morbidity is secondary to thrombosis rather than atherosclerosis, a conclusion supported by the Nurse Health study which found no increase in risk of myocardial infarction in former users of the OCP. As with cerebral embolism there does not appear to be a duration related effect between length of OCP use and risk.

Hypertension
It is generally quoted that between 1% and 5% of normotensive pill users will develop elevated blood pressure whilst taking an OCP which is reversible on discontinuation. These findings are not supported by all investigators and the clinical significance of the findings are not well documented. It is not clear in the reports reviewed whether the increases in BP reported represented an increase in BP of >5mmHg or rather that the blood pressure increased above that of clinical concern. A study by Brill of a low dose OCP reported that the blood pressure fell in more women than it rose by a significant amount, in only 5 out of 3267 patients did the BP increase by 1-10mmHg. Once again the possible hypertensive effects of the OCP are commoner with increasing age and positive family history and in most cases monitoring of BP in the first 3 months of use allows identification of the affected women.

Metabolic Effects
Both carbohydrate and lipid metabolism can be affected by the OCP. The effects on glucose tolerance are secondary to progestogen especially 19 nor-progestogens. Recent studies with third generation progestogens and low dose oestrogens demonstrated no significant effect on insulin metabolism and can be used in women with IDDM.

Oestrogens and progestogens are known to have effects on the metabolism of both HDL and LDL cholesterol producing an atherogenic lipid profile. These changes in lipid metabolism are not found in the third generation progestogens, gestodene and desogestrel, and the relevance of the changes are called into question by the finding that the changes in the wall of the blood vessels found in women with vascular disease are not atherosclerotic in nature.

The effects of the OCP on biliary cholesterol secretion are less clear. The RCGP study found an increase in the incidence of gallstones for the first 3 years of use only. The incidence of gallstones in OCP users was found to be lower than in the control population after 7 years use. Bagshaw expresses the opinion that the clinical effect of new low dose pills on lipid metabolism and atherogenic disease is minimal.

Cancer

The effects of the OCP on the incidence of cancers in general is complicated by the effects of the OCP on differing tumour types. The major outstanding question about the long term safety of the OCP relates to a possible association with breast cancer.

Breast Cancer

Despite the large number of studies the debate on the possible association between OCPs and breast cancer is far from settled. The overall evidence is reassuring as temporal trends indicate that there is no consistent evidence that breast cancer rates have been substantially influenced in any age group by the widespread use of the OCP.

La Vecchia quotes a review of 16 studies of a total of 12,000 cases which indicates that the risk of breast cancer is not higher among women who have used the OCP. The summary relative risk RR was 1.0 with very narrow confidence intervals of (0.9-1.1). Further analysis of these patients and meta-analysis of other studies have suggested that within this heterogeneous group of women exists sub-groups of women who are at increased risk. These sub groups may include women who are nulliparous or who had prolonged use of the OCP prior to their first pregnancy, women who used the OCP for >8 years and women aged 30-34 years.

Another meta-analysis by Rushton published in 1992 reviewed a total of 27 differing studies and attempted to employ regression techniques to explore the inter study heterogenicity. This study concluded that the overall relative risk was 1.16 (95 CI 1.07-1.25) for women age <45 yrs, 1.21 for nulliparous women (95% CI 0.99-1.47) and 1.27 (95% CI 1.12-1.44) for duration of use more than 8 years. The risk estimates were influenced by the individual study designs but suggested that the risk of developing breast cancer was increased by about 20% in the group of women who had been identified as being at increased risk.

Baird states in his review of the OCP that although the calculated increase in risk from meta-analysis is large enough to be discernible in national cancer registry data it has not been found. The WHO have reviewed the scientific data and concurred that there is no increase in risk of breast cancer amongst pill users and that no changes in family planning policy is necessary concerning advice to women about the OCP and breast cancer.

Cervical Cancer

The relationship between the use of the OCP and cervical cancer is not clear. There have been some reports of increased risk of cervical cancer in women who are long term users of the OCP. It cannot be determined whether these findings represent a causal relationship because of methodological problems which include diagnostic bias as women who use the OCP are more likely to have regular cervical smears than non

users. Several other confounding variables which cloud the issues of a possible link include OCP use and cervical cancer include sexual practices, age and race/religion of spouse, whether spouse is circumcised, smoking history, parity, past history of sexually transmitted disease. All of these variables have been linked to possible increasing a women's risk of developing cervical cancer, a trial to determine the increase in risk associated with the OCP would need to be massive to allow for matching of all these variables. Review of the papers fails to come to any consensus type decision about the management of women on the OCP other than recommending regular cervical cytology examination.

Liver Cancer

Whilst it is known that the OCP considerably increases the risk of developing hepatic adenoma by a factor of X10-20, there are only a small number of trials examining the risk of primary liver cancer. The largest single reported study appears to be the WHO Collaborative Study which examined the use of the OCP in women who developed primary liver cancer. The results of this study demonstrated a relative risk of 0.60 suggesting no association however this study was performed in a population with a high incidence of Hepatitis B virus carriage and in women who had only a short term exposure to the OCP.

A more representative study for NZ may be the Oxford Family Planning Study conducted by Vessey which has not reported any cases of primary liver cancer from a database of $>17,000$ patients collected over a 20 year period. Several smaller studies are reported by La Vecchia all of which have suggested an increased risk for primary liver cancer with a strong duration risk relationship ie RR 10 for OCP use >8 years. The incidence of primary hepatocellular carcinoma is extremely rare and therefore the increase in absolute risk is minimal.

Amenorrhoea and Delayed Fertility

The risk of amenhorrea after discontinuation of the OCP is reported as $<1\%$ in a paper by the American College of Obstetricians and Gynaecologists (ACOG) and is commoner in women who had irregular menses prior to commencing the OCP. It would appear that rather than causing oligomenhorrea the OCP may simply mask it by producing cyclical withdrawal bleeding. The delay in return to fertility has been reported by the Oxford Family Planning study as transient, lasting 2 months on average.

Effect on Height and Weight

Brill reports in his study of women using a low dose OCP for a period of 18 months that total weight change over this period averaged +/-0.2 kg. During the study period 71% of women remained within a body weight range of +/-2kg, which is regarded as the limits of physiological weight change. Concerns that use of the OCP in teenagers may have an effect on growth are unfounded. The ACOG report that the modern low dose OCP do not cause premature closure of he epiphyses or inhibit skeletal growth. By the time menarche occurs, endogenous oestrogen production has already initiated epiphysial closure which cannot be altered by small doses of exogenous steroids.

Interactions

Whilst there is extensive documentation of the effects of the OCP on the pharmacokinetics of several medicines and vice versa the overall incidence and significance of many of these interactions is unknown. In many respects the effects of the known interactions impact on the efficacy of the OCP in $<5\%$ of women than on exacerbating its safety profile. As stated in the Fotherby paper on interactions," the incidence of serious interactions is low and does not appear to have been reduced with low dose contraceptives, probably because of large intersubject variability in the pharmacokinetics of the oral contraceptives".

In summary it is now clear that the risks of vascular disease associated with use of the OCP in women with no other risk factors are minimal and cannot be separated from the increase in risk of CHD associated with aging. The excess mortality reported in several studies associated with the use of the OCP can be almost completely negated by removing women with known hypertension, clotting disorders and most especially smokers from the calculations of mortality. It is likely that reclassification of the OCP to allow OTC access for women aged under 35 who were non smokers would produce no discernible changes to the morbidity or mortality figures for deaths associated with OCP use. The Bagshaw paper demonstrates the relative risks of various activities compared to use of the OCP, as can be clearly seen the risks associated with simply staying at home are only marginally less than being aged 35 on the OCP and both are substantiably less risky than being pregnant. To put all these relative risks into some kind of perspective the paper by Fraser on contraceptive choices for women with risk factors estimates that the total number of oral contraceptive related deaths for women in low risk categories is approx 70 per year, from a population of OCP users of 10-15 million women. In comparison the USA mortality rates for all pregnancies is 1-2%.

Benefits

The benefits associated with use of the OCP curiously remain largely unknown and unappreciated by the majority of women and by many health professionals. Review of the scientific evidence available is unanimous in its support of the major health benefits for women associated with the use of the OCP. As Tyrer states in the introduction of her paper "Clearly for the general population the protection from risks associated with pregnancy alone is so profound compared with the risks associated with use of the OCP that it more than justifies its use for appropriate candidates. With the addition of significant health benefits which have become recognised in recent years the benefit/risk ratio with OCP use is even greater." This statement is echoed in statements by Grimes and again by Bagshaw who state that the OCP may be the only medicine that increases life expectancy and gives the anonymous gift of health.

The benefits obtained from the use of the OCP are found with both high and low dose formulations and extend beyond the risks associated with pregnancy to powerful protection against several life threatening diseases.

Ovarian cancer

The most important non contraceptive health benefit is protection against ovarian cancer which has a significant mortality in women aged 15-45 years. Review of the Cancer and Steroid Hormone (CHC) study and of the meta-analysis reports contained in the La Vecchia paper strongly support the reduction in incidence of ovarian cancer following use of the OCP. The reduction in incidence of ovarian cancer has been found following as little as 6 months OCP use and protection continues for up to 15 years after discontinuation of the medication. The protective effect is reported to be in the order of 40% in the CHC study independent of the specific OCP formulation and of the histological type of epithelial ovarian tumour. Both Wood and Tyrer report that the reduction in risk of developing ovarian cancer appears to increase with duration of use to a max of 80% (RR 0.2) after 10 years of continuous use of an OCP. It is stated in the La Vecchia paper that since the incidence of ovarian cancer is already appreciable in middle age and that as the prognosis is poor, the protection attributable to OCP use corresponds to several hundred lives saved per year.

Endometrial Cancer
Protection from endometrial cancer is in the same order of magnitude as that found for ovarian epithelial tumours. La Vecchia records the results of 6 separate trials which all demonstrate a consistent decrease in the risk of developing endometrial cancer in the order of 50% (RR 0.5) compared with never users of the OCP. Once again the protective effect appears to increase with duration of use and the protective effect appears to persist for up to 10-15 years demonstrating the causal nature of the association. Endometrial cancer has a relatively good prognosis and is largely a disease of older women rarely occurring during a woman's reproductive years. The lack of evidence of persistent protection in older age groups means that despite the proven impact of OCP use on the incidence of this tumour, its effects on mortality and morbidity are relatively limited

Pelvic Inflammatory Disease
ACOG reports that the risk of being hospitalised due to PID is reduced by 50% by the use of the OCP. It is thought that the OCP produces its protective effect through changes to both the cervical mucous and endometrial lining preventing ascent of infective agents. Grimes also states that the severity of PID, should it develop in a women using an OCP, is likely to be classed as less severe.
Although the exact mechanism of protection is unknown and the mortality of this condition is small, PID is a significant and serious condition affecting women's health. PID has profound effects on morbidity and due to its effects on the fallopian tube, where it causes scarring, it is probably the leading cause of infertility in the world. The relationship between previous PID and ectopic pregnancy is well recognised and as previously reported the latter condition is a significant contributor to pregnancy related mortality. Paradoxical as it may seem the use of the OCP may be one of the most effective ways of reducing the incidence of infertility after education about safer sex and how to avoid sexually transmitted disease.

Ectopic Pregnancy
The incidence of ectopic pregnancy is reduced by approximately 90% in users of the OCP compared to non users. Whilst it may appear obvious that a hormonal contraceptive which primarily prevents ovulation should prevent pregnancy at any site, it is reassuring to know that should conception occur the woman is not exposed to increased risk of ectopic pregnancy, unlike the situation where the IUCD has been used as a contraceptive.

Toxic Shock Syndrome
Epidemiological studies are discussed in both the ACOG and Grimes papers about the degree of protection from toxic shock syndrome offered by the OCP. ACOG reports an up to 50% reduction in the incidence of this potentially fatal condition. The protective effect appears to be mediated through use of less absorbent tampons in women using the OCP.

Several other conditions that have effects on the quality of life of women are also significantly improved by the OCP. Conditions such as dysmenhorrea which have measurable morbidity and effects on lifestyle and working ability in a proportion of women are completely relieved in many cases within a few months of OCP use.

The OCP also offers significant protection against functional ovarian cysts by its effects on blocking ovulation, and reduces the incidence of benign breast disease. The negative effects of menstruation on iron stores should not be overlooked when the benefits of OCP use are being examined. Iron deficiency and the anaemia which can accompany it can have serious effects on health and working learning ability. This type of problem is especially common in adolescents and in women who are post

partum. The protective effect of OCP occurs by decreasing menstrual blood flow resulting in decreased iron loss.

The literature contains reference to several other possible protective effects of the OCP which have not been well established. This list includes possible protection against osteoporosis, leiomyomata uteri, and rheumatoid arthritis

In summary, the benefits associated with use of the OCP are all clearly established and widely accepted as being both causal and genuine. Whereas figures concerning the possible excess mortality associated with OCP use are available, the literature does not appear to record any attempt to estimate the number of deaths prevented by use of the OCP in women aged 15-45. La Vecchia states that the effect of OCP on female hormone related neoplasms is similar to that of pregnancy. This opinion is supported by Tyrer who reports: "If in the future there should prove to be an overall OCP related increase in the risk of breast cancer, it would be more than offset by decreases in ovarian and endometrial cancers. It can safely be said that women who have used the OCP develop fewer cancers than never users". When this information is taken in conjunction with the apparent lack of adverse effect on vascular disease of the modern low dose OCP formulations in women with low or no risk factors the risk benefit analysis is overwhelmingly in favour of improving the access of women to the OCP.

Aspects of Dr Jessamine's report were discussed at some length. Members were still concerned about risks involved with oral contraceptives. Dr Herbert said he found it difficult to accept the safety of the medicine given the metabolic changes resulting from its use. While the pill could be seen as safe for medical use, it would be quite a different matter to view it as safe for OTC purchase. Dr Wilcox pointed out that there were still a large number of contraindications. He added that very little was known about the effects on the vascular system and expressed concern about the unknown factors which might be involved. The committee agreed that it would be difficult to eliminate at-risk groups such as smokers, migraine sufferers and women over 35 years of age but felt if there was a method of excluding risk groups, there would seem to be merit in making oral contraceptives more accessible to the low-risk group of users. There was general favour for some method of lengthening the prescription period to up to two years but acknowledgment that initial medical consultation was desirable. Dr Herbert commented that users were seldom suited immediately and it often took up to six months to establish a suitable regimen.

Mr Griffith had looked at the NZ situation and identified young women in the lower socio-economic group as those most likely to benefit from easier access to oral contraceptives. He said that women in NZ were reported as having the second highest fertility rate in thew developed world. He pointed out that an intersectoral steering group within the Ministry had recently produced a report entitled *Reproductive Health Policy Proposals to Reduce Unintended Pregnancy.* One of its three main recommendations was to improve access to contraceptive services. The committee felt that consultation with the intersectoral steering group would be of value.

There was also considerable discussion about possible means of widening accessibility to oral contraceptives but members agreed that they should first establish whether or not the medicines could be considered as safe enough for some kind of wider access before approaching the problem of how this could be implemented.

Summary

The committee concluded that from the summary of material available on the safety of oral contraceptives, the newer formulations of these medicines were sufficiently safe for further consideration to be given wider access. This might not necessarily involve a change of classification. They agreed that there were still risks involved and that any change in access would need to manage these risks in an acceptable and appropriate manner.

Consideration would need to be given to both the initiation of prescriptions, including counselling and screening for risk factors, and to the maintenance of supply.

It was agreed that to foster wider and informed debate on the suitability of the oral contraceptive pill for derestricted access, the MCC view of the safety data should be made available to interested parties. A first step should be consultation with the Ministry's intersectoral steering group investigating access to contraceptive services to see if this group would be interested in fostering wider and informed debate.

Consultation should then be initiated with the following as a minimum:
Pharmaceutical companies
College of General Practitioners
College of Obstetricians
Contraceptive choice
NZ Nurses Association
Family Planning Association of NZ
Fertility Action Group

Consideration should be given as to how consumers should be involved in the consultation process.

Dr Martindale suggested that to deal with the wide public consultation a project could be planned and budgeted for within the Ministry. A project group could be convened to report back to the committee.

It was agreed that there should be no rush to make a final recommendation and that the matter should be returned to the agenda of a subsequent meeting.

iii Emergency Contraceptive

Dr Martindale reminded the committee that the Ministry report on the safety of emergency contraception was incomplete at this stage as Dr Jessamine was still awaiting an issue of an American journal devoted entirely to ECP to arrive from the USA. From the literature review prepared by Dr Jessamine members noted that:

The papers contained in the EMBA review reflect the findings and thinking of physicians and pharmacists in both the USA and the UK. The figures quoted concerning the incidence of unplanned pregnancy and lack of information about the availability of emergency contraception (ECP) however are probably excellent indicators of the situation in New Zealand.

Drife states that almost half of all conceptions in the UK are unplanned a figure supported by other studies conducted in the USA and UK. Although unwanted pregnancy is largely a problem of the under 30 year old age group, it occurs in all age groups with a peak incidence in women aged 20-24 year. Drife has estimated that nearly 25% of women in this age group may have had an abortion. The overwhelming opinion expressed by all of the authors is that little is done to help young people avoid pregnancy and that marketing of contraception to the public is markedly inadequate.

Studies have shown that 70% of all unwanted pregnancies are predictable as the woman realises that she is at risk of pregnancy with about half of due to contraceptive failure. In such cases emergency contraception is 98% effective and yet, despite this proven efficacy, of the 70% of women who knew about the availability of ECP only 3% actually tried to use it. The barriers which prevented women from accessing ECP are essentially similar to those for the OCP. Delivery of the service is based on a medical model which restricts the time and place where contraception can be obtained and puts numerous social, psychological and financial barriers in the way of the user. It is likely that these barriers contributed in a significant way to reduce the number of women using ECP. Considering the original survey was conducted in urban centres it is possible that the situation concerning knowledge of availability and access to ECP in rural areas is even worse.

The efficacy of the Yuzpe regimen for ECP, two doses of oestrogen 100ug and 1mg of a progestogen taken 12 hours apart, has withstood the test of time and several studies have demonstrated that it is efficacious in 75-80% of cases. Efficacy is calculated as a measure of the ability to prevent fertilisation of an ovum if unprotected intercourse takes place at mid-cycle.
The Yuzpe regimen will prevent 75-80% of the 2-5% of pregnancies that would normally follow unprotected intercourse. The conception rate for the Yuzpe regimen is therefore in the order of 1-2%.

ECP produces its contraceptive effect by preventing ovulation, if taken early in the cycle, and through prolongation of the luteal phase and preventing implantation if taken after ovulation. By preventing implantation ECP is open to criticism and moral

judgement that ECP may be inducing early abortion. This subject is being extensively debated in letters to several pharmaceutical publications in the UK, where pharmacists are unhappy about the prospect of having to make this kind of ethical/moral decision.

The safety of ECP is the subject of intense debate relating to the absolute contra-indications. The data sheet contains the same advice as is found for the OCP, yet the evidence that ECP produces significant adverse changes to clotting factors has not been demonstrated. It is however felt to be prudent to continue to advise against the use of ECP in these high risk patients. Drife reports that there are no published reports of death or serious illness after use of ECP. A review of UK Family Planning clinics about contra-indications to ECP use reports that 17% of clinics listed established pregnancy as being the only contra-indication to use with 41% regarding thromboembolism as the only other contra-indication.

The Drug and Therapeutic Bulletins review of adverse effects of ECP list nausea and vomiting as the commonest adverse effect, occurring in up to 60% of women. Due to the high incidence of vomiting some physicians recommend that an anti-emetic should be given in conjunction with ECP. This co-administration of an anti-emetic should be considered as part of the MCC classification process. There is no evidence that use of the Yuzpe regimen increases the incidence of ectopic pregnancy in the situation where the regimen has failed to prevent pregnancy. Similarly there is no evidence that the regimen causes foetal harm or abnormality if administered in the early stages of pregnancy following fertilisation. This lack of adverse effect is due to the plenipotential abilities of the cells contained in the fertilised ovum at this stage of pregnancy.

The long list of risks quoted for the use of the OCP is due to long term exposure to the hormones it contains, they are simply not a factor in consideration of the short term use of the ECP.

The efficacy of the ECP is largely dependant on its correct use which is in turn dependant on the women giving an accurate coital history. It is necessary to give women advice on the likely effects of ECP on their menstrual cycle and to offer advice on what to do if they fail to menstruate. Consumer friendly information is necessary if women are to fully appreciate the benefits and limitations of the ECP. It is felt by several of the authors that abuse of ECP is unlikely, due to the high incidence of adverse effects, the cost of purchasing the ECP and its higher failure rate compared to use of the OCP. Consideration of the risks associated with even frequent use of the ECP are minimal compared to pregnancy.

It would appear that the hesitancy of prescribers to endorse frequent use of the ECP may have more to do with ethical issues than with assessment of the risk/benefit analysis. As with the OCP there is no evidence to support the contention that increasing the availability of the ECP would increase promiscuity, indeed there appears to be evidence to the contrary.

It was noted that Schering would remove PC4 from the market if it were to be reclassified as restricted medicine.

Members thought that it would be appropriate for emergency contraception to be available through emergency service nurses at 24-hour clinics but recognised that reclassification to restricted medicine would not make this possible.

The committee felt comfortable with the possibility of a restricted medicine classification for emergency contraceptives but agreed that further safety data should be considered first and that wider consultation should take place with the same bodies as suggested for oral contraceptives. These bodies should be informed of the committee's view at the time of consultation.

It was also agreed that methods of emergency contraception using other sex hormones such as danazole should be investigated. The matter would be returned to the agenda at the next meeting.

6 New Medicines for Classification

i Nadroparin calcium (Fraxiparine)

This new chemical entity was recommended for classification as a prescription medicine.

Recommendation
That nadroparin calcium be classified as a prescription medicine.

ii Recombinant mecassermin (Igef)

This new chemical entity was recommended for classification as a prescription medicine.

Mr Griffith had also looked at two other low molecular weight heparins which had not been classified individually but were prescription medicines under the group heading for heparins. These were dalteparin sodium and tinzaparin sodium. It was agreed that these should be named individually as prescription medicines in the schedule in line with current policy.

Recommendation
That the following be classified as prescription medicines:
recombinant mecassermin
tinzaparin sodium
dalteparin sodium

iii Recommended for Classification by MAAC

The following new chemical entities had been recommended as prescription medicines by the Medicines Assessment Advisory Committee:

dorzolamide	cladribine
pantoprazole	quinagolide
adenosine	

It was agreed that the secretary should send out before each meeting, a brief description of medicines classified by MAAC.

Recommendation
That the above medicines be classified as prescription medicines.

7 CORRESPONDENCE

i Letters on H2s from Gastroenterological Society and replies
ii Letter on sale of oral NSAIDs to patient on Zantac - G R Boyd

The two item above were for the information of committee members. No comment was required.

8 SUGGESTED ITEMS FOR THE NEXT MEETING

i Copper-containing IUCDs.

As these would be considered as devices rather than medicines under the new legislation it was agreed that there need be no review of the classification of copper-containing IUCDs.

ii Haemodialysis concentrates and peritoneal dialysis solutions.

The question of access to these was considered. It was agreed that Therapeutics Staff should investigate which scheduled medicines were contained in these medicines and that the committee would discuss at the next meeting the possibility of classifying all haemodialysis concentrates and peritoneal dialysis solutions under a blanket general sale classification.

iii Fluorides

The committee was informed that in the process of updating the medicines schedule a discrepancy had been discovered between the medicines regulations and the dietary supplement regulations. It was agreed that Therapeutics would seek a solution to this discrepancy and include the item on the agenda of the next meeting.

9 General Business

It was agreed that the secretary should produce an update of the Guidelines for making submissions for reclassification. A draft would be prepared and sent out to members before the next meeting. Comments could be returned to the secretary so that a final document could be confirmed at the next meeting.

These guidelines would later be incorporated into a wider set of guidelines covering the whole operation of the committee including those items discussed earlier in the meeting.

Agenda items 5ii, Oral contraceptives and 5iii, Emergency contraceptives were discussed at this point.

The meeting closed at 3:50pm