140/25/1

MINUTES OF THE EIGHTH MEETING OF THE DRUG ASSESSMENT ADVISORY COMMITTEE, HELD ON 14 MARCH 1973 IN THE BOARD ROOM, 7TH FLOOR, MACARTHY TRUST BUILDING, LAMBTON QUAY, WELLINGTON, COMMENCING AT 9.00 A.M.

PRESENT:

Dr. D.A. Andrews (Chairman)
Professor F.N. Fastier
Professor P.B. Herdson
Dr. G.S. Kellaway
Dr. M. Kingsford
Professor E.G. McQueen
Professor J.D.K. North
Dr. G.F. Shanks
Mrs. E.C. McKenzie (Secretary)

IN ATTENDANCE:

Mrs. M. Nolan
Miss S. Porter
Mr. S.V. Rea
Mr. M.J. Bennoson
Mr. I.A. Witty

1. INTRODUCTION:

Dr. Andrews welcomed all members and introduced Mr. I.A. Witty, the Senior Public Health Pharmacist in the Department.

2. MINUTES:

The Minutes of the Seventh Meeting having been circulated, were taken as read and were confirmed subject to the following corrections being made:

Page 2, paragraph 1 - Replace the word "generic" with the word "brand".

Page 2, paragraph 2, 4th line - Replace the words "in vitro" with the words "in vivo".

Page 2, paragraph 3, section (3) - Replace the word "nor" with the word "not".

Page 4, last paragraph heading - Replace the word "Suppositories" with the word "Syrup".

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3. MATTERS ARISING FROM THE MINUTES:

a) Report of the Sub-Committee on the setting up of In Vivo and Bioavailability Testing.

The Sub-Committee met on Tuesday, 13 March, to consider guidelines to be followed and the criteria in respect of the bioavailability of a drug which should be provided when application is made for consent to market a new therapeutic drug.

The report of the Sub-Committee was accepted in principle by the members. It was agreed that after errors were corrected, the report (attached) be circulated to members for consideration at the next meeting. Dr. Kingsford to prepare the Appendices to the report.

It was agreed that consideration be given to including the appropriate section of the report in the "Drug Distribution" booklet.

Dr. Andrews thanked the members of the Sub-Committee for their report and Miss Porter for taking the Minutes of their meeting and preparing the draft submission.

b) Public Relations.

The draft article was discussed and after minor changes the members agreed that it be submitted for publication in "The New Zealand Medical Journal". The article should include the fact that New Zealand does not allow representatives from drug firms to be present when their drug is being considered.

Dr. Andrews advised that it is planned to follow this article with one on the Drug Tariff and the functions of related advisory committees.

c) Meeting with Industry.

The two meetings held with Industry in November were very successful and extremely valuable.

It was unfortunate that some of the small drug firms did not send representatives as the purpose of the meeting was to assist them in particular. The Department will try to ensure that representatives from these small firms attend future meetings.

It is proposed to hold these meetings approximately annually, preferably when there is something concrete to discuss.

It was pointed out that the "Drug Distribution" booklet supplied to firms made no mention of specific requirements for clinical trials. The Department had been given the requirements, as set out in the booklet, by the Secretary of the Standing Committee on Therapeutic Trials. The competence of investigators cannot be certified from the scanty details that are submitted and it was agreed that the Standing Committee on Therapeutic Trials advise the Department of their full requirements and that these be incorporated in the booklet in future.

Members asked that they be advised of these requirements.

d) Consent by the Minister of Health to the Distribution of New Drugs.

Dr. Andrews advised that legally, consent to the distribution of a drug cannot be qualified or limited. The Committee had previously recommended a restricted distribution for the drug Blenoxane.

The Minister of Health has advised that he requires more information on drugs that are recommended for acceptance and also for drugs not recommended for distribution.

The question of liability of members was discussed. Advice was given that members were not legally liable for decisions made by them whilst serving on this Committee.

e) Hexachlorophane.

A letter from Sterling Pharmaceuticals Limited, together with supporting papers, had been received and were tabled. One of these papers demonstrated the absence of evidence of neurological abnormality in 24,322 babies washed with 3% hexachlorophane emulsion.

Tests in New Zealand have shown high blood levels in infants and there seems to be no doubt that toxic effects can be demonstrated in animals.

The members could see no reason for recommending a change in the Poisons Committee decision to make products containing 0.75% or more hexachlorophane a prescription poison.

The question of supply of hexachlorophane products to hospitals and industry arose. Professor Herdson stated that he disassociated himself with any decision to ban hexachlorophane from industry as it had not been proved hazardous to adults. He felt that these wide implications of the ban had not been fully understood during previous discussions by the Committee.

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Professor McQueen advised that the absorption level of hexachlorophane in adults generally was low and did not appear to be a hazard as with infants. Data available was mostly in respect of infants although very high levels in one adult had been demonstrated recently in Dunedin.

The Committee recommended that the Poisons Committee consider provision under the Poisons legislation for specific exemption to be made in the case of some industries. The Department could then point out to manufacturers that they could apply for exemption.

f) Patent Infringements.

There was discussion on patent infringement and members were advised that the Department could not legally ask firms for information about patents on new drug application forms.

At this point Dr. Andrews welcomed the Minister of Health, the Hon. Mr. R.J. Tizard, who was then introduced to members of the Committee and the Departmental staff present.

Mr. Tizard addressed the meeting and commented on the amount of work involved in the deliberations of the Committee. He stated that New Zealand is seen by overseas manufacturers as an expanding market and in some cases a testing ground for drugs.

Mr. Tizard thanked members for the enthusiastic way in which they dealt with the work and assured them of his great interest and support.

4. DEFERRED DRUGS:

a) Ativan.

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the therapeutic drug "Ativan" subject to the provision of satisfactory quality control data.

b) Combiase.

The Committee decided to confirm their original decision and defer this drug as members felt that the question of the association between 8-hydroxyquinolines and sub acute myelo-optic neuropathy had not been fully determined. Usage patterns in various countries were thought to explain, in part, differing incidence rates.

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A report from W.H.O. on this is awaited. Reports so far received refer to the halogenated hydroxyquinolines in general terms. Further details are required before the question can be finally resolved and an association with specific hydroxyquinolines is demonstrated.

The members agreed that any other drug applications containing 8-hydroxyquinolines be deferred until further information is received.

c) Nasomixin.

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the therapeutic drug "Nasomixin" subject to the provision of satisfactory quality control data.

d) Zumaril.

The World Health Organisation has reported a high incidence of adverse reactions with this drug. The members felt, however, that the benefit / risk ratio was acceptable and compared favourably with other anti-rheumatic drugs.

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the therapeutic drug "Zumaril" subject to the provision of satisfactory quality control data and that the labelling and promotional literature state the possible adverse reactions in pregnancy and diabetes and that anaphylaxis had been reported.

e) Ethrane.

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the therapeutic drug "Ethrane" subject to the promotional literature elaborating on the possible adverse reactions of the drug and clarification of gas liquid chromotography results.

f) Vaginex.

The Committee decided to recommend that the Minister of Health decline consent to the distribution in New Zealand of the therapeutic drug "Vaginex".

The members agreed with the report from Dr. R.J. Seddon, which confirmed original comments on insufficient clinical studies, quality control data and increased risk of sensitivity.

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g) Microval.

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the therapeutic drug "Microval" subject to promotional literature being approved.

The members pointed out that it had not been made clear in the original application that this drug was identical to the drug "Microlut" and that this had caused delay in its acceptance.

5. NEW DRUG APPLICATIONS:

a) Ondonid.

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the therapeutic drug "Ondonid" subject to the provision of satisfactory quality control data and attention being drawn in the promotional literature to recent epidemiological studies demonstrating vaginal carcinoma in the female offspring when similar products had been taken in early pregnancy.

The members asked if provision could be made for post-marketing studies of adverse reactions with this drug.

b) Anorex.

The Committee decided to defer for six months the application for the new therapeutic drug "Anorex" on the grounds of safety. Increasing evidence of abuse of other forms of this drug is noted and deferral will allow this trend to be studied further. Present restrictions on amphetamines may be influencing usage.

Members asked the Department to seek information on the amount of Tenuate and Ritalin being used. Increasing abuse of the latter has been reported.

The Committee agreed that Dr. G.G. Jenner be asked for his recent review of the literature before the drug is reconsidered.

c) Prinalgin:

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the therapeutic drug "Prinalgin" subject to the provision of satisfactory quality control data and that the promotional literature state the possible adverse reactions in pregnancy, diabetes and the incidence of allergic manifestations.

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d) Altacite.

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the therapeutic drug "Altacite".

The firm is to be asked to clarify some errors in quality control data.

e) Hiper.

The Committee decided to defer consideration of the application for the new therapeutic drug "Hiper" until further information is received from the firm on the bioavailability studies, particularly the investigators involved. Further quality control data is also required.

f) Fluzine.

The Committee decided to defer consideration of the therapeutic drug "Fluzine" until comparative bioavailability studies, details of investigators and further quality control data is received.

g) Mycin.

The Committee decided to defer consideration of the therapeutic drug "Mycin" until comparative bioavailability studies, details of investigators and further quality control data is received.

h) Xylonor Plain: Xylonor 2% Special: Xylonor 2% with Nor-Adrenaline.

The Committee agreed to accept Xylonor Plain subject to provision of satisfactory quality control data. Those products containing nor-adrenaline were declined in view of recent reports of adverse drug reactions to this and other similar formulations.

During the meeting it was learned that Xylonor with nor-adrenaline had been marketed before 1 April 1970 and that a new drug application was unnecessary. The Committee then advised that local dental and anaesthetics containing nor-adrenaline in concentrations above 1 : 80000 be withdrawn from the market.

i) Trental.

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the therapeutic drug "Trental" subject to the provision of satisfactory quality control data.

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j) Cellaforte Plus.

The Committee decided to recommend that the Minister of Health decline consent to the distribution in New Zealand of the therapeutic drug "Cellaforte Plus" due to some of the ingredients included in the drug being undesirable and of unproven safety, inadequate clinical studies and quality control data.

k) Orudis.

The Committee decided to defer consideration of the therapeutic drug "Orudis" until further information on clinical trials, (including those in New Zealand) and quality control data are received and the firm has advised on the possibility of renal damage in view of reports of this in animal studies.

l) Oxobid.

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the therapeutic drug "Oxobid" subject to the provision of satisfactory quality control data and a clear indication in the literature of dosage reduction necessary in the case of renal failure.

6. THERAPEUTIC DRUGS (PERMITTED SALES) REGULATIONS 1972. DRUGS TO BE CONSIDERED FOR INCLUSION IN THE SCHEDULE:

i) The Committee decided to recommend that the following drugs be included in the Schedule:

K. P. Life Salts
Vincent's Powder
Vincent's Tablets
Anacin
Quick-Eze
Dettol
Throaties
S.O.S. Cough Drops
Dettolin

ii)(a) Johnson's Burn Cream.

The Committee confirmed its original recommendation that "Johnson's Burn Cream" be included in the Schedule subject to the addition of the word "minor" in front of "Burn Cream" and the deletion of all references to "If burning is severe" on all literature.

b) Disprinex.

The Committee decided to recommend that "Disprinex" be included in the Schedule subject to the deletion of "lowering temperature in influenza" and "similar level of pain relief as obtained from two ordinary analgesic tablets" and the inclusion of the warning required by Section 50(a) of the Poisons Regulations and subject to the acceptance of the new drug application.

c) K. P. Hydrogen Peroxide 10 and 20 volume.

The Committee decided to recommend that "K. P. Hydrogen Peroxide 10 and 20 vol" be included in the Schedule subject to a check on the formula being made by the Department.

d) Listerine Antiseptic Liquid.

The Committee decided to recommend that "Listerine Antiseptic Liquid" be included in the Schedule subject to inquiry on the boric acid content being made by the Department.

e) Listerine Antiseptic Throat Lozenges.

The Committee decided to recommend that "Listerine Antiseptic Throat Lozenges" be included in the Schedule subject to the percentage of active ingredients being shown on the label.

f) Vicks Vitapirina.

The Committee decided to recommend that "Vicks Vitapirina" be included in the Schedule subject to the word "remedy" being deleted and replaced by the word "treatment" in all labels and admissable claims; and the words "and grippe" being deleted from the admissable claims.

g) Vicks Cough Syrup.

The Committee decided to recommend that "Vicks Cough Syrup" be included in the Schedule subject to the words "and flu" being deleted from the admissable claims.

h) Vicks Formula 44.

The Committee decided to recommend that "Vicks Formula 44" be included in the Schedule subject to the alcohol declaration being in the form required by Regulation 18† of the Food and Drug Regulations.

i) Vicks Vaporub.

The Committee decided to recommend that "Vicks Vaporub" be included in the Schedule subject to the word "remedy" being replaced by the word "treatment" in the package insert.

j) Heath and Heather Indigestion and Flatulance Tablets.

The Committee decided to recommend that "Heath and Heather Indigestion and Flatulance Tablets" be included in the Schedule subject to the correct manufacturer's name being printed on the label.

k) Heath and Heather Anti-Smoking Tablets.

The Committee decided to defer this application until the percentage of lobeline was ascertained as it felt the drug was possibly unsafe because the present dosage on the label could lead to an overdose. A dose of 1-2 tablets up to four times daily was suggested. It is possible that this drug could be included in Schedule 1 or 2 of the Poisons Regulations depending on the lobeline concentration.

l) Heath and Heather Pile Tablets.

The Committee decided to recommend that "Heath and Heather Pile Tablets" be included in the Schedule subject to the name being changed as there is no qualifying statement to the word "Pile" and only claims to relieve piles may be made.

m) Heath and Heather Stomach and Liver Tablets.

The Committee decided to defer this drug as the name and "Liverish conditions" could be misleading in view of the purgative nature of the ingredients.

n) Heath and Heather Kidney Tablets.

The Committee decided to recommend that "Heath and Heather Kidney Tablets" be included in the Schedule subject to the qualification of the name as this could include kidney stones.

o) Heath and Heather Rheumatism Tablets.

The Committee decided to recommend that "Heath and Heather Rheumatism Tablets" be included in the Schedule subject to consideration being given to a change being made to the name "Rheumatism" as there is no qualifying statement to the word "Rheumatism" and only claims to relieve may be made.

p) Heath and Heather Blood Purifying Tablets.

The Committee decided to defer this application until an explanation of the purpose of the drug is received.

q) Heath and Heather Diuretic Tablets.

The Committee decided to recommend that "Heath and Heather Diuretic Tablets" be included in the Schedule, however the Committee objected to the vagueness and possible misleading nature of the name of the drug.

r) Heath and Heather Buchi Tablets.

s) Heath and Heather Parsley Piert Tablets.

t) Heath and Heather Celery Seed Tablets.

The Committee decided to recommend that these three drugs be included in the Schedule subject to the dosage being shown in the same panel as the name of the drug which should be in non-serif capital letters.

u) Heath and Heather Pile Ointment.

The Committee decided to recommend that "Heath and Heather Pile Ointment" be included in the Schedule subject to more emphasis being put on the relief of piles on the label.

v) Heath and Heather Rheumatic Balm.

The Committee decided to recommend that "Heath and Heather Rheumatic Balm" be included in the Schedule subject to more emphasis being put on the relief of rheumatism on the label.

w) Heath and Heather Varicose (Ulcerated) Ointment.

The Committee decided to recommend that "Heath and Heather Varicose (Ulcerated) Ointment" be included in the Schedule subject to a statement being put on the label to make it clear that the ointment is for ulcers.

x) Heath and Heather Constipation Herbs.

The Committee decided to recommend that "Heath and Heather Constipation Herbs" be included in the Schedule subject to the deletion of the word "safe" in front of "gentle laxative" and the words "are not habit forming and do not offer undesirable side effects".

y) Floradix - Red Seal.

The Committee decided to decline this application as this drug is a Sechedule 2 poison and should only be available from pharmacies.

z) Biostrath - Red Seal .

The Committee decided to decline this application as this is a Schedule 2 poison and should only be available from pharmacies.

zz) Ritters Vital Power - Red Seal.

The Committee decided to decline this application as this is a Restricted Drug and should only be available on the prescription of a medical practitioner.

The Committee was concerned about many of these applications for herbal remedies on the grounds of misleading and vague therapeutic claims and names.

The Committee recommended that where appropriate such remedies should contain the following statement:

"If after a reasonable time the condition persists it is advisable to seek the guidance of your medical practitioner".

The Department is to consider the introduction of such a labelling requirement in appropriate regulations.

Due to the late submission of many applications for inclusion in the Schedule and the work load of this meeting, a large number of the applications could not be considered and were deferred to the June meeting of the Committee.

7. GENERAL:

a) Phenytoin in relation to Congenital Abnormalities.

There has been anxiety for some time on this problem. An appreciable number of cases have been reported from numerous sources e.g. W.H.O., U.K., and Australia as well as New Zealand. Reporting of congenital deformities is being included in amendments to the Obstetric Regulations. The Adverse Drug Reactions Committee hope to avail themselves of this information.

The problem has been discussed recently in an editorial in the New Zealand Medical Journal and in the Seventh Annual Report of the New Zealand Committee on Adverse Drug Reactions. Further publicity is to be given in a Clinical Services Letter.

The importance of estimating serum phenytoin levels was discussed and the availability of this test is to be investigated.

b) Association of Committee Members with Drug Firms.

Two members of the Committee have approached the Department on this question. The Department feels that with the expertise available amongst members of the Committee, it is unavoidable that such associations will occur. It considers no problems will arise if the member concerned states his interest in the drug under consideration or withdraws from the discussion if thought appropriate.

Dr Andrews stressed the need for strict confidentiality on all matters discussed by the Committee.

c) Vaxi-haler Flu Vaccine.

This new drug application contains last year's strain of the virus and is claimed to be 63% effective against the present strain. Although there is no intention to market this year, the firm will be enabled to introduce the new strain next year as a changed drug. The members asked to see the full application at the next meeting.

d) Radioactive Drugs.

An application for consent to distribute a radioactive diagnostic agent (intravenous) has been received. The members agreed that this and any such drug received in future should be considered by the Department, together with the National Radiation Laboratory. If there are doubts as to efficacy then referral to the Committee would be necessary.

e) Information Only Drugs.

i) Probexin - The Department was asked to check this drug against the criteria as set down in the report by the Subcommittee.

ii) Talusin - Professor North asked for further information on this drug and was advised that although no bioavailability studies were provided with the new drug application, comprehensive comparative clinical data was submitted. It was also indicated that Talusin had been available in Australia for a number of years.

iii) Maldison (Malathion) - This drug will probably be scheduled as a Prescription Poison when indicated for human use.

8. DATE OF NEXT MEETING:

The next meeting is to be held on Tuesday, 26 June 1973, commencing at 1.30p.m. and Wednesday, 27 June 1973, commencing at 9.00a.m.

The meeting closed at 4.40p.m.

Confirmed:.....
(Chairman)

Date:.....1973

140/25/1

MINUTES OF THE 14th MEETING OF THE DRUG ASSESSMENT ADVISORY COMMITTEE HELD ON WEDNESDAY, 19 MARCH 1975, IN THE BOARD ROOM 7TH FLOOR, MACARTHY TRUST BUILDING, LAMBTON QUAY, WELLINGTON AT 9.00 A.M.

PRESENT: Dr D.A. Andrews (Chairman)
Professor P.B. Herdson
Dr M. Kingsford
Dr P.W. Moller
Dr G.F. Shanks
Mrs E.C. McKenzie (Secretary)

IN ATTENDANCE:

Mr M.J. Bennoson
Dr K.H. Goh
Dr J.S. Phillips
Miss S. Porter
Mr I. Witty

APOLOGIES:

Professor T.V. O'Donnell
Dr G. Kellaway

1. INTRODUCTION:

The Chairman opened the meeting and introduced Dr Phillips, the new Principal Medical Officer and Dr Goh, the new Pharmacologist appointed to the Department.

2. DATE OF NEXT MEETING:

The next meeting will be held on Wednesday, 16 July 1975.

3. MINUTES:

The minutes of the 13th meeting, having been circulated, were taken as read and confirmed.

4. MATTERS ARISING FROM THE MINUTES:

(a) Eraldin (Practolol)

The Chairman outlined the events which had occurred since the last meeting.

An increasing number of adverse reactions had been reported, including some considered irreversible. The Pharmacology and Therapeutics Advisory Committee decided at its December 1974 meeting to restrict practolol to Hospital Board Specialist availability. At a later date Professor McQueen sought the opinion of all members of the Committee on Adverse Drug Reactions and they unanimously recommended that further restriction was necessary. After discussions with the Department, the manufacturer initiated a recall to retail level and the

Department decided to delete practolol from the Drug Tariff as from 1 April 1975. The drug will, however, still be available from hospital pharmacies to the small number of patients who require it, and application for free supplies may be granted under Section 99.

The Department is concerned about the possibility of general practitioners initiating treatment and the Committee agreed that this should be discouraged.

New Zealand is the first country to take definite action to restrict availability. The firm, I.C.U. (N.Z.) Limited, has been extremely co-operative throughout the whole proceedings.

(b) Minipress (Prazosin)

This Committee has reviewed Minipress on three occasions and at the last meeting recommended that general distribution be permitted.

The Company had previously restricted advertising and availability as requested. The last meeting of the Pharmacology and Therapeutics Advisory Committee recommended availability from retail pharmacy without restriction.

The amendment to the Drug Tariff was at printer's proof stage when Dr Halliwright, one of the trialists of this drug, advised that many of his patients had adverse reactions to the drug and he thought it should not be widely available. None of the adverse drug reactions which occurred in the multi-centre trials had been reported to the Committee on Adverse Drug Reactions or to the company.

The Department decided to restrict the availability of prazosin to Hospital Board Specialists only.

There was no decision required by this Committee on the matter, however, it will need to be reconsidered by the Pharmacology and Therapeutics Advisory Committee.

Professor Herdson reaffirmed that the original decision to handle this drug within the Department was incorrect and he was critical of the conduct of the multi-centre trial and of the firm.

(c) Hiper

The Chairman advised of a meeting with principals of the company and they did not disagree with the statement that the data provided was "too good" and they have agreed to conduct bioavailability testing in New Zealand.

There was discussion on the attitude that should be taken when faked data is suspected and it was felt that in such cases the credibility of the company must always be in doubt.

(d) Seguilar

The firm has asked the Committee for a definition of "ethnic groups relevant to New Zealand".

Discussion followed and it was agreed that trials carried out in Commonwealth countries and the U.S.A. were preferable as members were concerned at their lack of knowledge of the trialists in non-English speaking countries. The Committee considered that the original criticism was an unreasonable one in this case, although there is some evidence of clonal differences between some races.

It was agreed that some cases were studied for only a short length of time and in respect of oral contraceptives longer term cohort studies produce more meaningful results.

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of this drug subject to the provision of satisfactory quality control data.

The firm is to be asked if they have noted any differences in drug responses in various ethnic groups.

(e) Medicines Bill

The Departmental Draft of the Medicines Bill will be distributed in the near future and a short summary will be provided for members. Time will be made available at the next meeting for discussion of the draft Bill.

(f) Drug Monitoring

Dr Kellaway's paper was tabled and it was agreed to defer discussion to the next meeting. The Department will also prepare a paper for distribution prior to the next meeting.

5. DECLINED DRUGS:

(a) Ipradol

The Committee decided to confirm their original decision to decline this drug due to the lack of clinical supporting data, lack of comparison with appropriate drugs, inadequate numbers of clinical trials in countries other than Austria and Germany and inadequate quality control data.

The Committee will consider the further data submitted and any new papers which may be submitted at the July meeting.

There was discussion on the Committee's responsibility in respect of the need for certain drugs when there are many similar drugs on the market already.

Members felt that they were concerned with the safety and efficacy of drugs and should not be concerned with economic factors. Any other attitude would be politically unacceptable.

Some firms are submitting applications prematurely. The Committee is particularly careful in assessing drugs that have not been accepted elsewhere, but does not want any such submissions to be delayed before they are referred to them.

It was agreed that the Department discuss the problem of submissions not supported by sufficient data with the Pharmaceutical Manufacturers' Association.

(b) Nebcin

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of this drug subject to the firm agreeing to refrain from advertising, that it be restricted to hospital specialists only, that ongoing data especially on nephrotoxicity and ototoxicity be provided, that adverse reactions be reported by users and that satisfactory quality control data be provided.

The firm is to be asked to comment on the possibility of Nebcin destroying bacteroides with resultant dangers of superinfections in the bowel.

The Committee expressed concern at the over-use of antibiotics in general practice and discussed the action of clindamycin and lincomycin in destroying bacteroides.

6. NEW DRUGS:

(a) Lopresor and Betaloc

The Committee decided to defer this drug pending receipt of further data on long term clinical studies, particularly with regard to immunological abnormalities, reporting of adverse drug reactions and satisfactory quality control data.

The firm is to be complimented on the good presentation of the submission and advised that pre-clinical animal and toxicology data were satisfactory.

(b) Sotacor

The Committee decided to defer this drug pending receipt of further data on long term clinical studies, particularly with regard to immunological side effects, reporting of adverse drug reactions and satisfactory quality control data.

The firm is to be complimented on the good presentation of the submission and advised that pre-clinical animal and toxicology data were satisfactory.

The firm is to be asked for further information on the incidence of adeno-carcinoma in the pituitary gland of Beagles.

(c) Panquil

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of this drug subject to the provision of satisfactory quality control data.

(d) Pharmaton

The Committee decided to recommend that the Minister of Health decline consent to the distribution in New Zealand of this drug due to the lack of evidence of safety and efficacy, inadequate quality control data and the failure to conform with the requirements of the Committee for combination drugs.

(e) Androcur

The Committee decided to recommend that the Minister of Health decline consent to the distribution in New Zealand of this drug due to the lack of local clinical data, pre-clinical and toxicology data and unsatisfactory bioavailability and quality control data.

The firm is to be advised that this submission was poorly presented and if reports with journal references are submitted, bibliographies should be provided.

(f) Apernyl

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of this drug subject to the provision of satisfactory quality control data.

(g) Pro-Diaban

The Committee decided to defer this drug due to insufficient evidence of long term efficacy, lack of comparison with other similar drugs, unsatisfactory quality control data and lack of comment on the possibility of myocardial infarction.

The firm is to be advised that this submission was poorly presented, the indexing was inadequate, data were repetitive and meaningless, e.g. reports of one doctor with only one patient, and that better correlation of data is required.

The pre-clinical animal and toxicology data were satisfactory.

(h) Epilim

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of this drug subject to the provision of satisfactory bioavailability and quality control data, provided that distribution is limited to specialist use only with ongoing reporting required for assessment at the November 1975 meeting.

The advertising need not be restricted and the firm is to be advised of the Committee's concern at the lack of long term studies and requested to provide further data on hepatic and renal toxicity.

(i) Nicolex

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of this drug subject to the provision of satisfactory animal toxicology and teratology data.

(j) Zadine

The Committee decided to defer this drug until further information (as already requested), satisfactory bioavailability and quality control data are provided.

(k) Rivotril

The Committee decided to defer this drug until data on long term clinical trials carried out in more countries, long term hepato-toxicity data, testing for chronic toxicity, more information on blood level studies, paediatric side effects, satisfactory bioavailability and quality control data are provided.

Professor Herdson undertook to enquire about the incidence of cysts in pituitary glands of Beagles.

(1) Cornkil

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of this new drug.

Members were advised that in the case of all new, changed and Drug Tariff applications WHO and New Zealand Adverse Drug Reaction Reports are now checked routinely for information.

7. CHANGED DRUGS

(a) Cystex

Members stated that they were against self diagnosis and self treatment of potentially serious conditions and that this should be discouraged.

The Committee decided to defer this drug pending receipt of comparative studies and satisfactory quality control data.

The Department is to review all over-the counter products promoted for the treatment of urinary symptoms.

The Chairman advised that the draft Medicines Bill does not include provision for a Poisons Committee and that it may be appropriate eventually for this Committee to deal with the scheduling of drugs.

8. GENERAL

(a) "Stand-in" Members

It was agreed that "stand-in" members be nominated if a member cannot attend, however such a person should be mutually acceptable and have had sufficient time to become familiar with the data to be considered.

(b) Minutes

The Chairman advised that minutes of the meetings of the Australian Drug Evaluation Committee are received routinely by the Department and asked if members thought that the format of our minutes should be along the lines of the Australian minutes.

Members stated that the current minutes were sufficient. Members asked that when deferred or declined drugs are resubmitted the reason for deferral or declining be included in the summary.

(c) Cabinet Sub-committee on Efficiency in the State Services - Report on Pharmaceutical Services

This report, carried out by a private company, has been completed, but not published yet.

The report looked at cost, overall administration and efficiency, and although favourable, it was very superficial, glossing over any problem areas which are controversial, or where improvements or savings could be made, and therefore the report was disappointing.

A copy of the report, when published, will be sent to all committee members.

(d) Ferrum H.

The firm has been asked to comment on the lack of response in three patients, and to provide proof of efficacy and statistics of usage. All three cases have occurred in Dunedin, however, it may be occurring in other centres but not being recognised or reported.

It was agreed that informal enquiries be made: Professor Herdson in Auckland, Dr Moller in Christchurch, and the Department in Wellington and Waikato.

(e) Progyluton

The Committee agreed that the warnings regarding discontinuation during pregnancy and the connection between oestrogenic substances and thrombosis were not sufficient.

The warning to discontinue use during pregnancy should also be incorporated with the statement on page 1 "Progyluton is not a contraceptive".

The warning regarding thrombosis should be amended to highlight this contra-indication.

(f) Hormonal Pregnancy Tests and Birth Defects

Two hormonal pregnancy tests are currently available on the New Zealand market. Reports have been received from overseas that birth defects have occurred when hormonal pregnancy tests have been taken in early pregnancy.

The Committee were of the opinion that these preparations should be withdrawn from the market.

(g) Dental and Dermatology Departmental Consultant Advisors

It is hoped that these will be appointed shortly and members will be advised of the appointees.

(h) Camalox

The acid "rebound" effect of calcium carbonate has been well established for many years and the Committee agreed that the Department should handle this application.

(i) Phase I Clinical Trials

The Chairman advised that Phase I Clinical Trials may be carried out in the near future by Dr B.N. Singh of Auckland.

These would be the first Phase I Clinical Trials to be carried out in New Zealand and are unusual outside the U.S.A.

(j) The question of future proposals to reconsider the availability of existing drugs on the market as new drugs of a similar nature become available, was queried. It was considered that this was a present function, in many cases, of the Pharmacology and Therapeutics Advisory Committee.

The meeting closed at 4.15 p.m.

Confirmed _____ (Chairman)

Date _____

MINUTES OF THE 16TH MEETING OF THE DRUG ASSESSMENT ADVISORY COMMITTEE HELD ON WEDNESDAY, 26 NOVEMBER 1975 IN THE BOARD ROOM, 7TH FLOOR, MACARTHY TRUST BUILDING, LAMBTON QUAY, WELLINGTON, AT 9.00 A.M.

PRESENT: Dr A.G. Scott (Chairman)
Professor P.B. Herdson
Dr G.S.M. Kellaway
Dr M. Kingsford
Dr D. Macintosh
Dr P.W. Moller
Professor T.V. O'Donnell
Dr G.F. Shanks
Mrs E.C. McKenzie (Secretary)

IN ATTENDANCE:

Mr M.J. Bennoson
Dr K.H. Goh
Mr R.C. Griffith
Dr G.G. Jenner
Dr J.S. Phillips
Miss S. Porter
Miss L. Stanaway
Mr R. Withington

1. INTRODUCTION

The Chairman opened the meeting and introduced Mr Withington, the new Senior Public Health Pharmacist, and Miss Stanaway, the new Advisory Pharmacist.

2. DATE OF NEXT MEETING

The next meeting is to be held on Wednesday, 17 March 1976.

Dates for the remaining meetings for 1976 were also set. These are:

Wednesday, 14 July 1976
Wednesday, 24 November 1976

3. MINUTES

The minutes of the 15th meeting, having been circulated, were taken as read and confirmed subject to the following addition being made:

Page 7, Section 8 (b) - Add the following paragraph after the second paragraph:

"Dr Kingsford tabled a paper showing that standard sterility testing was unlikely to detect substandard batches unless either a high proportion of units in the batch were tested or there was a high incidence of non-sterile units."

4. MATTERS ARISING FROM THE MINUTES

(a) Restricted Release of Drugs

Pharmaceutical firms have generally been co-operative in this regard. The Department is concerned with the administrative problems which will arise if too many drugs are given voluntary restricted release at one time and also seeks guidance on the length of time for which such restrictions should continue.

It was agreed that there were two distinct categories for restricted release drugs:

(i) Those likely to be permanently restricted.

(ii) Those temporarily restricted in some way until specific aspects of the drug's action has been clarified.

It was agreed that restrictions be reviewed no sooner than 12 months after the restriction is imposed unless the firm produces very strong evidence for derestriction before this period has elapsed.

The firm is to be advised in which category of restriction the drug is to be included.

Drugs which have already been released with restrictions are to be included in the categories as follows:

Category I - Triazure, Prostin F2 Alpha and Anti-cancer drugs.

Category II - Nebcin, Amikin, Pexid, Epilim.

Restricted release should not prohibit inclusion in New Ethicals and should not preclude the Drug Tariff listing of the drug (with restriction).

Monitored release would not restrict the drug to specialist use necessarily but only to those doctors who are willing to monitor the drug and return protocols.

(b) Rauwolfia

The Committee on Adverse Drug Reactions reviewed this drug at their last meeting where after discussion of the three recent U.S. studies and a Lancet review it agreed that no action was currently necessary.

Members agreed that no further action was necessary.

(c) Fees

The daily fee for the Committee has been increased from $32.00 to $45.00.

Consideration has been given to increasing the fee per drug probably effective in the next financial year.

(d) Aldactone (Spironolactone)

The Committee on Adverse Drug Reactions considered the possible association of Spironolactone with breast cancer in relation to recent correspondence in the Lancet in which five cases had been reported and that Committee felt that no action was required.

Members also agreed that no action was necessary at this stage.

(e) Drug Monitoring

Some drug firms have already stated that they are in favour of drug monitoring.

It was felt that the Department should have overall control of drug monitoring but that firms should collect and collate data.

There is no legal power at present to insist on drug monitoring being carried out, it would be purely voluntary. The Medicines Bill makes provision for drug monitoring and the regulations will set out the details.

The number of patients to be monitored will have to be flexible and be decided for each drug or group of drugs and such factors as cost, usage, duration of treatment, etc., will need to be considered. The figures of 10,000 - 20,000 (as set out in Dr Kellaway's report) may be too high. Some firms will be in a better position than others to carry out drug monitoring especially those that have a medical department.

The monitoring of drugs will not release firms from clinical trial requirements for new drug applications.

Although ideally there should be international co-operation in drug monitoring, there are too many associated problems to make it practical at this stage. However if New Zealand can demonstrate that drug monitoring is workable, other countries may follow.

It was agreed that the obvious way to start would be to monitor selected drugs only. It would be impossible to implement drug monitoring for all new drugs.

There was discussion on who should be responsible for the collection and collation of data. Neither the Department or the Committee have the time or the facilities to do this at present. For this reason it was agreed that firms should be responsible and should then report to the Department. The question of unfavourable reports being withheld by firms was raised. It was felt however that the majority of drug firms are responsible.

It was agreed that there are five main steps required for drug monitoring:

(i) Protocol
(ii) Data and protocol education
(iii) Drug distribution
(iv) Data collection
(v) Payment to doctors.

It was agreed that a subcommittee be set up to prepare a paper setting out guidelines for the implementation of drug monitoring. The paper is to be circulated to members before the March 1976 meeting.

The subcommittee is to comprise Dr Kellaway, Professor Herdson and a representative from the Department.

It was agreed that drug monitoring could be applied to beta-blockers and Pexid in the first instance.

(f) Medicines Bill

The bill is currently at departmental draft stage.

It was suggested that the following be moved from Part I to Part II of the Schedule to the Bill:

Arthritis, Influenza, Ruptures, Ulcers of the Gastrointestinal Tract, and

that Urinary Tract Disorders should be included in Part I of the Schedule.

(g) Beta-Blockers

After discussion it was agreed that no new beta-blockers should be released for marketing until the monitoring programme has been implemented. At this stage if a new beta-blocker demonstrates definite therapeutic advantages, e.g., cardio-selectivity, then it should be considered on merit.

In adopting this viewpoint members were governed more by their concern about the serious side effects with beta blockers than with the minor nuisance side effects. It was agreed that any moves towards further release should still be cautious.

Pfizer have advised that Tolamolol has been withdrawn from clinical trials because preliminary results of long term toxicity studies in rats and mice have shown an increased incidence of mammary carcinoma at the highest dose level and a low, but apparently dose-related, incidence of hepato-cellular carcinoma.

5. DUTCH AND DRUGS

(a) Glibenese

The Committee decided to defer this drug pending receipt of further long term clinical studies (at least 600 patients over a 2 year period) and satisfactory quality control data.

(b) Lopresor and Betaloc

The Committee decided to defer these drugs until the drug monitoring scheme is implemented. Members felt that there were insufficient clinical data in terms of time and number of patients to enable evaluation. The quality control data were un-satisfactory.

Dr Kellaway said that he was aware of patients who had demonstrated positive antinuclear factor after being treated with practolol. A negative antinuclear factor resulting from withdrawal of practolol could again become positive when treatment was recommenced with another beta-blocker. He was concerned that patients might have been presensitised to other beta-blockers and possibly to other drugs which were known to cause a positive antinuclear factor.

(c) Rivotril

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the new therapeutic drug Rivotril subject to the provision of satisfactory bioavailability data.

(d) Clinoril

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the new therapeutic drug Clinoril.

Some quality control queries are outstanding but these should not hold up acceptance.

(e) Hiper

The Committee decided to defer this drug pending clarification of bioavailability data to enable proper evaluation to be carried out.

The firm is to be advised that the data was badly presented and not suitable for interpretation and that the number of subjects studied was extremely low.

There was general discussion on the facilities available for bioavailability studies to be carried out in New Zealand.

6. DECLINED DRUG

(a) Androcur

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the new therapeutic drug Androcur subject to its use being restricted to appropriate specialists only (psychiatrists) and to the provision of satisfactory quality control data. The restriction on specialist use is likely to be permanent.

7. NEW DRUGS

(a) Calcitonin - Sandoz

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the new therapeutic drug Calcitonin - Sandoz subject to its use being restricted to appropriate specialists only (temporary restriction) and to the provision of satisfactory quality control data.

(b) Dopram

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the new therapeutic drug Dopram subject to the provision of satisfactory quality control data.

(c) Exirel

The company has advised that further data has been

received from overseas and asked that consideration of this drug be deferred until the next meeting.

The data already forwarded to members will be held in the Department.

There was a general discussion on the question of holding or returning literature provided for declined and deferred drugs.

(d) Ludiomil

The Committee decided to recommend that the Minister of Health decline consent to the distribution in New Zealand of the new therapeutic drug Ludiomil due to the lack of long term clinical studies, danger of arrythmias, foetal skeletal growth retardation, the potential toxic effects, the potential narrow therapeutic/toxic range and unsatisfactory quality control data.

The firm is to be advised that the presentation and format of the application was good, but the Committee was concerned about the trials carried out in 100 children particularly when it is know that the drug may retard skeletal growth.

(e) Nipride

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the therapeutic drug Nipride subject to the provision of satisfactory quality control data.

(f) Vermox

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the new therapeutic drug Vermox subject to the provision of satisfactory quality control data.

(g) Desurin

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the new therapeutic drug Desurin subject to the provision of satisfactory quality control data.

8. CHANGED DRUG

(a) Vibramycin

An application has been received for a 200 mg capsule. The Committee supported the application as there is an occasional need for this strength of capsule in severe and anaerobic infections.

9. GENERAL

(a) Aerosol Propellants

as the data currently available is only experimental however it could be suggested to firms that they use the less toxic propellants.

(b) Parenteral Nutrition

Members felt that not enough information had been provided for them to be able to make any recommendation.

The Department is to write to Wellington, Auckland, Christchurch, Dunedin and Waikato Hospitals requesting information on usage and demand.

(c) Recent Drug Recalls

Mr Bennoson advised on two recent drug recalls:

Medical Supplies, Manufacturing Division (previously Dale Laboratories) instituted a recall of over 30 galenical products due to an error in the use of industrial methylated spirits (IMS) instead of ethanol. The error resulted from the faulty installation of under-ground storage tanks and the associated pumps, pipes and outlets for ethanol and IMS: insufficient instructions and checking by the company resulted in the IMS tank supplying the ethanol outlet and vice versa.

A recall of three batches of Periactin Syrup was undertaken by Merck, Sharp and Dohme following the detection of Actinomyces/Nocardia contamination. Supplies of Periactin and Tryptanol will be imported from Australia until the problem in the liquid manufacturing area has been resolved.

(d) Meetings with Industry

Meetings with Industry were held on 11 November (Auckland) and 19 November (Wellington) where among other items the new edition of the Guide to Drug Distribution (published - September 1975) was discussed.

(e) Visit to Hungary by Professor J.D.K. North

The first contact with Medimpex occurred in September 1974 through the New Zealand Consulate in Vienna and a short list of local agents was sent to them. Medimpex have been dealing with the New Zealand Import-Export Corporation but are considering obtaining a more commercially orientated New Zealand agent.

(f) Chinese Herbal Remedies

This was referred to the Committee for information. The situation is still being watched closely.

(g) F.D.A. Labelling Requirements for Contraceptives

The new requirements are that patients over the age of 40 years should be warned of the increased danger of myocardial infarction and thromboembolic phenomena. This requirement was based on articles in the Lancet earlier this year.

The Maternity Advisory Committee considered this requirement and thought that the current New Zealand product literature requirements were sufficient.

(h) Over the Counter Laxatives, Anti-diarrhoeals, and Anti-emetics

A survey of proprietary preparations of the above drugs has been carried out in the U.S.A. and the drugs have been classified into three groups as follows:

Group I - generally recognised as safe and effective

Group II - not generally recognised as safe and effective or misbranded

Group III - recognised as safe but of unproven efficacy.

The meeting closed at 4.45 p.m.

Approved as a true and correct record

W. L. Scott
(Chairman)

17 March 1976
(Date)

CONFIDENTIAL

140/25/1

MINUTES OF THE 19th MEETING OF THE DRUG ASSESSMENT ADVISORY COMMITTEE HELD ON WEDNESDAY 24 NOVEMBER 1976, IN THE COMMITTEE ROOM, 1st FLOOR, MACARTHY TRUST BUILDING, LAMBTON QUAY, WELLINGTON, COMMENCING AT 9.00 a.m.

PRESENT:

Dr A.G. Scott	(Chairman)
Dr N. Eggers	
Professor P.B. Herdson	
Dr G.S. Kellaway	
Dr D. Macintosh	
Professor T.V. O'Donnell	
Dr G.F. Shanks	
Mrs E.C. McKenzie	(Secretary)

IN ATTENDANCE:

Dr K.H. Goh
Mr R.C. Griffith
Dr J.S. Phillips
Miss S. Porter
Mr J. Smith
Miss L. Stanaway
Mr R. Withington

APOLOGIES:

Dr M. Kingsford	(Absence)
Dr D. Macintosh	(Lateness)
Dr P.W. Moller	(Absence)

1. INTRODUCTION:

The Chairman welcomed Dr Eggers who was acting as deputy for Dr Kingsford and introduced Mr Smith, the new Scientist (Good Manufacturing Practice) in the Department. The Chairman congratulated Dr Kellaway on his appointment as Associate Professor of Clinical Pharmacology at the Auckland School of Medicine.

2. DATE OF NEXT MEETING:

The next meeting of the committee is to be held on Wednesday 16 March 1977.

The suggested dates for the July and November 1977 meetings were not suitable and it was agreed to hold these on 27 July and 30 November provided absent members were agreeable.

3. MINUTES OF THE LAST MEETING:

The minutes of the 18th meeting having been circulated were taken as read and confirmed subject to the following amendment:

Page 3, last line; replace the word "carditis" with the word "pericarditis".

4. MATTERS ARISING FROM THE MINUTES:

(a) Intensified Adverse Drug Reaction Reporting Scheme

The Chairman outlined the scheme and answered some queries. He advised that there has been a slight delay in printing but it was hoped that the first cards would be issued with the next New Ethicals Catalogue and firms should also be distributing cards by February 1977. The scheme is swinging gradually into action rather than on a set starting date.

The problem of reporting in the hospital environment was mentioned and it was agreed that an extra effort will be needed in this sphere.

Professor McQueen will be attending a WHO Conference in Honolulu in January 1977 when the whole question of adverse drug reporting will be discussed. He has undertaken to report anything of interest.

5. DEFERRED MEDICINES:

(a) Medihaler - Pulmadil

The committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the new medicine Medihaler - Pulmadil.

The firm is to be advised that the acceptance is not due to the quality of their submission but rather to the drug having been used without untoward event in the United Kingdom for 2 years. Members asked that when deferred or declined drugs are referred to them in the future that a full section A be provided. The Department agreed to do this.

(b) Vumon (VM 26- Sandoz)

The committee decided to recommend that the Minister of Health decline consent to the distribution in New Zealand of the medicine Vumon due to the high toxicity of the medicine, and lack of definition of its place in oncology.

The firm is to be advised that this was not a well organised submission.

(c) Colestid

The committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the new medicine Colestid subject to the firm's agreement to a two year shelf life.

(d) Mexitil

The committee decided to defer consideration of this medicine due to insufficient experience of adverse drug reactions in long term usage, as it appears to be fairly potent, highly toxic and with marked side effects. There are also inadequate data on quality control.

6. NEW MEDICINES:

(a) I.V. Solutions in Plastic Bags (McGaw)

There was lengthy discussion on the use of plastic bags for i.v. solutions. It was considered that the advantages of plastic bags over glass bottles should be kept in mind and although there were questions concerned with the leaching of plasticizers, stability, etc., it should be remembered that some related questions with the currently used glass containers were as yet unresolved. It was essential to ensure that pyrogens were excluded and it was probable that the fundamental manufacture of the i.v. solutions was the most important factor. Quality control in all stages of manufacture of the plastic is essential and warranted attention because the various operations are carried out by more than one company.

The committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of McGaw Plastic Bags subject to clarification of basic specifications, the provision of adequate quality control data, and the institution of satisfactory in-process and finished product testing.

(b) I.C.I/TVL Plastic Bags

This submission was not as well presented as the previous one.

The committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the I.C.I/TVL Plastic Bag subject to clarification of basic specifications, the provision of adequate quality control data, and the institution of satisfactory in-process and finished product testing.

The committee asked to be kept informed on the developments concerning specifications for both plastic bags.

(c) Pevaryl

The committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the new medicine Pevaryl subject to the provision of satisfactory quality control data.

(d) Moban

The committee decided to recommend that the Minister of Health decline consent to the distribution in New Zealand of the medicine Moban due to insufficient long term studies in sufficient patient numbers, the high incidence of side effects, concern about the possible toxicity of this medicine and inadequate quality control data. Further information concerning leucopenia in long term studies is also to be sought.

The standard of the histopathology work was queried and also the choice of strain of experimental animals.

(e) Ocusert

The committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the new medicine Ocusert subject to the provision of satisfactory quality control data.

(f) Mitomycin-C

The committee decided to recommend that the Minister of Health decline consent to the distribution in New Zealand of the medicine Mitomycin-C due to its severe and wide-spread toxic effects, the lack of evidence of efficacy in combination with other cytotoxic drugs, lack of definition of its place in current oncological practice, absence of current literature and inadequate quality control data.

(g) Meriston

The committee decided to defer consideration of this medicine due to the absence of published papers, insufficient long term clinical studies and unsatisfactory quality control data.

(h) TRF-Roche

The committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the new diagnostic agent TRF-Roche subject to the provision of satisfactory quality control data.

(i) Benoral

The committee decided to defer consideration of this medicine due to insufficient long term clinical data being provided and inadequate quality control data.

7. THERAPEUTIC DRUGS (PERMITTED SALES) REGULATIONS 1972

(a) MY Iron Tablets

The committee decided to recommend the inclusion in the Schedule of this drug.

8. RESTRICTED RELEASE MEDICINES:

(a) Epilim

Members were concerned that if this medicine was released for general availability that side effects reporting would decrease. It was decided that it should be included in the Intensified Reporting Scheme. Some members felt that the restriction should not be removed and felt it was still under evaluation internationally. It was agreed after discussion, that the restriction on distribution of Epilim should remain and also that a letter be sent to specialists wishing to use this medicine setting out the Committee's concern about side effects, especially in view of the occurence of thrombocytopenia and seeking specialists' co-operation in the reporting of all adverse drug reactions.

(b) Androcur

No further information has been received from the firm; they advise that they have not been actively supporting the indications claimed by some specialists of precocious puberty and hirsutism and that they have only been supplying the drug to psychiatrists.

The Committee were concerned about the use of this drug for these new indications and re-affirmed that when this drug was recommended for marketing it was only for the treatment of hypersexuality in adult males. If Androcur is to be promoted for other indications, a changed drug notification will need to be lodged together with full supporting data.

It was agreed to re-affirm the original decision to approve this medicine only for the treatment of hypersexuality in adult males and to extend the use of the medicine to all appropriate specialists for this indication only.

It was noted that hospital pharmacies were potential suppliers of Androcur to doctors intending use for non-approved purposes. This should be communicated to the company.

9. GENERAL BUSINESS

(a) Sub-acute Myelo-optic Neuropathy (SMON)

There is very little literature describing the occurence of this penomenon outside Japan. No cases have been reported in New Zealand and it was generally felt by members that clioquinol was of very little value therapeutically.

The committee were concerned about the possible hazards of this drug and its continued availability and recommended that the Minister of Health be advised of this concern. They also requested that this concern should be reported to the Pharmacology and Therapeutics Advisory Committee.

(b) Local Production of Pituitary Hormone

Dr Scott outlined the current arrangements for the production of pituitary hormone and the proposal to establish a National Pituitary Hormone Laboratory in Auckland.

(c) Status of Barbiturates

Dr Scott outlined the proposed action and advised that the revised commencement date for the restriction of certain barbiturates to hospital pharmacies was 1 February 1977. There was a body of opinion in both the Pharmacology and Therapeutics Advisory Committee and the Poisons Committee that barbiturates should be made prohibited substances. The original stimulus for considering restrictions came from the deletions of barbiturates, with the exception of phenobarbitone, from the latest edition of the British National Formulary. In addition there was evidence of increasing abuse of, and dependence on, this group of medicines. The restrictions in New Zealand will not apply to phenobarbitone or to barbiturates used in anaesthesia.

Some members felt the restriction was unfortunate as the alternatives available may not prove to be as efficacious, safe or cheap, while other members agreed with the restriction.

(d) Oral Contraceptives and Liver Nodules

The relationship between liver nodules and oral contraceptives is still not very clear, as they occur only very rarely. It was suggested that records of liver pathology could be kept as a routine at autopsy and that retrospective study of the effect of oral contraceptives on liver could then be carried out.

It was agreed that paragraph d) (regarding hepatic cell adenomas) should be retained in the information required on oral contraceptive package inserts for physicians.

(e) Oestrogens and Endometrial Carcinoma

Some regulatory bodies are requiring that warnings be included on labelling for oestrogens: that they should be used cyclically, in low doses and for short periods of time.

Members agreed that there is an association between the use of oestrogens and endometrial carcinoma and that the following contraindications should be included in the literature:

(1) Known or suspected cancer of the breast except in appropriately selected patients with progressing inoperable or radiation resistant disease.

(2) Known or suspected oestrogen - dependent neoplasia.

(3) Known or suspected pregnancy.

(4) Undiagnosed abnormal genital bleeding.

(5) Cerebro-vascular or coronary artery disease (except when used in the treatment of breast or prostatic malignancy).

(6) Thrombophlebitis or thromboembolic disorders.

(7) A past history of thrombophlebitis or thromboembolic disorders associated with previous oestrogen use (except when used in treatment of breast or prostatic malignancy).

Warnings should be given of the possible induction of malignant neoplasms, gall bladder disease, thromboembolic disease, hepatic adenoma, elevated blood pressure, decrease of glucose tolerance, and in patients with breast cancer and bone metastases, of hypercalcaemia.

The literature should emphasise the following warnings:

(a) Pregnant women should never be given oestrogens because of the damaging effect on the offspring.

(b) Products containing diethylstilboestrol but not labelled for postcoital contraception must have the following warning: "This product should not be used as a postcoital contraceptive."

(c) There is an increased risk of endometrial cancer with prolonged use. The lowest dose to control symptoms is recommended for use in treating menopausal symptoms; medication should be discontinued as soon as possible. When prolonged treatment is indicated, the patient should be re-assessed at least every 6 months. "There is no evidence at present that 'natural' oestrogens are more or less

hazardous than 'synthetic' oestrogens."

(f) Chloroform - Carcinogenic Potential

The problem of how these reports, and future reports, expected from the N.C.I. which is testing approximately 350 compounds in carcinogenesis bioassay, should be dealt with was discussed, and the question of the safety of alternative (untested) compounds raised.

It was felt that the metabolism in rats is not relevant to humans and that there appeared to be no reason for a dramatic reappraisal of chloroform. It was agreed that no action should be taken at present. It was suggested that the propriety of such experiments on animals was questionable. Industrial use was suggested as a possible matter of conern.

(g) Triazure

This was referred for information

(h) Carbon Black, Ponceau Red (No. 4) and Food Colourings

This was referred for information.

(i) Aspirin in the last 3 weeks of pregnancy

It was agreed that no action to include such a warning be taken at present. The committee however suggested that the attention of obstetricians be drawn to the articles and that it also be referred to the Committee on Adverse Drug Reactions for their consideration.

(j) Tranquillisers in pregnancy

Some of the tranquillisers on the New Zealand market contain a general warning against use in pregnancy and it was agreed that attention be drawn to this question in a Clinical Services Letter.

(k) Depo-Provera

This drug was approved for marketing in New Zealand before this committee was formed. It has been withdrawn from the U.S.A. market, not approved in the United Kingdom and not marketed in Australia. No problems have occurred in New Zealand although it has recently been suggested that progestogen in breast milk might have long term effects in infants.

It was agreed to consider this drug at the next meeting when a full submission will be presented.

The Chairman advised that this would be the last meeting that Mrs McKenzie would be attending as she was leaving the Department in February 1977.

The Chairman also advised that Professor Herdson who will be

overseas next year will be replaced at two or three meetings by Professor J.D.K. North.

The meeting closed at 4.15 p.m. with the Chairman wishing all present the compliments of the festive season.

Confirmed ..... Date .....
(Chairman)

MINUTES OF THE 20TH MEETING OF THE DRUG ASSESSMENT ADVISORY COMMITTEE HELD ON WEDNESDAY 16 MARCH 1977 IN THE BOARD ROOM, 7TH FLOOR, MACARTHY TRUST BUILDING, LAMBTON QUAY, WELLINGTON COMMENCING AT 9.00 A.M.

PRESENT:

Dr A.G. Scott (Chairman)
Dr G.S. Kellaway
Dr M. Kingsford
Dr P.W. Moller
Professor J.D.K. North
Professor T.V. O'Donnell
Miss L.G. Woolstencroft (Secretary)

IN ATTENDANCE:

Dr K.H. Goh
Mr R.C. Griffith
Dr J.S. Phillips
Miss S. Porter
Mrs N.A. Stagg
Miss L. Stanaway

APOLOGIES:

Dr D. Macintosh (Absence)
Professor J.D.K. North (Lateness)
Dr G. Shanks (Absence)

1. INTRODUCTION:

The Chairman welcomed back to the Committee Professor North, who was deputising for Professor Herdson (at present overseas), and Mrs Stagg, Secretary of the Poisons Committee, was introduced.

2. DATE OF THE NEXT MEETING:

The next meeting of the Committee is to be held on Wednesday 27 July 1977.

Dr Moller will be overseas from June 1977 until July 1978. He has suggested that Professor Jellett should deputise for him during his absence. Members had no objection to this suggestion and Professor Jellett will be approached.

3. MINUTES OF THE LAST MEETING:

The minutes of the 19th meeting having been circulated were taken as read and confirmed.

4. MATTERS ARISING FROM THE MINUTES:

(a) Intensified Adverse Drug Reaction Reporting Scheme

Dr Phillips advised the Committee that the scheme is now underway. He outlined the results of the meeting with representatives of the firms presently involved, reporting their enthusiasm.

He advised that it would be important to know the number of patients being treated with each drug under surveillance but this is difficult to ascertain. The companies offered to supply usage figures and it is hoped that by checking numbers of patients treated at one or two large hospitals that it may be possible to convert the usage figures into a useful estimate of patients under treatment.

Concern over the effectiveness of the existing scheme, especially in hospitals, was raised. It was the general feeling of the Committee that hospital pharmacists would be most willing to assist as this kind of involvement would help improve their professional status and also their communication with general practitioners. They will inevitably be key figures in the success of the scheme in hospitals and it was suggested that a conference be held involving hospital pharmacists to embody their co-operation. The holding of the conference was to be considered by the Department.

Professor McQueen's report on his recent visit to Honolulu to discuss adverse reaction reporting was considered likely to be of interest. Subject to permission from Professor McQueen, his report to the Adverse Drug Reaction Committee will be circulated.

(b) Epilim

The Committee was informed that a Clinical Services Letter has been written concerning this preparation. It was agreed that applications for free supply under section 99 should only be available when the application is made personally by an appropriate specialist.

(c) Status of Barbiturates

A meeting has been held with the pharmaceutical and medical professions. The combined meeting recommended that no change be made in the availability of barbiturates as usage is generally dropping, but there is still some misuse of the drugs in the community and some over-prescribing on the part of some doctors.

A working party has been set up to devise educational programmes for both the medical profession and the public. These are to include information on sleep patterns, especially in the elderly. The identification of excessive prescribing is also required. A joint letter from the Director-General of Health and the Chairman of Council of the New Zealand Medical Association will be circulated to all practitioners.

(d) Aspirin in the last three weeks of pregnancy

No cases of prolongation of labour have been reported in New Zealand but efforts will be made to inform medical students and doctors in large maternity hospitals.

(e) Tranquillisers in Pregnancy

A Clinical Services Letter will be circulated drawing attention to this question.

(f) Depo Provera

It was the general view of the Committee that this drug was of particular value to this country. However, it was felt that doctors ought to be informed of regulatory decisions made overseas concerning this product and about the possible difficulties in conceiving after cessation of therapy. It was felt that for this reason use in young people may not be appropriate.

As there is no specific evidence for the alleged increase in cancer or for long term effects on infants of the progestogen in the breast milk, it was felt better to caution doctors rather than impose restrictions.

The relevant article in the Clinical Services Letter should be referred to the company concerned before being distributed.

(g) Triazure

Attention was drawn to the fact that consent to market this medicine was given in New Zealand at approximately the same time as it was withdrawn in the U.S.A.

However the Committee felt that consent to market in this country should remain as the risks associated with Triazure are justified in relation to the serious disability associated with severe psoriasis in certain patients.

The firm is not proposing to market the product in New Zealand as a result of the U.S.A. withdrawal. It is proposed that the company be asked to let the Department know if and when they bring the medicine into the country. It was also agreed that the Department should look favourably at any section 16 applications for use in special cases.

5. DEFERRED MEDICINES

(a) Trandate

The Committee decided to defer this application owing to insufficient experience concerning the incidence of adverse drug reactions in long term usage.

It was felt that data on increasing numbers of patients for a longer duration were needed as information on anti-nuclear factor was insufficient and too little was known about the effect of its affinity for melanin in the eye. There were also some quality control matters as yet unresolved.

It was considered that this would be a useful medicine once these questions have been resolved.

(b) Voltaren

The Committee decided to defer this application. It was felt that further experience was needed with more patients on long term therapy. The opinion was expressed that the multi-centre trial showed insufficient attention to data collection and as a result was not reliable enough to show safety, particularly as regards to the liver; more data are required on liver toxicity. It was further pointed out that where there are one or two patients only in any one centre they should not be included in the trial numbers.

(c) Norpace

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of a new medicine Norpace subject to the provision of satisfactory quality control data.

(d) Prodiaban

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the new medicine Prodiaban.

The Committee expressed some concern that there was no literature published outside Germany and that there have been no trials of the medicine in New Zealand.

6. RESTRICTED RELEASE MEDICINES:

(a) Androcur

The Committee has previously recommended the approval of this medicine for use only in adult male hypersexuality.

The Department has since then received applications from doctors requesting free supplies of the medicine for the treatment of precocious puberty, acne and hirsutism.

The Committee reaffirmed its attitude that the medicine should be restricted to the use of the appropriate specialists. It recommended that the use of the medicine be extended to include precocious puberty but it firmly opposed the use of Androcur for the indications acne and hirsutism. There was some concern about the paucity of long term experience, the suspicion of testicular dysfunction on stopping treatment and the suggestion of adrenal failure in some cases.

7. NEW MEDICINES:

(a) Urotrast

The Committee recommended that the Minister of Health consent to the distribution in New Zealand of the new medicine Urotrast subject to the provision of satisfactory quality control data.

Its regulatory history in Australia was considered of interest. It was agreed that the Department inquire about this.

(b) Tagamet

The Committee decided to defer consideration of this medicine for further data on long term studies and advice from the company on how post marketing surveillance is to be ensured. Some quality control matters were still unresolved.

(c) Anginin

The Committee decided to recommend that the Minister of Health decline consent to distribution in New Zealand of the medicine Anginin due to a lack of proven efficacy, lack of data on its metobolic fate and inadequate quality control data.

(d) Bronsecur

The Committee decided to recommend that the Minister of Health decline consent to distribute in New Zealand the medicine Bronsecur. Further data concerning more patients on longer duration therapy, and more comprehensive quality control data are required.

There is a need for further studies involving comparison with similar, more recently developed, products.

(e) Topisolone

The Committee deferred consideration of this medicine due to a paucity of comparative studies with presently available similar preparations.

Efficacy is regarded as proven but the relative therapeutic efficacy/safety ratio has not been established. Also further quality control data are needed.

The pre-clinical section of the presentation was considered well conducted.

(f) Flexiban

The Committee decided to defer consideration of this medicine for further information.

It was considered that there was a notable absence of published work on this substance in view of the length of time it had been available and that the company should be asked to report on this. It was also considered that data involving comparison with Orphenadrine were necessary along with further information on longer term use in larger patient numbers.

Some further quality control data are also required.

(g) Prostin E2

The Committee decided to recommend that the Minister of Health consent to distribution in New Zealand of the new medicine Prostin E2 subject to its restriction to use by specialists in obstetrics. Some further quality control data are required. The Committee endorses the restriction proposed by the firm that "Prostin E2 will be distributed only to those hospitals with an obstetric and gynaecological unit and which have full 24 hour obstetric and gynaecological specialist cover.

(h) Relefact

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the new diagnostic agent Relefact subject to the provision of satisfactory quality control data.

(i) Acupan

The Committee deferred consideration of this new medicine. It was considered that the data on pharmacological effects in man were insufficient and that the human studies were inadequate in terms of toxicity and efficacy.

Some quality control matters are as yet unresolved.

8. THERAPEUTIC DRUGS (Permitted Sales) Regulations 1972

(a) Ru Mari Compound

The Committee decided to recommend the inclusion, in the Schedule, of this drug subject to the satisfactory editing of the claims made on the container and insert.

(b) Ru Mari Lotion

The Committee decided to recommend the inclusion, in the Schedule, of this medicine subject to satisfactory editing of the claims.

(c) Slendrets (Slimming tablets)

The Committee decided not to recommend the inclusion, in the Schedule, of this medicine until satisfactory evidence of the efficacy is provided.

(d) De Milo Herbal Slimming Tablets

The Committee decided not to recommend the inclusion, in the Schedule, of the medicine until satisfactory evidence of its efficacy is provided.

(e) Healthway's Sleeping Tablets

The Committee decided to recommend the inclusion, in the Schedule, of this medicine subject to the alteration of the recommended dosage regimen by removal of the recommendation to take the tablets after meals.

(f) Healthway's Tranquility Tablets

The Committee decided to recommend the inclusion, in the Schedule, of this medicine.

9. CHANGED MEDICINES:

(a) Rhythmodan Injection

The Committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the changed medicine Rhythmodan Injection subject to the provision of satisfactory quality control data.

(b) Deaner

In November the Department was advised on an increase in deaths associated with the use of Dimethylaminoethanol (DMAE) ester in elderly, infirm patients. In December 1976 a changed drug notification was lodged for a tablet containing 250 mg of DMAE as the pacetamidobenzoic acid. (Deaner).

A notification was in the interim referred to the Minister of Health to stay distribution of the new preparation.

The dose of the original product was 25-75mg/day. The changed medicine has a recommended daily dose of 600-1500mg which is well above the 300 mg danger level referred to in the World Health Organisation circular.

After consideration the Committee decided to recommend that the Minister of Health declines consent for distribution in New Zealand of the changed medicine Deaner 250mg.

The Committee requested that the poor quality of photocopying be drawn to the attention of the firm.

(c) Duromine 40mg.

The Committee decided to recommend that the Minister of Health decline consent to the distribution in New Zealand of the changed medicine Duromine 40mg due to inadequate data concerning its therapeutic ratio.

10. GENERAL BUSINESS:

(a) Tartrazine Hypersensitivity

Considering the widespread use of the compound as a colouring agent, a warning on each package would be a massive undertaking.

The Committee was concerned that the agent was being used in broncho-dilators and decided that further information on the severity of the allergic reaction should be obtained from Dr Lefkowitz at the National Jewish Hospital and Research Centre, Denver. The issue could then be considered further.

(b) Carcinogenicity of Timolol (Blocadren)

The Committee was informed that the Australian Drug Evaluation Committee had deferred the timolol application and required further information on carcinogencity. The Department will keep in touch with the Australian proceedings and report any further events. No further action in New Zealand is contemplated at the moment.

c) Deadline for receipt of data

For the first time applications for some new drugs were not brought to the meeting because of the pressure of numbers and time. As a result the deadline for the receipt of data has been brought forward to three months before the Drug Assessment Advisory Committee meeting.

It was agreed that the Department would expedite the applications for particularly useful drugs, to allow their consideration at the earliest meeting.

) Bromocriptine

Bromocriptine was recommended for marketing at the 14 July 1976 D.A.A.C. meeting. The application did not include the indication acromegaly but the Department is currently receiving a number of requests for free supplies of the drug for acromegalics.

The Committee indicated that the company should be asked to make application for the use of the medicine in acromegaly and in the meanwhile doctors seeking to use the medicine for this purpose should request supplies from the company.

(e) Approval for Trials

The Committee suggested that the Medicines Bill should be changed to make allowance for the Standing Committee on Therapeutic Trials of the Medical Research Council, as an alternative to the proposed D.A.A.C. Subcommittee, to consider protocols as well as investigators proposed for clinicals trials. The Standing Committee on Therapeutic Trials should be given the right to approve the protocol of the trial as well as the investigators.

The Committee wished their thanks and good wishes to be forwarded to Mrs E. McKenzie..

The Chairman closed the meeting at 4 p.m.

confirmed ..... Date 27.7.77

(Chairman)

MINUTES OF THE 23RD MEETING OF THE DRUG ASSESSMENT ADVISORY COMMITTEE HELD ON WEDNESDAY, 22 FEBRUARY 1978 IN THE FIRST FLOOR COMMITTEE ROOM, MACARTHY TRUST BUILDING, LAMBTON QUAY, WELLINGTON, COMMENCING AT 9.00 A.M.

PRESENT:

Dr A.G. Scott (Chairman)
Professor P.B. Herdson
Professor L.B. Jellett
Professor G.S.M. Kellaway
Dr M. Kingsford
Professor T.V. O'Donnell
Dr G. Shanks
Miss L.G. Woolstencroft (Secretary)

IN ATTENDANCE:

Mrs M.S. Combly
Dr K.H. Goh
Mr R.C. Griffith
Dr J.S. Phillips
Miss L. Stanaway
Mr R.M. Trow
Mr R. Withington

The chairman opened the meeting by welcoming all members.

An apology had been received from Dr Macintosh and was accepted by the chairman.

1. DATE OF THE NEXT MEETING

The next meeting of the committee will be on 14 June 1978.

2. MINUTES OF THE LAST MEETING

The minutes of the 22nd meeting, having been circulated, were taken as read and were certified as a true and accurate record subject to the correction of a typographical error.

3. MATTERS ARISING FROM THE MINUTES

(1) Intensified Adverse Drug Reaction Reporting Scheme

Following the last meeting, a letter was sent to Professor E.G. McQueen making the committee's comments. An interim reply was received from Dr D. Coulter, Assistant to the Medical Assessor, and was reported to the committee.

The discussion that followed drew attention to the ideal of reporting any particular untoward happening experienced by the patient while on the medicine; the necessity for those involved to see reports; and

the request of the Drug Assessment Advisory Committee that an annual report and two interim reports be forwarded during each year to be available at each meeting.

It was agreed that the manufacturers should also officially receive information relating to any of their products. All reports should clearly state that reported events or adverse reactions were in association with the use of the product and were not necessarily as a result of its use.

It was requested that Dr D. Coulter be notified of the concern that was felt by the forwarding of the six month report to private practitioners and not to all medical practitioners. It was felt that, in future, the report should be circulated to all practitioners.

The committee was informed that beta blockers would be available in retail pharmacies from 1 April 1978 and that this was expected to increase usage of these products.

(2) Tartrazine Hypersensitivity

A letter was received from Dr R.S. Buswell replying to the request for further information.

It was noted that the Food and Drug Administration in the USA had banned the use of Tartrazine in several types of products but it was considered that no action was necessary in New Zealand.

(3) Urotrast

The committee was advised that Urotrast has been accepted with the agreement of DSIR. It was noted that this was the first product from Yugoslavia accepted in New Zealand.

(4) Seatone

The committee was advised that the firm marketing the product Seatone had succeeded in their appeal against the department on three of five points. The appeal against the prosecution for the sale of an unregistered medicine was amongst the successful points. It was agreed that it would appear essential to contest the verdict at the Court of Appeal as the whole concept of registering medicines under the Food and Drug Act 1969 appeared to be in jeopardy.

The matter at present is with the department's office solicitor to assess the grounds on which an appeal could be based.

(5) Medicines Bill

The Bill continues to be discussed and progress is slow.

(6) Information Submitted on Medicines Deferred

After discussion it was agreed that the company should make two to three complete copies of the original data available when a deferred medicine appeared again before the committee. It was expected that such an amount would be able to be compiled from the material returned to the secretary after the meeting at which it was deferred. Members should advise the secretary if they wish to review this data before the meeting at which it is to be reconsidered. Members also agreed to return as much as they could at the conclusion of each meeting.

4. DEFERRED MEDICINES

(1) Voltaren

The committee decided to defer consideration of this medicine for further information on long term studies. It was also suggested that the firm be asked for any published papers on the medicine.

Doubt remained about liver toxicity in man.

(2) Uronase

It was considered that there was no evidence that any of the clinical data related specifically to Uronase and such material was therefore irrelevant. The committee would still like to see comparative clinical evidence involving Uronase in western countries.

The question of its microbiological purity was raised.

A reference to a standard for urokinase for investigational use in the USA has again not been produced by the company.

The committee re-affirmed its decision to defer consideration of this medicine.

(3) Rohypnol

The committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the new medicine Rohypnol subject to the provision of satisfactory quality control data.

The committee felt that although the medicine was not an advance and had all the disadvantages of the currently marketed benzodiazepines there was no reason to withhold approval.

5. NEW MEDICINES

(1) Mefoxin

Overall it was felt that the application had been made a little too early.

The question of how this antibiotic compared with current cephalosporins with regard to its administration to patients with severe renal failure on concurrent diuretic treatment had not been satisfactorily resolved. This information should however be available from its ongoing usage. It was also considered that the paediatric dosage should be determined.

Concern that the antibiotic may be over-used was expressed, however, the medicine was considered an advance on present alternatives and definitely would be useful. It was therefore decided to recommend that the Minister of Health consent to the distribution in New Zealand of the new medicine Mefoxin subject to its inclusion in the intensified adverse drug reaction reporting scheme where special attention should be paid to the monitoring of renal function during its use.

(2) Trasidrex

It was agreed that the fixed combination ratio was unsuitable for marketing in this country and that the ratio of beta blocker to diuretic would be better determined for the individual patient. It was considered that compliance would not be significantly affected by the use of such a combination. The committee then decided as a matter of policy to disapprove of such combinations generally. In the case of Trasidrex there were also questions about the dosage uniformity of cyclopenthiazide and tablet stability.

It was, therefore, recommended that the Minister of Health decline consent to the distribution of this new medicine.

(3) Piportil

The committee decided to defer consideration of this medicine for further information on long term studies with more patients. The suppression of follicle stimulating hormone was considered wanting further definition during and following therapy.

It was considered that the present trials should be continued. Reports on the ongoing carcinogenicity mutagenicity trials should also be provided. There were some quality control matters to be resolved.

(4) Tiberal

The committee decided to defer consideration of this medicine for further information on efficacy in Bacteroides infections, amoebiasis and lambliasis; for clinical experience in a western country; for

clarification of the appropriateness of the dosage to be recommended in relation to the trials reported and for further quality control data.

(5) Zaditen

It was agreed that this drug application had been presented prematurely. Data demonstrating the prophylactic capabilities of the medicine in asthmatics in a setting where artificial challenge was not used, i.e. over one or two pollen seasons, were required. It was also suggested that in the trials involving asthma a placebo control would have provided more useful information. The question of drug interaction with anti-hypertensive, anti-diabetic and psychotropic drugs was raised. In addition the full text on the pharmacokinetic data should be provided.

The committee decided to defer consideration of this medicine.

(6) Iridus

The committee decided to recommend that the Minister of Health decline consent to the distribution in New Zealand of the new medicine Iridus.

The submission was considered deficient in proof of efficacy, especially in long term use, adverse reaction prevalence reporting and quality control. It was felt that it was necessary for some metabolic mechanism to be shown in support of the claim for central activity. The compatibility of the claims on central and peripheral activity was queried.

If the company intends to resubmit this medicine it is recommended that the name of the medicine be changed.

(7) Danol

The committee decided to recommend that the Minister of Health consent to the distribution in New Zealand of the new medicine Danol subject to the provision of adequate quality control data. The consent for distribution should be restricted to the treatment of endometriosis by specialists in obstetrics and gynaecology.

The committee considered that there was an absence of information on the long term effectiveness, the relapse rate and the reversibility of androgenic effects. It also felt that the submission lacked information on the advantages of this therapy over progestogen/oestrogen therapy; however, as this was an extremely difficult disorder to treat, Danol would be advantageous in some patients. It was most unlikely that a patient would continue to be treated with the medicine unless an adequate response was being shown.

It had been suggested that the release should be monitored but this was rejected in view of the limited numbers of patients being used.

6. CHANGED MEDICINES

(1) Ponderax

The committee decided to recommend again that the Minister of Health not consent to the distribution in New Zealand of the changed medicine Ponderax owing to the marginal evidence of efficacy, its potential for abuse and the paucity of clinical experience reported with diabetics.

7. GENERAL BUSINESS

(1) Vanquin

A report on the mutagenicity associated with Vanquin was received from Parke Davis and Co. The committee felt that no action was necessary at this time.

(2) Epilim

A report of six patients who had developed jaundice while receiving treatment with Epilim in the United Kingdom was received. The committee agreed that this medicine should remain under surveillance and that the report presented should be forwarded to the Committee on Adverse Drug Reactions. No action was considered necessary at this time.

(3) Clioquinol Containing Preparations

The committee was advised that when Entero-Vioform was deleted from the Drug Tariff the company indicated that it would remove the product from the market. It now appears that the parent company wishes to hold a meeting of independent experts under the auspices of the World Health Organisation with a view to making a recommendation on suitable indications.

It was agreed that the committee would await the report of the proposed meeting.

(4) Progestasert

Correspondence and reports on the relationship between the Progestasert system and ectopic pregnancies was presented to the committee. The committee expressed its wish to be kept informed of developments with this preparation.

(5) Trandate

The first report prepared from data derived from the United Kingdom monitored release scheme had been circulated.

The committee received the report but no action was considered necessary.

(6) Dimethyl Sulphoxide

A preparation consisting of DMSO was introduced to New Zealand under the name of Dermasorb in 1965 and withdrawn after six months following reports of changes in the refractive index of lenses of eyes in animals in the United Kingdom and the United States of America.

It is apparently now being used increasingly in New Zealand, mostly combined with idoxuridine for the treatment of herpes zoster.

It was requested that a bottle of the preparation being used be obtained by the visiting pharmacist and brought to the next meeting.

It was also suggested that a Clinical Services Letter on the subject be forwarded to all medical practitioners cautioning them.

(7) Saccharin

Information regarding action taken by Canada and the United States of America on the use of saccharin in foods, drugs and cosmetics was provided.

No similar action was deemed necessary. The committee suggested that a statement be issued indicating that in the opinion of the DAAC there is no satisfactory evidence to suggest that the use of saccharin should be restricted in human medicines.

(8) Guidelines for Clinical Trials in USA

It was generally agreed that the guidelines as written could be usefully used as an encyclopaedic reference or check list but that they should not be imposed in New Zealand. They would be a useful guide for New Zealand doctors taking part in clinical trials for American companies.

It was suggested that copies be made available to university medical schools, schools of pharmacy, pharmaceutical firms and the Standing Committee on Therapeutic Trials.

The chairman closed the meeting at 3.30 p.m. with his thanks to members for their attendance.

Certified ..... A. G. Scott

Date ..... 14 June 78

MINUTES OF THE 31ST MEETING OF THE DRUG ASSESSMENT ADVISORY COMMITTEE HELD ON WEDNESDAY 8 OCTOBER 1980 IN THE CONFERENCE ROOM, 6TH FLOOR, NATIONAL MUTUAL CENTRE, THE TERRACE, WELLINGTON, COMMENCING AT 9.10 AM.

PRESENT

Dr J S Phillips (Chairman)
Dr H Guy
Professor P B Herdson
Dr M Kingsford
Dr D Macintosh
Professor T V O'Donnell
Dr G F Shanks
Mr R C Griffith (Secretary)

IN ATTENDANCE

Dr R Boyd
Dr D Feeney
Dr K H Goh
Dr C Sri-Ananda (Acting Chairman during items 5(2) to 5(5))

The chairman welcomed Dr Guy who was standing in for Dr Moller and introduced Dr Feeney an Assistant Director in the Division of Clinical Services.

1. APOLOGIES

Apologies were received from Professor Kellaway and Dr Moller.

2. MINUTES

The minutes of the thirtieth meeting were accepted with two typographical errors corrected.

The meeting dates for 1981 were agreed at 11 March, 3 June and 7 October.

3. MATTERS ARISING FROM THE MINUTES

(1) Sulphinpyrazone and re-infarction

Recent events in the USA were outlined in relation to the findings in the trial recently completed there. It appeared that there was some doubt about the value of sulphinpyrazone in reducing morbidity and mortality associated with re-infarction. It was noted that Ciba had ceased promoting Anturan for this indication in New Zealand. The committee agreed that further developments should be awaited.

(2) Combined oral contraceptives - patient information

Three proposed formats for the patient information had been received from the Pharmacology Department at Auckland Medical School. These formats were then collated in the Department with all the separate ideas included and this draft provided to the committee. At this meeting three additions and one alteration to the

draft were suggested

- the potential loss of contraceptive cover whilst the patient was taking antiepileptics or rifampicin;

- the patient should be advised to consult her doctor about starting the pill again after the end of a pregnancy;

- the relevant phrase should read "Tell your doctor if you or your family have a history of high blood pressure" etc;

- the sources of advice should be re-ordered to place "doctor" first.

(3) Colouring agents for medicines

Dr Kingsford had suggested, on reviewing the situation since the last meeting, that since an exhaustive list would be very lengthy, that a shorter list with latitude for exemptions would be preferable. The chairman suggested that pharmaceutical manufacturers be asked to advise the colours they considered essential - the collated list would then be provided to the next meeting. The committee agreed with this and also the premise that a declaration of colour(s) contained should not be required on the label of a medicine.

(4) Epilim and the Intensified Adverse Drug Reaction Reporting Scheme

It was agreed that valproate was now established and widely known anti-epileptic therapy, hepatic dysfunction and thrombocytopenia appeared the adverse effects of most concern. Some further elucidation of reported increased incidence of fits with valproate and interaction with amitriptylline and with carbamazepine was desirable. The committee then decided that Epilim should be removed from the "Intensified Reporting Scheme" as soon as was practicable - January 1981 was suggested.

(5) Fees

The chairman advised that fee structures were currently under review in the Department. It was considered by one member that fees paid by government, for services like this committee, should not be taxable. It was pointed out that individual members could make written submissions presenting their point of view if they so wished.

4. PRIORITIES OF APPLICATIONS

The chairman reviewed the situation that had given rise to the Minister deciding that generic medicines which offered the potential of considerable savings of public funds should receive some priority in being processed as new drug applications. It was indicated that the consideration of new chemical entities was not and would not be delayed by this altered approach;

the Department was not wilfully encouraging "generic" companies at the expense of research based companies but accepted that there was an international trend to more commercial competition over many established drugs. It was suggested by one member that the move towards bringing more uniformity to new drug applications internationally may be facilitated by the pre-clinical data being evaluated in a few locations, the clinical data would, however, still foreseeably be required by most regulatory authorities. It was agreed that a list of applications pending would be provided to the next meeting.

5. DEFERRED/DECLINED APPLICATIONS

(1) Corgard (Nadolol)

At the meeting of October 1979 the committee had recommended that this application be declined because there was insufficient assurance of the long term safety. The applicant had now provided further results on ANA and eye slit lamp examinations but the number of such investigations was still considered inadequate. The committee then decided to defer making another recommendation so that further data on ANA, eye lamp slit examinations and a report from the US post-marketing survey initiated, could be provided.

(2) Cytadren

This application for aminoglutethimide had been declined following consideration of the application by the committee in November 1978; on that occasion it was considered that clinical experience was too limited whilst the drug had many side effects. It now appeared that the application had been recompiled and was more extensive in terms of experience. The committee then agreed that the application should be approved, the indication disseminated breast cancer as in the Section A, was the only appropriate indication.

(3) Zadine

This application for azatadine had last been reviewed in July 1977 and the making of a recommendation deferred because insufficient data had been provided on safety in long term use. The information now provided by the applicant related to the extent of sales in Australia and apparent absence of unexpected side effects. The committee agreed that this information would suffice although it was not what had been asked for; accordingly, it was decided to recommend that the application be approved.

(4) Visderm

This application for topical amcinonide had been reviewed in June 1979 when the committee deferred making a recommendation so that long term safety, further reports on potency compared with other topical steroids and some further quality control data could be provided.

The applicant had now responded on the various issues but contended that long term investigation in man was not justifiable because of the consequent hazards. It was recalled that long term application to monkeys had been reported on previously and gave no cause for disquiet. It was then decided to recommend that the application be approved subject to a few quality control matters being resolved.

(5) Triglobe

This sulphadiazine/trimethoprim combination had been reviewed at the meeting of June 1979 - a large number of queries had resulted in relation to an efficacy comparison with the individual ingredients, further safety data in animals and man, further bioavailability and quality control data. Some further information had now been provided but it was agreed that no substantial case had been made for the efficacy of the combination over trimethoprim alone. The committee then recommended that the application be declined.

6. NEW MEDICINE APPLICATIONS

(1) Romilar decongestant cough mixture

It had been requested at the last meeting that the committee review this application. Dr Boyd indicated that the Department had recently asked Roche to withdraw their application for another cough mixture containing paracetamol/guaiaphenesin/dextromethorphan. The decongestant mixture appeared to meet the requirements of the panel which advised the FDA on cough and cold medicines. It was then agreed by the committee that the application should be approved subject to some minor quality control queries being resolved.

(2) Platinol

It was agreed that this anti-neoplastic agent cisplatinum II had a large number of toxic effects on particularly bone marrow, kidney and lung but it did appear to provide an advance in the treatment of testicular and ovarian carcinoma. There were a number of queries on the specifications and stability of the product which needed to be resolved. The committee then decided to recommend that the application be approved subject to the chemistry queries being resolved.

(3) Syraprim

This was an application for a 300mg trimethoprim tablet. In the ensuing discussion it was advanced that trimethoprim was the active ingredient of consequence in co-trimoxazole and that the evidence that there was a rise in resistance to trimethoprim where it was used not in combination was not convincing. Whether macrocytic anaemia was a problem

of concern with trimethoprim remained to be seen. The committee then decided to recommend that Syraprim be approved for the treatment of acute urinary tract infections subject to the bioavailability study being evaluated and found satisfactory.

The committee was also interested in obtaining further details about the usage and problems with resistance to trimethoprim in Turku, Finland.

(4) Pevisone

This application for a combination of econazole and triamcinolone in a cream was discussed at some length. The application presented evidence that was not convincing as to the value of including triamcinolone in the preparation; it appeared much better practice to have a steroid incorporated in the cream should the need arise for a short period of combined therapy. It was then agreed that the application should be declined on the grounds that the benefits of including the steroid were trivial compared with the risks from its too prolonged use.

(5) Netilin

This application was for netilmicin which is the N-ethylated derivative of sisomicin. Netilin appeared to have the toxicity problems generally associated with aminoglycoside antibiotics but could have value in treating Klebsiella and Psuedomonas infections refractory to other therapy. However, there was no pressing need for it to be available at this juncture and clinical experience with it was relatively limited. The committee then decided to defer making a recommendation on Netilin so that further clinical reports could be provided, the prescribing information could be re-drafted by the applicant where necessary and some outstanding quality control queries could be resolved.

(6) Eldisine

This anti-neoplastic agent vindesine appeared to be safer than vincristine and had well defined indications. Accordingly the committee decided to recommend that the application be approved subject to the decomposition chemistry and shelf life being determined.

(7) Nubain

This application was for nalbuphine HCl injection 10 mg in 1 ml. The efficacy and safety of the preparation appeared to be adequately defined excepting in relation to the abuse potential, which, it was agreed, may be difficult to establish precisely but would appear to be less than morphine. It was then agreed that the application should be approved with the prescribing literature containing a statement that "physical dependence on nalbuphine has been demonstrated in patients with a history of narcotic abuse". There were also a number of

queries on quality control to be resolved and the draft product literature required amendment in respect of some other statements.

(8) Travogen

It was decided to defer making a recommendation on this application for topical isoconazole so that further clinical reports might be provided. There were also some questions on product stability and quality control.

(9) Travocort

This application was for a topical combination of isoconazole and diflucortolone. It was decided that the application should be declined for similar reasons to Pevisone (item 6(4)) ie, the benefits of including the steroid were trivial compared with the risks.

(10) Betaloc Comp

This was an application for a combination of 100 mg metoprolol and 12.5 mg hydrochlorothiazide. The general and specific issues of beta-blocker/diuretic combinations had been discussed at some length at the previous meeting. With this specific combination of drugs it did, however, appear that for optimal therapy the doses of each drug could be subject to a wide range of variation across a number of patients - the case for a modal dose of each ingredient had not been made. Accordingly it was decided that the application should be declined because it was an inappropriate combination.

(11) Capoten

This application was for captopril which was regarded as the most innovative of the new drugs discussed at this meeting. It appeared effective for the indications severe hypertension and refractory congestive heart failure as sought in the application. There are problems with the toxicity of captopril and conceivably medicines which may be developed later with a similar mode of action may be safer. The committee noted that to date the clinical investigations were only short term and the longer term consequences of inhibiting angiotensin converting enzyme were obscure. However, it was agreed that under adequate supervision the benefits of therapy were worth while. It was then decided to recommend that the application be approved for the indication refractory congestive heart failure, Capoten should be included in the Intensified Adverse Drug Reaction Reporting Scheme, its promotion should be to specialists only and a caution should be included in the prescribing literature to the effect that there were dangers associated with the use of potassium supplements or potassium sparing diuretics during therapy. It was also agreed that a note should appear in a Clinical Services Letter advising that renal biopsy should be considered where a patient suffered proteinuria. Additionally there was some clarification

required of the application in relation to the relevance of the bioavailability trials reported and the assessment of product stability before the application was approved.

7. GENERAL BUSINESS

Antimitochondrial antibodies and Labetalol

A pre-publication report from Professor J Wilson relating to a much higher prevalence of antimitochondrial antibodies found in labetalol treated patients than otherwise treated or untreated hypertensives or healthy subjects was discussed briefly. It was agreed that although the significance of these findings was obscure the situation should be generally made known.

Acebutolol - ANA and suspected adverse drug reactions

A review of this situation had recently been provided by May and Baker. The committee agreed with the advice given that patients on acebutolol should have ANA estimated prior to and at six monthly intervals during therapy, any patient developing signs of a lupus syndrome should be withdrawn from therapy and followed for not less than two years.

Clofibrate - carcinogenicity in rats, follow-up on WHO co-operative trial

The committee noted these two reports (the first Reddy and Azarnoff in Nature 283, 24 Jan 1980, the second from Lancet August 1980) and a statement by the CSOM on the WHO trial.

It was agreed that no action was currently necessary: the usage of clofibrate was decreasing in New Zealand.

Indications for minor tranquillizers

A letter was tabled suggesting that the indications for benzodiazepine tranquillizers should be more clearly defined to exclude "everyday stress". The committee agreed that the policy in New Zealand should be rather to advocate only short term therapy bearing in mind that there was no acceptable evidence of long term effectiveness. It was suggested that the Department could usefully review current advertising for such products.

Depo Provera

The Department had received from two US addresses two reviews relating to adverse effects in mothers and babies associated with the administration of Depo Provera. A number of the assertions provided by the National Women's Health Network and The Institute for the Study of Medical Ethics were based on findings in animals. The committee noted the reports; they were considered unbalanced appraisals containing considerable conjecture on the relevance of the animal studies.

It was considered tenable that different countries would see in Depo Provera different risk/benefit assessments.

The committee agreed that democratic societies should allow for such presentations but that there was no cause for change in the status of the drug in New Zealand.

Changes to supply of new drug application material

A proposal had emanated from the Clinical Services Division whereby NDA material presented to the committee for the first time would be mailed directly by the applicant for the drug rather than through the Department as at present. The committee members were opposed to such a proposal because they wished to avoid direct contact with pharmaceutical companies in such matters.

Chloroform in toothpaste

The committee was advised that Beecham had ceased using chloroform in toothpaste in New Zealand because of pressure of the Press. It appeared that a toothpaste made for Woolworths was the only brand still containing chloroform - it was agreed that the Department would ask Woolworths to remove the chloroform.

Caffeine and pregnancy

The committee was provided with the recent statement by the FDA on the situation. It was agreed that in pregnancy moderation was wise with caffeine containing beverages as with other foods.

Toxic Shock Syndrome

A recent Press clipping from the New Zealand Herald and a report from the Centre for Disease Control, USA (19 September 1980) were tabled for brief discussion. The known etiology of the syndrome and recent actions of the Department and the Press in relation to tampons were briefly discussed. It was indicated that the Department would update the situation next week. The aspects of care in use of tampons, the effects of vaginal drying and abrasion resulting from tampon use, had to be considered. It was agreed that the syndrome was a very rare event.

Professor O'Donnell left the meeting at this juncture.

Laetrile

A brief discussion of the Sidel Clinic and the planned visit of Dr Santo to New Zealand took place. It was agreed that there was a case for a controlled investigation of the laetrile used at the Sidel Clinic and there was adequate reason that this should be conducted in New Zealand.

Fixed Drug Combinations

A recent publication by the Royal Society of Medicine on fixed drug combinations was suggested as a good background for the types of decisions required of the committee and the Department.

The chairman closed the meeting at 4.14 pm.

MINUTES OF THE 32ND MEETING OF THE DRUG ASSESSMENT ADVISORY COMMITTEE HELD ON THURSDAY 12 MARCH 1981 IN THE BOARDROOM, SEVENTH FLOOR, MACARTHY TRUST BUILDING, WELLINGTON, COMMENCING AT 9.12 AM

PRESENT

Dr J S Phillips (Chairman)
Professor P B Herdson
Dr M Kingsford
Dr P M ller
Professor T V O'Donnell
Dr G F Shanks
Mr R C Griffith (Secretary)

IN ATTENDANCE

Dr R Boyd
Miss M Bullock
Mrs S Combly
Dr D Feeney
Dr K H Goh
Dr C Sri-Ananda

The chairman welcomed the members and introduced Miss Bullock who had recently commenced duties as a scientist in medicines registration in the Division of Clinical Services.

1 APOLOGIES

Apologies were received from Professor O'Donnell for his late arrival (for the list of applications pending) and from Dr Macintosh because he was unable to attend.

The chairman then outlined progress with the Medicines legislation the Select Committee referral, the trend of submissions received by the committee and the possible effects of the legislation on the role of the DAAC.

2 MINUTES

The minutes of the thirty-first meeting were accepted with two amendments:

Page 2 (5) should refer to Dr Shanks rather than "one member";

Page 8, reference is to the Cydel clinic (not Sidel).

3 MATTERS ARISING FROM THE MINUTES

(1) The Chairman indicated that following the drawing up of the draft "patient information for users of combined oral contraceptives", the parties involved had been circulated but to date not all had forwarded their comments.

270

(2) Colouring agents for medicines

The Chairman advised that the Pharmaceutical Manufacturers' Association was unwilling to provide a list for discussion. ICI (NZ) had provided a list of colours used in its products. It was agreed that the department would compile a list for discussion at the next meeting.

(3) Epilim and the Intensified Adverse Drug Reaction Reporting Scheme

The Chairman and Professor Kellaway outlined events with Epilim and the Committee on Adverse Drug Reactions since the last DAAC meeting. The prevalence of liver dysfunction appears to be higher than was thought earlier, the events of hyperammonaemia and pancreatitis reported and the actions in Australia were discussed. It was now proposed by the Medical Assessor (of CADR) to seek, with a questionnaire from all recent prescribers of Epilim, details that would allow identification of patients and reports of any adverse reactions seen with Epilim. The committee agreed that Epilim should, under the circumstances, remain under intensive surveillance.

(4) List of Applications Pending

A list compiled in February had been circulated and was discussed. It was agreed that the department should make efforts to reduce this lengthy list of approximately 150 applications largely for generic prescription and proprietary medicines. The recently appointed scientist in the Division should assist the appraisal process. It was agreed, Dr Kingsford dissenting, that a bio-availability trial should be a standing requirement for generic prescription medicines. Dr Kingsford agreed to provide an updated list of drugs known or suspected of bio-availability problems.

(5) Capoten

At the last meeting the committee had recommended that this new drug application be approved for the treatment of refractory congestive heart failure. A problem had arisen between the Squibb Company and the department, since the applicant considered that the product literature would have to refer to the treatment of hypertension. After discussion the committee agreed that the previous recommendation should be altered to include refractory severe hypertension as an indication but that its use in

mild-moderate hypertension was not justifiable. The Chairman indicated that a Clinical Services letter would shortly make reference to the availability of captopril.

(6) Fees

Dr Moller asked whether the department would consider the DAAC members being retained as consultants - the consequence being a more realistic fee. The Chairman indicated that the department would be unlikely to set such a precedent, but agreed that it would be investigated.

(7) The Chairman outlined recent events with tampons and toxic shock syndrome.

4 DEFERRED/DECLINED APPLICATIONS

(1) Tiberal

This application for ornidazole tablets had been deferred in March 1978 for further information on the efficacy in Bacteroides infections, amoebiasis and lambliasis, for clinical reports from a western country, clarification of the dosage recommendations and some quality control problems. It was noted that an injection was now additionally applied for. After discussion, it was agreed that the making of a recommendation should again be deferred until more substantial evidence relating to the treatment of bacteroides infections was provided. Additionally, since the injection was proposed for the prevention and treatment of infections associated with abdominal surgery, reports relating to its use in these situations should be provided.

(2) Flenac

This application for fenclofenac had been deferred in June 1980 so that some further information on efficacy, safety and the quality control could be provided. On this occasion, it was again agreed to defer making a recommendation because of questions remaining concerning the safety and some further time was required to allow interpretation of the pharmacokinetic findings. The safety questions related to the occurrence of skin rashes which, although usually transient, were relatively common (7-15% of patients), effects on the eye in long term use and it appeared that some further information should be available on long term safety since Flenac had been approved for sale in the United Kingdom in 1978. There also remained a question about the shelf life of Flenac tablets.

(3) Feldene

This application for piroxicam had been deferred in June 1980 so that reports of further clinical experience (New Zealand and elsewhere) and comment on the prevalence of adverse reactions could be sought. A number of questions had also arisen on the pharmacokinetics and quality control. After discussion, it was agreed that the information sought had been provided and was acceptable. The application should be approved.

(4) Kebilis (Roussel chenodeoxycholic acid)

At the June 1980 meeting, the committee had decided to defer making a recommendation on this application so that further safety data in long term (two years) use in man could be provided. The applicant considered this request unreasonable. On this occasion, the committee decided that a recommendation that the application be approved could be made on the basis of the clinical data submitted, but that prior to approval, the department should ensure that the product literature recommend discontinuation of treatment if one year's treatment had brought about no dissolution and the product literature should refer to the potential of CDA for causing neoplastic disease. The committee also expressed some dissatisfaction with the tone and wording in some of the recent company correspondence.

5

(1) Tonocard

It was decided to recommend that this product be approv subject to inclusion in the IADRRS. There were also a few queries on the pharmaceutics and bio-availability testing that needed resolving. Advantages were seen in tocainide being more active than procainamide and quinidine and having a longer half life, CNS side effects appeared less troublesome than with lignocaine. The intensified monitoring could be useful in defining the prevalence of ANF alterations and whether restricti pulmonary effects were of concern.

(2) Baypen

It was decided to defer this application for mezlocillir so that clarification of the indications proposed, published clinical reports and further details on the microbiological findings in the clinical reports supplie could be supplied. Additionally the quality control data had to be recompiled so that it was amenable to assessment.

(3) Noctamid

It was decided to defer this application for lormetazepam so that some further information could be provided on safety in man, the bio-availability trials reported and the quality control of the drug and the product. With regard to human safety, it was considered that, since the drug would on occasion be used over extended periods, its liability in causing dependence in such circumstances should be investigated, reports should also be sought on adverse effects associated with long term use. There was also a lack of published reports.

(4) Cefsulodin

It was considered that further clinical reports relating particularly to renal safety (with and without frusemide) were warranted before a recommendation could be made. There were also some quality control/ pharmacokinetic queries arising.

(5) Cefotiam

For this cephelosporin it was agreed that further reports relating to clinical experience especially in Caucasian patients were warranted, for the clinical trials reported the microbiological findings should be provided and information on the stability of the reconstituted injection should be supplied. Accordingly, it was decided to defer making a recommendation.

(6) Pipril

This application was for piperacillin injection. It, like a number of applications for antibiotics under discussion at this meeting, suffered from a lack of detail on the microbiological findings in the clinical trials reported - there was consequently a lack of demonstrated value relating to individual pathogens. Clarification of the indications was needed, comment on the incidence of resistance of Pseudomonas where piperacillin was the sole antimicrobial drug should be provided. Additionally, there were a number of queries on quality control and stability assessment. It was then decided to defer this application.

(7) Zelmid (zimelidine)

It was decided to defer this application so that further information and comment could be provided on mutagenicity testing, further clinical reports relating especially to the treatment of phobias could be provide effects on the retina in long term use, the relevance t

man of the testicular atrophy reported in animals, the pharmacokinetics and the quality control of the tablets could be further reported.

A satisfactory case had been made for a greater safety margin in overdose situations with this drug than with tricyclic antidepressants.

(8) Zomax

It was decided to recommend that this application for zomepirac be approved subject to it being used only for short term analgesia and not in arthritis, it being contra-indicated in treating the pain of myocardial infarction until there was some acceptable information on its haemodynamic effects in such situations, the prescribing information indicating that food and milk inhibit absorption. Additionally, but independent of the registration, data on the potential for causing dependence in man and the findings of the post-marketing surveillance on urinary tract adverse reactions should be provided.

(9) Surgam

This application related to tiaprofenic acid, an anti-inflammatory analgesic developed by Roussel in the 1960's and early 1970's, registered only in France and under clinical investigation in the United Kingdom since 1973. The committee decided to defer making a recommendation so that the reasons for the lengthy UK trial period could be sought, comment on effects on the thyroid in man and some recent clinical publications could be provided. Additionally, there were some questions arising on the bio-availability trials and quality control.

(10) Claforan (Cefotaxime)

It was decided to recommend that this application be approved subject to some questions on the synthesis and stability being resolved. The committee considered that the clinical experience with this cephalosporin was extensive, the drug had advantages in that it penetrated the meninges but was not suitable for treatin Pseudomonas infections as sole therapy.

(11) Romilar Cough and Cold Syrup

This cough mixture - dextromethorphan/guaiaphenesin/paracetamol had been referred to the committee because the department considered the inclusion of paracetamol

inappropriate. The committee decided that there were no compelling reasons for declining the application - there remained only some questions on the stability of the mixture to be resolved. It was then agreed that the application should be approved subject to the chemical stability being found acceptable.

6 CHANGED MEDICINE NOTIFICATIONS

(1) Danocrine

Danazol is currently approved in New Zealand for treating endometriosis and hereditary angio-oedema. This notification proposed its use for treating fibrocystic disease of the breast. Reservations were expressed in that the use of danazol could delay the diagnosis of breast cancer, however, after discussion it was agreed that availability of the drug to surgeons and gynaecologists only should provide adequate assurance on this point. The post-registration discussions with Winthrop Laboratories over danazol had earlier failed to resolve questions raised concerning the inadequate data provided on the bio-availability of Danocrine tablets. The committee then decided to recommend approval subject to its use/ availability being restricted as above and the bio-availability issue being resolved.

7 GENERAL BUSINESS

(1) Particles in Large Volume Parenteral Fluids

The department had for some years required that such fluids meet BP standards and this had been more recently endorsed in the New Zealand Transfusion Advisory Committee standard. McGaw Ethicals wished to import i.v. fluids tested against the USP standard, which was acknowledged to be less strict. The committee considered that these standards were not set on bases of safety, there was no evidence that would differentiate between the USP and other standards in terms of safety and accordingly the USP standards were acceptable.

(2) Asthma Deaths

Recent publicity where there were suspicions of an association between the use of aerosol sympathomimetic bronchodilators/theophylline and an increase in asthma deaths was briefly reviewed and the advice given to doctors discussed. It was agreed that Professor O'Donnel would vet the statement proposed by the department to draw attention to precautions in asthma therapy, particularly where theophylline is used.

(3) An abstract of a statement recently made by the International Medical Advisory Panel of the IPPF after a meeting in London in October 1980 where Depo Provera

(medroxyprogesterone acetate) was reviewed was tabled. It was noted that the panel considered DMPA favourably but acknowledged that long term monitoring should continue.

(4) A recent report of a meeting held in Auckland to promote chelation therapy was discussed briefly. The committee noted that the potential ramifications of chelation therapy on state-funded medicines and medical services were very far-reaching.

This being all the business, the Chairman closed the meeting at 5.00 pm.

MINUTES OF THE THIRTY-SEVENTH MEETING OF THE DRUG ASSESSMENT ADVISORY COMMITTEE HELD ON 20 OCTOBER 1982 IN THE BOARD ROOM MACARTHY TRUST BUILDING WELLINGTON

PRESENT

Dr J S Phillips	Chairman
Professor I R Edwards	
Professor P B Herdson	
Professor G Kellaway	
Dr M Kingsford	
Dr P Moller	
Professor T V O'Donnell	
Dr G Shanks	
Mr R C Griffith	Secretary

IN ATTENDANCE

Mrs S Combly
Dr K H Goh
Dr S M Martindale

1 The chairman welcomed Professor Edwards and mentioned with regret that Dr Kingsford had indicated that he would be resigning after this meeting.

2 MINUTES OF 36TH MEETING

The minutes were accepted as read.

3 MATTERS ARISING FROM THE MINUTES

Benoxaprofen

Recent events in the United Kingdom relating to the withdrawal of the licence for Oraflex were discussed. The aspects of the introduction of new medicines on a large scale shortly after registration, the unwarranted readiness of doctors to prescribe new medicines and the obligations of health authorities to explore better means of detecting uncommon, serious adverse effects during phase IV were highlighted. It was accepted that it was, in this regard, the responsibility of the Department of Health to bring to the attention of doctors recent findings of serious adverse effects although the incidence of such effects were not usually able to be clearly defined. Whilst this procedure would influence and possibly bias the reporting rate it would allow earlier resolution of the question as to whether the benefit/risk balance of a drug had altered significantly or not.

It was agreed that two aspects of New Zealand practice should be investigated by the department for the next meeting. These were, the increasing practice of companies instigating releases to the daily press on newly approved medicines - the department would compile a dossier of recent events of this sort. The other general question was that of the scope of publicity that could be given to DAAC recommendations. The chairman undertook

to find out whether these could be made known more widely than to the Minister of Health whom the committee specifically advises.

Erythromycin Bioavailability

At the March 1982 meeting it was agreed to ask the then current suppliers of erythromycin products to comment on their products in relation to bioavailability criteria proposed by D G Fraser in the American Journal of Hospital Pharmacy in 1980. Responses had been received from the four companies. The Upjohn product was considered acceptable. Lilly Industries had recently been asked for referenced papers and letters from their response to the last meeting - these had only just been received and could not then be discussed before the March 1983 meeting. The Abbott response recently received made some points of criticism of the Fraser article but provided no specific information on the Abbott products in New Zealand - this was then to be sought. Douglas Pharmaceuticals had recently responded to say that there had been no difference in efficacy demonstrated clinically between the various erythromycin compounds and there was then no need for change to availability or prescribing instructions in New Zealand. Douglas had in reply provided no bioavailability data on their product. The department undertook to ascertain whether this was available.

Ranitidine and Pregnancy Caution

At the last meeting the committee had recommended approval of Zantac tablets and injection with the proviso that the prescribing information include a statement that it should not be used in pregnancy. This was because of its affinity for melanin and its occurrence in the foetal eye of rabbits and rats.

Glaxo had objected to the pregnancy contra-indication and had provided for the committee's consideration the reports available concerning teratology investigations in rabbits, and chronic toxicology in dogs, mice and rats, plus three alternative statements embodying a use in pregnancy caution with qualifications derived from these animal studies.

The evidence and statements were discussed at length together with a chapter from "The Retinal Pigment Epithelium" by Zinn and Marmor, published by Harvard University Press 1979. This, it was agreed, showed that in the case of the retino-toxic compound piperidyl chlorophenothiazine, neither rabbits, rats nor dogs showed retinopathy on chronic exposure as seen in man, whilst cats did. The committee then concluded either that the contra-indication should be included or the applicant should show that ranitidine is not retino-toxic in man.

4 DEFERRED APPLICATIONS

Natrilix

This application for indapamide had last been considered in July 1978 when it was deferred for a carcinogenicity report,

further comparative trials with commonly used antihypertensive agents, long term safety data in a larger number of patients and some further quality control data. The responses were considered adequate excepting the points that the order of administration for the three-way bioavailability trial had not been provided and the applicant had not indicated that a single tablet assay would be used in quality control. It was then recommended that the application be approved when these points had been resolved.

Hexabrix

This application for the general purpose radiographic ioxaglate, had been deferred in October 1981 so that the renal toxicity relative to similar agents could be more clearly defined. The applicant had provided subsequently further animal and clinical data where renal effects were further investigated including those of other radiographic agents. After discussion it was agreed that the application should now be recommended for approval and that the few outstanding quality control queries could be dealt with separately.

Merital

This application for the anti-depressant nomifensine had been considered in November 1976 and deferred because of insufficient long term clinical data, absence of publications and unsatisfactory quality control data. The quality control and publications issues were answered in the supplementary data but there had been no co-ordinated attempt to define the long term safety - the obligation was on the applicant to draw together the available data and this had not been done. It was then agreed that the application should remain deferred so that adequate long term clinical data together with updated information on registration status could be provided.

Corgard

This application had been considered last in October 1980 and deferred so that the data sought earlier on anti-nuclear antibody tests and eye slit lamp examinations in 200-250 long term patients could be sought. The applicant had recently presented 6 month and 12 month data on groups up to 129 and 234 for the respective examinations. These showed no trend toward abnormality and the committee then decided to recommend that the application be approved. It was suggested that since the bioavailability of nadolol was poorly defined in the trials provided any substantial change of formula should be required to be supported by more precise data.

Zelmid

This application had last been reviewed in March 1982 when the making of a recommendation was deferred so that the hypersensitivity reaction then reported could be better defined both as regards incidence and nature. A few queries on the metabolism, bioavailability and quality control had also remained. In the ensuing discussion it was pointed out

that the prevalence of the hypersensitivity reaction was much higher in a number of the countries with more reliable adverse drug reaction reporting schemes; this was about 8-13% in those countries against about 1.5% elsewhere but as monitoring in New Zealand did not appear a worthwhile proposition it was agreed that the prescribing information should make reference to the adverse reaction. It was pointed out that there was still very little information about the fate of zimelidine in man. The committee did decide to recommend approval with a request to the applicant that an updated report on the hypersensitivity reaction be furnished, after 1 years use in New Zealand had been seen.

5 APPLICATIONS NOT PREVIOUSLY CONSIDERED

Zovirax

This application related to acyclovir in eye ointment and injection for the treatment of herpes simplex infections. It appeared acceptably safe and effective in use. Intravenous infusion should be slow to avoid the possibility of crystalluria, highest concentrations of the drug appeared in kidney, eye, liver and bone marrow in animal studies. It appeared likely to be useful for genital herpes infections but not for herpes simplex encephalitis since brain penetration is poor. The injection would be suitable for specialist use only. The committee then agreed that the application should be approved with the proviso that because of its novel mode of action Zovirax be included in the intensified monitoring scheme. There were a number of outstanding quality control matters but these could be followed up separately.

Augmentin

This application was for amoxycillin 250 mg plus clavulanic acid 125 mg in tablets and dispersible tablets. In the discussion it was advanced that the in vitro evidence for a synergistic effect was good but the clinical data was less convincing with respect to the margin of benefit over amoxycillin alone. However some trials showed clear evidence of effectiveness where amoxycillin failed and it was then agreed that the application should be approved subject to some quality control matters being resolved, the claim on absorbtion being unaffected by food being deleted. The applicant was also to be asked for reports relating to the mutagenicity testing of clavulanic acid.

Bezalip

This application for bezafibrate provided good evidence that the preparation was effective in lowering blood lipids and it appeared not less effective than clofibrate in this regard. It was noted also to have a shorter half life than clofibrate. There were however a number of questions on safety arising from the toxicology studies because administration of the drug in man was likely to be long term. The committee decided then to defer the application so that clinical publications, data on its safety in pregnant women, reports on its effects on gallstone formation in patients and some

further quality control data could be provided. It appeared that while some members had seen the carcinogenicity test data others had not and therefore that any resubmission should include this.

Razoxin

This was for 125 mg razoxane tablets for the treatment of soft tissue, osteo- and chondro-sarcomata in combination with radiotherapy. The data provided suggested that this drug would mostly be used in combination drug therapy since its value was limited with radiotherapy alone. There were a substantial number of publications relating to its use. It was then agreed that the application should be approved subject to the product stability being defined as adequate.

Hypnomidate

Etomidate is a general anaesthetic without analgesic properties proposed for the induction and maintenance of anaesthesia by intravenous injection/infusion. Its prime advantage would be the short recovery time on bolus administration although it appeared that this advantage could be dissipated after infusion because of accumulation. It appeared to have advantages over thiopentone with lesser effects on cardio-vascular and respiratory systems but was often painful when administered, not infrequently caused myoclonic effects and it was apparent from the Dunedin clinical trial that disturbing emergent psychotic events were not rare. The committee then concluded that its claimed benefits were outweighed by the disadvantages, it was recommended that the application be declined.

Stadol (butorphanol)

This application was referred to the committee on a request made at the last meeting. After a brief discussion the committee agreed that the application should be accepted with the proviso that the prescribing information contra-indicate its use in pregnancy and for treating the pain of myocardial infarction.

Menophase

This application was for five mestranol plus norethisterone combinations taken serially in a cyclical regimen for treating symptoms of the climacteric. The application was supported by three clinical trials two of which were controlled and although the oestrogen content was lower than in low dose oral contraceptives there was no advice given as to whether smoking was a contra-indication. There was a problem with the stability test data provided because of erratic assay findings and the testing not being conducted in the blister pack intended for sale. The committee decided to recommend that the application be approved subject to the product stability being demonstrated.

Aldoretic

This application was for a combination tablet of amiloride 2.5 mg hydrochlorothiazide 25 mg and methyldopa 250 mg for

the treatment of hypertension. This was regarded as an inappropriate combination because of the variability in doses of the drug types required in patients. It was also pointed out that the diuretic combination did not preclude the development of hypokalaemia. It was agreed that the application should be declined.

Lidaprim

This was another combination product where 400 mg and 800 mg sulphametrole were combined with respectively 80 mg and 160 mg trimethoprim. The committee noted that it had, in the last few years, considered two like products, Triglobe and Tibirox both of which were declined primarily because there was no clinical evidence that the sulphonamide (in both cases sulphadiazine) contributed to the effectiveness of the preparation. With Lidaprim the applicant had provided acceptable in vitro evidence that the components had synergistic antibacterial activity and the efficacy claim included that for a lesser development of drug resistance in clinical practice. Sulphametrole it was noted was not available in New Zealand and it was not possible to know whether it was more or less safe than sulphamethoxazole. It was then decided to defer making a recommendation on the application so that further clinical experience especially with regard to the safety of sulphametrole could be reported. The committee also noted that the original preparation of this type, cotrimoxazole had been approved for sale in New Zealand prior to the advent of the DAAC. It was agreed that should Lidaprim be reconsidered by the committee then Triglobe and Tibirox should concurrently be reconsidered.

Frisium

This application related to clobazam, a benzodiazepine, for which there were claims of lesser psychomotor effects than with existing preparations. On the evidence provided there was however, no basis for differentiation from existing long half-life benzodiazepines. It appeared likely that, as with similar compounds, a dose reduction would be necessary in the elderly. The committee then decided to recommend approval of the application subject to some quality control matters being resolved and the prescribing information including a caution concerning its use in elderly patients where accumulation of the drug and metabolites was likely.

Tigason

This application was for etretinate in the treatment of a number of hyperkeratotic conditions including psoriasis. This drug would provide an alternative to methotrexate in severe psoriasis and appeared there to be effective in about 50% of cases. There was concern with its teratogenic potential in women and it was suggested that the prescribing information could usefully indicate if there were any preferred forms of contraception considering the lengthy period necessary for

the substance to disappear from the body. The committee then decided to recommend that the application be approved and that its promotion should be restricted to dermatologists.

Professor Edwards left the meeting during the discussion on Tigason. Earlier the meeting dates for 1983 had been discussed - the dates 9 March, 22 June and 19 October were settled upon on condition that no clashes were advised within a week.

Baratol

This application related to indoramin an alpha-adrenergic blocking agent for treating hypertension. It appeared only to have moderate effects on elevated blood pressure; although tachycardia resulting from the mechanism of action was not a problem and there were no side effects of concern, its sedative effects appeared to make it unacceptable to a large number of patients. It was noted that indoramin also possesses anti-serotonin and anti-histaminic activities and causes failure of ejaculation in a high percentage of males. The committee after further discussion agreed that the application should be approved at such time as a number of queries on quality control were resolved.

Human Insulin (Novo)

This was prepared by substituting a threonine residue for alanine at the end of the B chain of porcine monocomponent insulin. The human insulin had been investigated in animals, subjects and patients and appeared acceptable although no advantage generally had been shown to date over existing insulins. There were some questions arising on the inactivation of the trypsin used for cleavage and the stability of the product. was then decided to recommend that the application be approved bject to the purity/stability matters being resolved.

INTENSIFIED ADVERSE DRUG REACTION REPORTING SCHEME

is item was included to allow a review of the medicines listed on the scheme. They were discussed one by one.

Epilim - it was agreed that the adverse effects of valproate were now adequately defined and that since an adequate cohort of users was now on computer it could now be delisted.

Sotacor - had now seen wide use in other countries although not in New Zealand but there was no good reason for keeping it on the list - agreed to be delisted.

Tonocard - tocainide had to date seen little use in New Zealand and very few reports concerning it had been received at the registry of adverse drug reactions. It was pointed out that with the pending Drug Tariff listing in December that reporting would probably increase to provide a more useful cohort of patients - it was agreed that Tonocard remain listed.

Cordarone-X - there were still findings and suspicions of new adverse effects arising - amiodarone should then remain on the list.

Capoten - because of the difficult patients in which captopril was used and its more serious adverse effects it was decided to keep Capoten on the list.

Adalat - members also considered that it was preferable that nifedipine remain on the list.

It was noted that Zovirax would be added so that the scheme would comprise five drugs after the next amendment.

The committee noted with interest the proposals current in Australia on a drug monitoring scheme.

7 GENERAL BUSINESS

Canrenoate

The department had recently been provided by Searle with a report concerning findings of myelocytic leukaemia and mammary tumours in a chronic rat study in Japan. Although animal toxicology studies with spironolactone there had in no previous study been a dose response correlation. In the ensuing discussion it was suggested that whilst mammary tumours were not surprising because of the high doses and effects on aldosterone the myelocytic leukaemia was unexpected and could have resulted from an impurity in the rat diet or a peculiarity in the rat metabolism of canrenoate. No action was considered necessary.

Phenoxybenzamine

The department had been recently provided by Smith, Kline and French with final reports on a number of mutagenicity investigations on phenoxybenzamine in vitro and in vivo systems. Because of the absence of any definitive carcinogenicity study on the substance a 2 year rat study had commenced. Smith Kline and French indicated that Dibenyline prescribing information would be amended shortly to mention the mutagenicity findings.

Buprenorphine

The chairman advised that there had recently been an upsurge in attempts by drug abusers to obtain buprenorphine; whether this was because it had effects attractive to abusers or because it had simply become fashionable was not known. It was intended to promote caution with prescribers by indicating this in a Clinical Services Letter shortly.

Before closing the meeting the chairman spoke appreciatively of Dr Kingsford's contribution to the committee and to pharmaceutical science in New Zealand. His advice would be sorely missed.

The meeting was closed at 5.12 pm.