PHARMACEUTICALS

12. MATTERS ARISING FROM THE MINUTES OF THE PREVIOUS MEETING (CONSIDERATION OF POST-MEETING SUBMISSIONS UNDER 42ZCZ)

12.1 LEVONORGESTREL

PURPOSE

The Committee considered post-meeting submissions in relation to the June 2003 initial decision to reschedule levonorgestrel in a two-tablet pack, of 0.75 mg per tablet, for emergency post-coital contraception from Schedule 4 to Schedule 3 of the SUSDP.

BACKGROUND

The June 2003 Meeting considered the scheduling of levonorgestrel for emergency contraception (EC). The Committee agreed to include levonorgestrel in a two-tablet pack, of 0.75 mg per tablet, for emergency post-coital contraception in Schedule 3 of the SUSDP. The decision was based on established safety and efficacy of the product, the need for timely access and its OTC availability in several countries for a number of years. Additionally, the distributor's undertaking to provide appropriate training and educational materials to aid pharmacists in giving professional advice and counselling to consumers on the safe and effective use of this product was taken into account. An Appendix H listing for levonorgestrel was also proposed but was not considered by the Committee due to insufficient information.

DISCUSSION

Members noted that a large number of post-meeting submissions were received. Some submissions were from those who did not make a pre –meeting submission and therefore, did not comply with regulation 42ZCZ of the Therapeutic Goods Regulations 1990. Nonetheless, the Committee agreed to consider all submissions received for this item. The submissions are summarised in Attachment 2.

The Committee noted that XXXXXXXXXX, XXXXXXXXXX, the XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX and XXXXXXXXXX supported the decision. It was submitted that women in both the metropolitan and rural (including remote) areas would benefit from the decision, and it may lead to reduced abortion rates. However, the additional endeavours including education, monitoring programs, inclusion of advice on methods of ongoing contraception, access to testing for sexually transmitted diseases (STDs) and recommended medical review to exclude ongoing pregnancy in the Product Information had been suggested. The sponsor committed to ensuring the provision of adequate training and educational materials for pharmacists, including advice about the risk of ectopic pregnancy, adverse effects and potential needs for medical management.

The Committee considered the arguments opposing the rescheduling proposal contained in the post-meeting submissions from several professional groups and the general public. Almost without exception, the issues raised in the June 2003 post-meeting submissions had been dealt with at the June 2003 meeting. The following issues were again raised in the post-meeting submissions received and the Committee considered information that should allay concerns about these issues:

The perceived abortifacient action and legal liability of pharmacists
Levonorgestrel is not considered by the Committee to be an abortifacient. This view was determined by the TGA at the time of registration of XXXXXXXXXX and would not be changed by the rescheduling of levonorgestrel for EC from S4 to S3. The legal implications of a pharmacist providing levonorgestrel EC were considered to be no different to the supply of any other S3 product. One post-meeting respondent suggested that by supplying levonorgestrel EC directly, ie. without a prescription, a pharmacist could be "procuring a miscarriage" which would be a criminal offence. In the Committee's view, a pharmacist could only be "procuring a miscarriage" if they were supplying an agent deemed to be an abortifacient, which levonorgestrel is not.

Concerns about toxicity and contraindications
The Committee noted that worldwide post-marketing surveillance that covered over 15 million uses of the product has not (with the exception of ectopic pregnancies) identified any new or emergent adverse events. WHO considers only unexplained vaginal bleeding, current breast cancer, pregnancy and hypersensitivity to levonorgestrel to be absolute contraindications. All can be assessed using history taking by pharmacists rather than specific diagnostic tests or medical examination. Pharmacists are already well trained in the techniques of appropriate questioning prior to supply of S3 substances. The risks and consequent need for doctor monitoring associated with long-term ongoing use of oral contraceptives (minipills at S4) are quite different to those associated with a single use of two 0.75 mg tablets of levonorgestrel. For example, thromboembolism is more likely linked to ongoing exposure than the brief, albeit higher dose of this product (< 0.03% with levonorgestrel as EC). The oestrogen content in contraception products is mainly responsible for the risk of thromboembolism. Most women presenting for levonorgestrel emergency contraception are likely to be otherwise healthy and relatively young. The potential for serious adverse events to occur with levonorgestrel emergency contraception is low and less of a public health issue than the adverse events and social problems associated with both abortion and unwanted pregnancies.

Concerns about the risk of ectopic pregnancy
Spontaneous reports to the XXXXXXXXXX in the UK and XXXXXXXXXX indicated that use of levonorgestrel EC may be associated with a very small increase in incidence

of ectopic pregnancy. It is now advised by XXXXXXXXXX and XXXXXXXXXX that any woman who does not have a menstrual period within the expected time frame or has abnormal bleeding or pelvic pain after taking levonorgestrel EC, should seek medical advice. This advice can be adequately conveyed to the consumer.

Concerns on existing pregnancy and potential teratogenesis
The WHO document entitled "Emergency Contraception: A guide for service delivery" directs providers to exclude the possibility of pregnancy by establishing the date and nature of the last menstrual period and establishing the time of the first and last episodes of unprotected intercourse since the last menstrual period. Other assessments such as laboratory tests and pelvic examination are unnecessary unless the answers to the questions about menstrual period and sexual intercourse indicate that current pregnancy is possible. Similar to any other S3 product where use in pregnancy is not advised, pharmacists would be able to question the client appropriately to determine the chance of pregnancy. If the pharmacist has any doubt as to whether the woman may be pregnant they can refuse to supply the drug and refer the woman to a doctor.

A pregnancy which occurs as a result of failure of the levonorgestrel emergency contraception would not be at risk. The half-life of levonorgestrel is approximately 24 hours, and levels are likely to be undetectable 5 days after taking the dose. Since implantation usually occurs 7-10 days after ovulation, the likelihood of exposure of the developing baby to levonorgestrel is quite remote. With respect to teratogenicity, the product information for XXXXXXXXXX makes it quite clear that based on previous experience with combined oral contraceptives, an increase in congenital abnormalities would not be expected except where levonorgestrel is administered at or after eight weeks post-conception. This use would be outside the registered indications.

Some of those who made submissions referred to a 1975 paper by Nora and Nora which described a collection of congenital anomalies known as the VACTERL syndrome. Although a few women in this paper were treated with a progestagen alone (medroxyprogesterone in a 10 mg dose), most were treated with combined oestrogen/progestagen and of the 19 patients whose babies were born with the VACTERL anomalies, 6 were not treated with any hormonal agents and of the 13 who were, 3 had taken other potential teratogens as well. Members were of the view that this study was too small and the confidence intervals too wide for any real conclusions about teratogenicity from progestagen exposure to be drawn. Also of note was the fact that more recent publications including the product information documents for XXXXXXXXXX made no mention of this syndrome.

Concerns about waiving of the "2 year rule"
Levonorgestrel has been available OTC in other similar countries, e.g. the UK and France, for at least 2 years, and by prescription in the UK and USA for longer. Furthermore, two doses of 25 tablets each of the 30 microgram levonorgestrel "XXXXXXXXXX" had been used "off label" by a number of doctors and Family Planning Clinics for emergency contraception prior to the formal marketing of XXXXXXXXXX. The actual clinical use of levonorgestrel EC in Australia is longer than the period of availability of XXXXXXXXXX, and on this ground, waiving of the 2-year rule is reasonable.

Concerns about potential drug interactions
Pharmacists are experienced in counselling about drug interactions and counselling about interactions with levonorgestrel EC is no different. All the potential interactions listed are not that levonorgestrel affects the drug already being taken but the opposite: that the levonorgestrel may be less effective mainly due to decreases in levonorgestrel levels due to hepatic enzyme induction. All the drugs listed in the Product Information for XXXXXXXXXX as potential interactions would meet the Schedule 3 criterion of being commonly used drugs or foods.

Concerns about repeated use and potential use as an ongoing form of contraception
Specific clinical trial data was presented at the June 2003 meeting which addressed both these concerns. The two main arguments presented in June indicating that repeated use of levonorgestrel EC is unlikely to be attractive still stand: firstly, side-effects such as nausea and interruption of the menstrual cycle are likely to be barriers and secondly, levonorgestrel EC is less efficacious than other ongoing contraceptive methods. It was shown by the data that pharmacy availability in the UK had resulted in increased usage of levonorgestrel EC, which might have only reflected better availability of levonorgestrel EC (the very thing that moving to S3 is trying to achieve) rather than increased sexual promiscuity. A study performed in Ghana by Lovvorn and others (2000) reported that "Our data did not suggest that the availability of EPCs increased the frequency of unprotected intercourse". Similarly, a controlled study of 263 women who presented to a family planning clinic in San Francisco also found that advance provision of emergency contraception did not result in reports of higher frequencies of unprotected sexual intercourse (Raine et al 2000). On the other hand, provision on prescription does not preclude the possibility of a woman deliberately seeking repeated use of levonorgestrel EC by going to different doctors or different hospital emergency departments, or obtaining a prescription for XXXXXXXXXX with multiple repeats, as has repeatedly occurred.

Concerns about risk of missing the chance to test for sexually transmitted diseases (STDs)
Pharmacists can be trained to counsel appropriately about the need for STDs screening depending on the woman's circumstances. Material already developed in the UK lists specific questions which pharmacists can use in this situation. Also of note is that for some STDs, e.g. Hepatitis B and C and HIV/AIDS, an immediate blood test is inappropriate and the patient will still have to make another visit to the doctor or remember to go to a pathology laboratory 3 months later to be adequately tested.

Concerns that availability on prescription has not been shown to reduce abortion rates
Abortion rates are influenced by many factors including the legislative environment of the country where they are being measured. The reasons why abortion rates alone may not be the best measure of the public health benefit of wider availability of levonorgestrel EC were well elucidated at the June 2003 meeting.

Concerns about lack of privacy and training for consultation in pharmacies The manufacturer has committed to ensuring that training materials and other materials such as those developed in the UK will be readily available to pharmacists. In some states, the relevant pharmacy organisations are already well on the way to developing training programs and materials for use by pharmacists who may be asked to provide levonorgestrel EC. Regarding lack of privacy in pharmacies, a woman still has the option of visiting her doctor for a prescription, if she is concerned about the lack of privacy in a pharmacy. All the methods suggested by XXXXXXXXXX to encourage timely access of levonorgestrel EC as a S4 drug, such as advance prescriptions, dispensing following a telephone call with a written prescription to follow and emergency medical appointments, are already available yet do not appear to be well known or well utilised.

Concerns about supply to patients under 16 years of age
Members noted that the cut-off age for supply was mentioned by several correspondents, and both medical and legal arguments were presented opposing supply by pharmacists to those under 16 years. The product information for XXXXXXXXXX does suggest that data in the 14 and 16 year age group is limited. In the UK, supply by pharmacists directly is limited to females 16 years or over. Members were also informed that the legislation in Queensland prevented pharmacists from providing S3 medicines to people under the age of 16 years, except when such medicines were sought under a doctor's prescription. Pharmacists may recommend that any woman under 16 years seeking levonorgestrel should go to a doctor for a prescription, or call from the pharmacy for a doctor's appointment. This would be a matter of professional judgment based on each individual circumstance.

Inclusion in Appendix H
The Committee confirmed the view taken out the June 2003 Meeting that an Appendix H listing for levonorgestrel was not warranted due to insufficient information available to support an informed decision about advertising.

Overall the Committee reiterated that levonorgestrel EC in a dose of 2 x 0.75 mg tablets clearly conforms to the criteria for a Schedule 3 medicine both in terms of the characteristics of the drug and the indications for use. The main reason for rescheduling to Schedule 3 is to provide timely access to the substance remembering that 95% of expected pregnancies are prevented if levonorgestrel emergency contraception is taken within 24 hours of unprotected intercourse, 85% if it is taken between 24 and 48 hours and only 58% if it is taken between 48 and 72 hours.

DECISION 2003/39 – 18-Confirmation of Amendment (Decision 2003/38 – 25)

In accordance with subregulation 42ZCZ(3), the Committee confirmed the amendment (Decision 2003/38-25) made at the June 2003 meeting, with minor editorial changes, to include levonorgestrel in a two tablet pack, of 0.75 mg per tablets, for emergency post-coital contraception in Schedule 3 of the SUSDP. The decision was based on the following:

- Enabling timely access to levonorgestrel for EC to achieve high efficacy.
- A well-established safety profile in terms of toxicity, contraindications and drug interactions.
- Levonorgestrel for EC use has been available in several countries for a number of years including use as a non-prescription product.
- The product satisfies the criteria for Schedule 3 listing.
- The sponsor commits to provide appropriate training and educational materials for pharmacists.
- The pharmacist is required to provide professional advice and counselling to consumers to ensure that the product is used safely and effectively.

Schedule 3 - New entry

LEVONORGESTREL in tablets each containing 0.75 mg of levonorgestrel, in a primary pack containing two such tablets, for emergency post-coital contraception.

Schedule 4 - Amendment

LEVONORGESTREL **except** when included in Schedule 3.

12.2 IBUPROFEN

PURPOSE

The Committee considered further public submissions in relation to June 2003 decision to exempt small packs of ibuprofen from scheduling.

BACKGROUND

2. The June 2003 NDPSC Meeting made an initial decision to exempt from scheduling divided preparations containing 200 mg or less of ibuprofen per dosage unit in packs containing 25 or less dosage units when labelled with a recommended maximum daily dose of 1200 mg of ibuprofen. The decision was based on the Committee's opinion that:

- The proposed indication and the product are suitable for self-identification and self-treatment without professional advice;
- The safety profile of low dose ibuprofen in the OTC setting is good;
- A comparison with similar unscheduled analgesic products (aspirin and paracetamol in small pack sizes) indicated that short term intermittent use of low dose ibuprofen had a relatively good safety profile.

- Ibuprofen administered orally has been demonstrated to have a wide therapeutic index and the risk of masking a serious disease is very low.
- Ibuprofen has a very low to absent potential for abuse.
- There is considerable OTC marketing experience in Australia as well as considerable international marketing experience with prescription, pharmacy and general sales. The spontaneous reporting rates of adverse events in Australia and overseas has also been low.

DISCUSSION

Members noted that a large number of post-meeting submissions were received (Attachment 3). Some submissions were from those who did not make a pre –meeting submission and therefore, did not comply with regulation 42ZCZ of the Therapeutic Goods Regulations 1990. Nonetheless, the Committee agreed to consider all submissions received up to 17 September 2003 for this item.

The consideration commenced with a presentation by an expert member who had reviewed in detail the submitted references. The Committee discussed the following points raised in post-meeting submissions opposing the decision to exempt low dose ibuprofen from scheduling.

Concerns about the PAIN study
The Committee noted that several submissions enclosed or quoted an article recently published in Australian Pharmacist by Professor Gregory Peterson (University of Tasmania) regarding the PAIN study referred to in the sponsor's submission. The PAIN study was a large randomised clinical trial investigating the tolerability of aspirin, ibuprofen and paracetamol for short-term analgesia. XXXXXXXXXX expressed doubt on the methodology and hence the strength of evidence presented in the PAIN study on which he believed the down-scheduling decision was based. He pointed out that the published paper did not include comprehensive inclusion and, in particular, exclusion criteria for patients included in the study.

A copy of the final clinical trial report for the PAIN study, which contained more details than the published version, had been obtained by the Secretariat and reviewed by an expert member. It was noted that the exclusion criteria in the PAIN study were essentially the contra-indications associated with ibuprofen, aspirin and paracetamol, which included gastrointestinal ulcer, pregnancy or lactation, allergy to NSAIDs and severe asthma. Members were of the view that it seemed probable that the cohorts studied in the PAIN Study were similar to those who would take appropriately ibuprofen purchased on unrestricted sale. It was noted that the contraindications and precautions associated with the use of ibuprofen were to be covered by appropriate labelling of the small packs.

The Committee noted that after excluding patients with a history of upper gastrointestinal ulcer in the PAIN study, the incidence of drug-induced abdominal pain and dyspepsia

was lower in the ibuprofen-treated group than with other groups. On this basis, it was reasonable to conclude that based on the findings of the PAIN study, low dose ibuprofen for intermittent and short term use had a better gastrointestinal safety profile compared to aspirin and paracetamol for the same use.

Concerns on gastrointestinal complications
The Committee noted that several submissions expressed concern on the potential gastrointestinal (GI) complications induced by ibuprofen. The FDA report (Memorandum from RA Bonnel et al, 2002) referred to by XXXXXXXXXX, reviewed 197 cases of GI bleeds, ulceration or perforation reported for over-the-counter NSAIDs in the US during 1998-2001, including 105 cases for ibuprofen. FDA reviewers concluded that the patients in the study were at increased risk for GI bleeding in the setting of a past GI event, other significant inter-current illness or past medical history, consumption of alcohol, tobacco use or use of another OTC or prescription medication concomitantly. The expert member noted that the FDA report did not include a reference to the denominator of exposure during the specified time and therefore, a true incidence of GI events could not be determined for this OTC use. Furthermore, another reference provided by XXXXXXXXXX (McCarthy et al 1999) which estimated the risk of adverse events in patients using various classical NSAIDs based on outcome studies of large databases suggested ibuprofen to be considerably safer in terms of upper GI complications compared to other NSAIDs including aspirin, naproxen, diclofenac, piroxicam and ketoprofen.

The Committee agreed that any potential gastrointestinal complications could be covered by an appropriate warning statement.

Concerns about the elderly users and potential risks.
Members noted that although the majority of users of unscheduled analgesics would be healthy individuals aged under 50, based on the sponsor's claim which was accepted by the NDPSC, there would be a population of users at or over 65 years. Several submissions expressed their concerns on the potential risks for ibuprofen use in this sub-population given its side effects and contraindications.

The Committee noted information cited by XXXXXXXXXX and XXXXXXXXXX (from Newspoll survey) that "nearly a quarter of a million Australian could potentially take low-dose aspirin and ibuprofen together". The Committee also noted information cited by XXXXXXXXXX (from survey of pharmacists) that 1% of the total pharmacy response had reported intervention by the pharmacist in a requested sale of ibuprofen to someone already taking low-dose aspirin. The Committee noted that concern about the possible interference of ibuprofen with the cardioprotective effects of low-dose aspirin was based on a study of the effects of cyclooxygenase inhibitors on antiplatelet effects of aspirin (Catella-Lawson et al, NEJM, 2001) and a study of clinical events using a clinical record database (MacDonald TM, Wei L. Lancet 2003). In this latter study, the patients had had their medication supplied by a hospital system and may have been taking ibuprofen long term. Members indicated that it was not possible to draw firm conclusions relevant to the general sale of ibuprofen from this study as there was a lack

of information on doses and duration of treatment with ibuprofen, and no adjustment for severity of diseases and other risk factors (e.g. smoking) was made for each treated group.

Members were of the view that although long term use of ibuprofen might interact with the cardioprotective effects of low-dose aspirin, this effect was unlikely to be a significant concern with short term use of low dose ibuprofen based on available information. The Committee decided that inclusion of a precautionary statement relating to use of ibuprofen in elderly patients, such as "Unless a doctor has told you to, don't use this product if you are taking other medicines containing aspirin or other anti-inflammatory medicines or other medicines you are taking regularly" would reduce possible risks associated with self-administration of ibuprofen in patients taking low dose aspirin.

Concerns on women users and the risk of miscarriage

The Committee noted that several post-meeting submissions mentioned the findings of a cohort study conducted in the US and published in the British Medical Journal (Li et al 2003), which suggested an increase in relative risk for miscarriage in users of NSAIDs. The cohort study was based on interviews of 1055 pregnant women recruited immediately after confirmation of pregnancy, about the use of NSAIDs, aspirin and paracetamol. The paper did not provide an analysis for each of the NSAID used by the subjects in the study except aspirin, and had the limitation of being a *post hoc* analysis of a study originally designed to assess the prenatal exposure to magnetic fields. Whilst it was noted that the cohort study concluded that paracetamol had no effect on the risk of miscarriage, members' attention was drawn to an early finding of a heightened risk of spontaneous abortion or foetal death in paracetamol overdose during pregnancy (Riggs et al, Obstet Gynaecol 1989).

Based on available information, there was no compelling evidence to suggest that ibuprofen was associated with a higher incidence of miscarriage compared to other NSAIDs. However, the Committee agreed that it was appropriate to include a precaution not to use ibuprofen if pregnant on the product label.

Concerns on NSAIDs-related renal failure ("triple whammy")

Members discussed the potential risk of drug-related renal failure associated with the use of NSAIDs together with ACE inhibitors and/or diuretics. Some recent Australian data (ADRAC, 1990-2002) were provided. These indicated that the number of reported cases of renal failure implicated with 1). ibuprofen alone, 2). Ibuprofen and ACE inhibitor or diuretic, or 3). Ibuprofen, ACE inhibitor and diuretics represented only 3-4% of the total reports of renal failure attributed to all NSAIDs, alone or in combination. While great caution was needed to interpret spontaneous reports data it was suggested that ibuprofen showed fewer reported adverse renal effects compared to other NSAIDs.

The XXXXXXXXXX representative expressed concern that the Committee was down-playing the importance of the ADRAC reports of renal failure and was potentially

showing a lack of consistency in decision-making. The Committee considered that these concerns would be addressed through appropriate labelling.

NSAIDs-induced asthma
Members were aware of the concerns on NSAIDs-induced asthma by several respondents. Similar to that for aspirin, a warning statement for NSAID-induced asthma was already proposed for ibuprofen products.

Concerns on the pack size of the product
XXXXXXXXXX claimed that 25-dose forms representing a 4-day treatment was an excessive pack size for open sale ibuprofen. However, XXXXXXXXXX did not provide any evidence to support the safety concern raised with the 25-tablet (5 g ibuprofen) pack size, which the Committee noted was equivalent to the pack size of general sale aspirin (7.5 g) and paracetamol (12.5 g). On this basis, the Committee agreed that the pack size limit of 25 tablets (total of 5 g ibuprofen) remained appropriate.

Consultation to doctors / pharmacists
Several pharmacy organisations raised the issue that use of ibuprofen required pharmacist consultation, given the potential side effects. The Committee noted that the current S2 classification did not require intervention by a pharmacist in each sale. The Committee also noted that the potential side effects associated with short-term use of ibuprofen would be dealt with in the warning statements that would be required for general sale products. In addition, the Committee emphasised that a decision to exempt a product from scheduling does not preclude the sale of such a product in pharmacies where access to a pharmacist is available to consumers.

Current availability
Ibuprofen in divided preparations containing 200 mg or less of ibuprofen per dosage unit in a pack containing 50 or less dosage units and labelled with a recommended daily dose of 1200 mg or less of ibuprofen was included in Schedule 2 (S2) in May 1995. S2 means that pharmacist intervention is not mandatory at the point-of-sale, and that the request for advice is initiated by the purchaser. During this period of S2 availability, no significant safety issues were submitted to the Committee. In addition, a member advised that ibuprofen was an S2 product in NSW, which was allowed to be sold in country stores without pharmacists, and this had not given rise to major adverse cases being reported.

Consistency with other NSAIDs in scheduling
The Committee confirmed that ibuprofen was a NSAID with a good safety record that was comparable to paracetamol and better than aspirin, particularly, in relation to gastrointestinal events. Although paracetamol was generally considered as the first line analgesic agent, ibuprofen was safer than paracetamol in overdose, due to the hepatotoxicity associated with paracetamol overdose.

The Committee concluded that there was sufficient evidence to support the exemption from scheduling requirements of intermittent low dose and short-term use of ibuprofen, provided that appropriate warning statements were included on the product label.

DECISION 2003/39 – 19 - Variation of Amendment (Decision 2003/38 – 23)

In accordance with subregulation 42ZCZ(3), the Committee agreed to vary the amendment (Decision 2003/38-23) made at the June 2003 meeting to exempt divided preparations containing 200 mg or less of ibuprofen per dosage unit in packs containing 25 or less dosage units when labelled with a maximum recommended daily dose of 1200 mg of ibuprofen from scheduling, by amending the label Warning Statements.

The decision was based on the following reasons:

- The indications for low dose (≤1200 mg/day) oral administration of ibuprofen are suitable for self-identification and treatment without professional advice.
- Ibuprofen has a comparable safety profile to existing unscheduled analgesic products (aspirin and paracetamol in small pack sizes) indicated for the same use.
- Ibuprofen products have been available for general sale in the USA since 1984, and in the UK since 1996 with no significant safety issues arising over that time, and there is considerable OTC marketing experience in Australia as an S2 medicine.
- Ibuprofen has a wide therapeutic index, and the risk of masking a serious disease is very low.
- Appropriate warning statements for GI complications, pregnancy, asthma and use in certain age groups have been included to reduce the risks in sensitive sub-populations.
- Ibuprofen has a very low to absent potential for abuse.

Schedule 2 - Amendment

IBUPROFEN - amend entry to read:

IBUPROFEN in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen:

(a) in liquid preparations when sold in the manufacturer's original pack containing 4 grams or less of ibuprofen; or

(b) in divided preparations, each containing 200 mg or less of ibuprofen, in packs of 100 or less dosage units **except** when:

(i) as the only therapeutically active constituent other than an effervescent agent;

(ii) packed in blister or strip packaging or in a container with a child-resistant closure;

(iii) in a primary pack of 25 or less dosage units;

(iv) the primary pack is labelled with a warning statement to the following effect:

WARNING - This medication may be dangerous when used in large amounts or for a long time (period);

CAUTION - This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. Prolonged use without medical supervision could be harmful; or

CAUTION - This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. Prolonged or excessive use without medical supervision could be harmful; and

(v) the primary pack is labelled with warning statements to the following effect:

Don't use [this product / name of the product]:
If you have a stomach ulcer
In the last 3 months of pregnancy [*This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea*]
If you are allergic to ibuprofen or other anti-inflammatory medicines; and

Unless a doctor has told you to, don't use [this product / name of the product]:
For more than a few days at a time
With other medicines containing aspirin or other anti-inflammatory medicines or other medicines that you are taking regularly
If you have asthma
In children 6 years of age or less
If you are aged 65 years or over
If you are pregnant [*This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea*].

Schedule 4 - Amendment

IBUPROFEN - amend entry to read:

IBUPROFEN **except**:

(a) when included in or expressly excluded from Schedule 2; or

(b) in preparations for dermal use.

12.3 TERIPARATIDE

PURPOSE

The Committee considered post-meeting comment relating to the June 2003 meeting recommendation to include the new medicine, teriparatide, in Schedule 4 (S4) of the SUSDP.

BACKGROUND

Teriparatide is a recombinant human parathyroid preparation XXXXXXXXXX.

DISCUSSION

Members advised that a mechanism was in place in the jurisdictions where patients in remote areas with no immediate access to specialists could obtain on-going prescriptions through a GP under the direction of a specialist.

DECISION 2003/39 – 20 - Variation to Amendment (Decision 2003/38-31)

In accordance with subregulation 42ZCZ(3), the Committee agreed to vary the amendment (Decision 2003/38-31) made at the June 2003 meeting to include teriparatide in paragraph 1 of Appendix D for public health and safety reasons. The Committee was of the view that inclusion in Appendix D would put in place additional controls on supply and availability in addition to Schedule 4 to ensure that the 18-month total lifetime treatment limit was not exceeded and thereby minimise the potential risk of osteosarcoma.

Schedule 4 – New entry

TERIPARATIDE.

Appendix D, Paragraph 1 – New entry

TERIPARATIDE for human use.

12.4 FLUCONAZOLE

PURPOSE

The Committee considered the inclusion of fluconazole in Appendix H.

BACKGROUND

The June 2003 Meeting considered the rescheduling of fluconazole. The Committee agreed to include fluconazole in Schedule 3 for single-dose oral preparations containing 150 mg for the treatment of vaginal candidiasis. The decision was made on the basis of its similar safety profile to topically applied antifungal agents, and was considered appropriate for similar S3 availability.

DISCUSSION

The Committee noted that the sponsor XXXXXXXXXX made a post-meeting submission seeking approval to advertise fluconazole 150 mg single dose when included in Schedule 3 of the SUSDP, with the following main points:

- Fluconazole has high efficacy as a single-dose treatment for vaginal candidiasis and a favourable safety profile. Its OTC availability should have the advantage of patient preference and improved compliance.
- Brand advertising would alert women to the fact that there is an oral alternative to topical drug therapy available for the treatment of thrush.
- Advertising would allow women to make a choice of therapy (in consultation with the pharmacist), which best suits their needs with respect to rapidity of relief of symptoms and convenience.
- Advertising would be expected to raise the level of consumer knowledge about vaginal candidiasis.
- OTC advertising would direct women to health professionals who are able to provide the best advice on the condition and treatment options, and who can direct the women to a doctor if required.
- The likelihood of advertising leading to inappropriate patterns of medication use is low.

Members noted the following points highlighted in the expert's assessment on the Appendix H inclusion of the substance:

- Comparable vaginally applied treatments for the same condition are permitted to be advertised, and alerting women to the availability of an alternative orally administered product could be considered a useful public health message.

- The sponsor committed to adhere to the Therapeutic Goods Advertising Code, to include the importance of initial medical diagnosis and the pharmacists' counselling role, and provide CMI and other material needed to educate product users.
- Low potential for advertising to promote inappropriate use.

The Committee noted that MEC had recommended (Item 8.1 of the October 2003 MEC Meeting) that Appendix F Warning Statement No 64 (ie. "See a doctor if no better after three days") be include on the labels of Schedule 3 fluconazole products. A period of "three days" was set as the vaginal mucosa would not necessarily have recovered earlier than this after a single dose fluconazole treatment.

In addition, it was noted that XXXXXXXXXX considered fluconazole to be a valuable first line treatment which could be life-saving when used for the treatment of cryptococcal infections, particularly in AIDS patients. After extensive discussion, the Committee was of the view that it was unlikely for resistance to develop with fluconazole given the treatment of vaginal candidiasis comprises of a single and discrete oral dose of fluconazole.

The Committee also agreed to include fluconazole in Appendix H when it was included in Schedule 3, given that there should be reinforcement through appropriate advertising that the product was recommended as a second-line treatment for vaginal candidiasis after the failure of a topical antifungal.

DECISION 2003/39 – 21 - Variation to Amendment (Decision 2003/38-29)

In accordance with subregulation 42ZCZ(3), the Committee agreed to vary the amendment (Decision 2003/38-29) made at the June 2003 meeting to include fluconazole in Appendix F and Appendix H of the SUSDP. The decision at the June 2003 meeting to include fluconazole in single-dose oral preparation containing 150 mg or less of fluconazole for the treatment of vaginal candidiasis in Schedule 3 was made on the basis of comparable safety profile to other topical azole products for the same indication. Inclusion in Appendix F (Warning Statement 64) and Appendix H was also consistent with other Schedule 3 imidazole antifungals for vaginal use.

Schedule 3 – New entry

FLUCONAZOLE in single-dose oral preparations containing 150 mg or less of fluconazole for the treatment of vaginal candidiasis.

Schedule 4 – Amendment

FLUCONAZOLE – amend entry to read:

FLUCONAZOLE **except** when included in Schedule 3.

Appendix F, Part 3 – New Entry

Fluconazole
Warning Statement …… 64

Appendix H – New Entry

Fluconazole

13. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

13.1 SILICONES

PURPOSE

The Committee considered an amendment to the Appendix C entry for silicones foreshadowed at 38th (June 2003) Meeting.

BACKGROUND

During the consolidation of SUSDP No.17, many inconsistencies and editorial errors were discovered. One such inconsistency was the silicones entry in Appendix C. The Committee agreed, at Meeting 38, to change the Appendix C entry for silicone by adding the words "or implantation" to provide consistency within the SUSDP and to reflect the original intent of the Committee at the time that the entry was made.

DISCUSSION

The Committee was advised that the proposed amendment was included in the Pre-October 2003 gazette notice and was returned to the Committee for finalisation. No public submissions in relation to this matter were received.

Members confirmed the foreshadowed amendment.

DECISION 2003/39 - 22

The Committee agreed to modify the Appendix C entry for silicones as foreshadowed at Meeting 38.

APPENDIX C – Amendment

SILICONES – amend entry to read:

SILICONES for tissue augmentation by injection or implantation.

13.2 PSEUDOEPHEDRINE

PURPOSE

The Committee continued its consideration of the scheduling of undivided, combination and slow release preparations of pseudoephedrine in Schedule 2.

BACKGROUND

The June 2002 Meeting agreed to reschedule all OTC single-active immediate release pseudoephedrine preparations from Schedule 2 to Schedule 3, and foreshadowed the consideration of scheduling of S2 pseudoephedrine formulations at the October 2002 NDPSC Meeting.

However, preliminary information available at the October 2002 meeting did not provide sufficient evidence to support scheduling action on compounded, undivided and modified release pseudoephedrine preparations in Schedule 2. Nonetheless, the Committee remained concerned over the potential for the remaining Schedule 2 products to be diverted to the illicit drug trade and agreed that it would continue its consideration of the matter at the February 2003 meeting following further public consultation. This approach was viewed as an opportunity for the Committee to be informed of the outcome of ongoing investigations on all OTC pseudoephedrine products by XXXXXXXXXX, and for sponsors to indicate their plans for existing and future product lines.

The February 2003 Meeting and the June 2003 agreed to defer further consideration of the scheduling of undivided, combination and slow release (SR) pseudoephedrine preparations in Schedule 2 to allow more time to review the findings of XXXXXXXXXX investigation. This was specifically the extractability of pseudoephedrine from various OTC formulations and agreed to defer any further scheduling until the October meeting. It was considered prudent to allow consideration of the outcomes of the extraction research and other measures agreed to by the National Working Group. The Committee also agreed to carry over all public submissions for pseudoephedrine from previous meetings

DISCUSSION

The Committee noted pre- October 2003 meeting comment was received from XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX and XXXXXXXXXX which supported the present scheduling requirements for pseudoephedrine. Additionally, pre-meeting comment from XXXXXXXXXX requested the right to make a post-meeting submission on any recommendations made on pseudoephedrine. Also members were informed that XXXXXXXXXX has issued a draft determination for the "*Code of Conduct - Helping Prevent the Diversion of Non-Prescription Medicines Containing Pseudoephedrine*" for a period of 5 years.

Advice from XXXXXXXXXX member indicated that the National Working Group on the Diversion of Precursor Chemicals (NWG) research and its analysis were, to date, not finalised.

Members were informed that the NWG that met on 26 June 2003 provided funding for the analytical research and that initial results from other research undertaken to date indicate extraction of pseudoephedrine from multiple component pharmaceutical preparations via liquid-liquid extraction is relatively uncomplicated and an average recovery of 78% is achievable.

The Committee discussed recent police action which uncovered approximately 7000 tablets in a vehicle in XXXXXXXXXX. It suggested that this finding may not necessarily indicate that pharmacists are becoming less vigilant in observing anomalous purchasing behaviour with pseudoephedrine in Schedule 3.

The Committee believed that single active preparations of pseudoephedrine were most likely the problem with diversion to the illicit drug trade.

As the NWG analytical report was not available discussion was held on whether the research findings would be sufficient to proceed with any scheduling action, it was suggested that this may be pre-empting the NWG if this was undertaken. The industry representative advised that previous discussions with the XXXXXXXXXX on pseudoephedrine revealed that they perceived no scheduling changes were warranted at this stage.

The XXXXXXXXXX representative noted that pharmacists were being advised by their representative organisations of any actions recommended with illicit drugs within a few days of Health Department recommendations.

It was agreed that the Secretariat prepare a letter for XXXXXXXXXX asking that the NDPSC be advised by January 30 2004 of any NWG outcomes so that it can be reported and considered at the February 2004 meeting.

OUTCOME

The committee agreed to:

- defer any further scheduling action until the February 2004 meeting to allow consideration of the outcomes of the extraction research and other measures agreed to by the National Working Group; and,
- carry over all public submissions for pseudoephedrine from previous meetings.

13.4 MITRAGYNINE

PURPOSE

The Committee considered the foreshadowed inclusion of mitragynine and *Mitragyna speciosa* in Schedule 9 of the SUSDP.

BACKGROUND

Mitragynine (also known as Kratom) is one of the alkaloids found in the leaves of the South-East Asian tree *Mitragyna speciosa*, which is used extensively in Thailand to increase work output and tolerance of direct sunlight. Mitragynine has psychoactive properties and has been associated with being used as an opium substitute. Kratom leaves are usually chewed, smoked or drunk as tea to achieve the desired affect. *Mitragyna speciosa* is regulated in the same way as cocaine and heroin in Thailand and carries the same restrictions and penalties as cocaine. There have also been reports of use of mitragynine in Malaysia. Poisindex indicates that in adults, a dose of 50 mg of pure mitragynine has produced motor excitement, rombergism, giddiness and tremors of the face, extremities and tongue. In 1975, a study of 30 Thai Kratom users considered chronic (more than 5 years use) noted that the leaves were chewed three times to 10 times a day, with stimulant effects occurring after five minutes to 10 minutes.

The February 2003 Meeting considered preliminary information in relation to mitragynine and M*itragyna speciosa*. This consideration was initiated by an inquiry to the TGA from an Australian resident wishing to import mitragynine and concern regarding its potential for abuse. Members discussed the pharmacology and toxicology of mitragynine, its potential for abuse, and the potential impact of its inclusion in the SUSDP. The Committee agreed that there were grounds for inclusion of mitragynine and M*itragyna speciosa* in the SUSDP, based on mitragynine's mode of action. To allow appropriate public consultation, the Committee agreed to foreshadow the inclusion of mitragynine and M*itragyna speciosa* in Schedule 9 of the SUSDP, for consideration at the June 2003 meeting.

The June 2003 Meeting noted the studies which showed that mitragynine exerted agonistic effects on opioid receptors in *in-vitro* studies as well as an antinociceptive action, which suggested that mitragynine has a morphine-like action on gastric acid secretion. A member pointed out that tramadol is a mu-opioid receptor agonist included in S4 and that it has a low potential for producing dependence. Members noted that the information from Poisindex (Micromedex Healthcare) indicated that addiction and withdrawal symptoms had occurred with chronic use of M*itragyna speciosa*. The Committee subsequently agreed to defer further consideration of the foreshadowed decision on the view that additional information was required to better characterise the physiological effects and mechanisms of action of mitragynine.

DISCUSSION

The Committee noted the advice received from XXXXXXXXXX stating that it had not seen conclusive evidence relating to abuse or misuse of *Mitragyna speciosa* or mitragynine. XXXXXXXXXX submitted that evidence on addiction and other harms seen with *Mitragyna speciosa* or mitragynine had been largely anecdotal, and in some instances contradictory. XXXXXXXXXX was of the view that given the range of psychoactive substances being advertised on internet web sites, the limited user base and the nature of use, it was unlikely that abuse of *Mitragyna speciosa* would become widespread in Australia.

The Committee noted the literature review of pharmacological and toxicological data on mitragynine prepared by the Secretariat. Animal experiments with mitragynine had shown that it possessed pain threshold-elevating and antitussive properties. A series of pharmacological studies in animal models, *in vivo* and *in vitro*, indicated that similar to morphine, mitragynine and its derivatives produced central antinociception, inhibition of intrinsic activity or electrically elicited guinea pig ileum contraction and drug-induced gastric acid secretion, and inhibition of cAMP content. It was demonstrated in receptor binding studies that these effects were mediated by opioid receptors and that further studies also indicated that the pharmacological actions of mitragynine were selectively blocked by antagonists for some sub-types of opioid receptors, predominantly mu- and delta-receptor subtypes. (*Matsumoto et al, Eur J Pharmacol 1996; Thongpradichote et al, Life Sciences 1998; Tohda et al, Biological & Pharmaceutical Bulletin 1997; Tsuchiya et al, Eur J Pharmacol 2002; Takayama et al, J Med Chem 2002; Yamanoto et al, General Pharmacol 1999*).

Based on available data, members noted that habitual users of mitragynine could develop marked withdrawal syndromes, including hostility, aggression, rhinitis, inability to work, excess tears, muscle and bone aches and jerky limb movement. Members concurred with the view that there was a strong possibility of addiction if mitragynine was used in doses high enough for mu-receptor crossover (*1974-2003 Thomson Micromedex. Micromedex(R) Healthcare Series Vol. 115)* and agreed to restrict the use of the substance.

Members discussed whether similar restrictions should be imposed on the plant species, *Mitragyna speciosa,* in the light of reports that the leaves of the plant were being used for smoking and chewing, and the leaf extracts drank as tea, to achieve the 'desired' effects. A member also raised the issue that there was a possibility that the plant was being used for ornamental purposes and that the Committee should defer confirmation of the foreshadowed decision to the next meeting to allow further information to be sought on this matter.

DECISION 2003/39 – 23

The Committee agreed to take a pro-active approach and included mitragynine in Schedule 9 of the SUSDP based on its potential for abuse. The Committee recognised

that whilst there were no widespread reports of abuse of mitragynine in Australia at this time, the information relating to the use of mitragynine for psychoactive effects, particularly in Asian countries, was well documented and easily found on the internet.

Schedule 9 – New Entry

MITRAGYNINE.

OUTCOME

The Committee agreed to consider the foreshadowed inclusion of the plant species, *Mitragyna speciosa,* in S9 of the SUSDP at the February 2004 to seek additional information on the plant's uses.

Foreshadow for consideration at the February 2004 meeting

Schedule 9 – New entry

MITRAGYNA SPECIOSA.

13.5 TRICHLOROACETIC ACID

PURPOSE

The Committee considered the scheduling of trichloroacetic acid in dermal preparations.

BACKGROUND

Trichloroacetic acid (TCA) was first included in Schedule 6 of the SUSDP at the March 1972 Meeting and the alkali salts of trichloroacetic acid were included in Schedule 5 in October 1980 'out of session'.

XXXXXXXXXX received a complaint regarding a treatment described as "chemobrasion" which is a form of chemical skin peeling. The applicant alleged that following application of a 20% TCA solution by an enrolled nurse, the consumer was left with injuries attributed to the procedure and has since undergone remedial treatment. XXXXXXXXXX also received a subsequent unconfirmed report that beauty therapists were also applying TCA. The XXXXXXXXXX Member referred this matter to the NDPSC with a recommendation to include trichloroacetic acid for dermal use in Schedule 4 of the SUSDP with an exemption for wart and tattoo removers.

The 38th (June 2003) NDPSC considered this matter and agreed to foreshadow the inclusion of trichloroacetic acid for dermal use, except when used for the removal of warts, in Schedule 4 of the SUSDP. The Committee also agreed to consider the inclusion of a cut-off in the proposed Schedule 4 entry to exempt TCA when used for the removal of warts and tattoos at specified concentrations, rather than exempting wart removal

preparations completely, and to include this intention in the pre-October 2003 gazette notice.

DISCUSSION

The Committee noted that no public submissions were received.

It was recalled that the 38th (June 2003) meeting noted an extemporaneous preparation Upton's Paste was listed in the Australian Pharmaceutical Formulary and Handbook and was used for wart removal. As this preparation is prepared and labelled for an individual patient's use and the pharmacist counsels the patient prior to dispensing the preparation, Members considered that the use of TCA for the removal of warts could be exempted from the requirements from scheduling.

Members noted that the concentration of trichloroacetic acid in Upton's Paste was greater than 10% and agreed to exempt wart preparations at a maximum concentration of 12.5%.

DECISION 2003/39 - 24

The Committee agreed to include trichloroacetic acid for dermal use in Schedule 4 of the SUSDP and the subsequent amendment to the Schedule 6 entry for trichloroacetic acid on public health and safety grounds. The Committee was of a view that that inclusion of the substance in Schedule 4 except preparations containing 12.5% or less for wart removal except for the treatment of warts (other than anogenital warts) should significantly reduce the potential for inappropriate use of the substance.

Schedule 4 – New entry

TRICHLOROACETIC ACID for human dermal use **except** when in preparations containing 12.5 per cent or less of trichloroacetic acid for the treatment of warts other than anogenital warts.

Schedule 6 – Amend entry

TRICHLOROACETIC ACID – amend entry to read

TRICHLOROACETIC ACID **except**:

(a) when included in Schedule 4 or 5; or

(b) in human dermal preparations containing 12.5 per cent or less of trichloroacetic acid for the treatment of warts other than anogenital warts.

13.6 MEMANTINE

PURPOSE

The Committee considered the scheduling of the new chemical entity, memantine

BACKGROUND

Memantine is a rapid, strongly voltage dependent, uncompetitive NMDA receptor antagonist.

The 38th (June 2003) NDPSC meeting considered the scheduling of memantine and noted that in New Zealand memantine is classified as a prescription medicine.

In order to meet the statutory requirements the Committee agreed to foreshadow, for consideration at the October 2003 meeting, the inclusion of memantine in Schedule 4 of the SUSDP.

DISCUSSION

The Committee noted that while animal studies have reported adverse effects of memantine on the visual system, no conclusive evidence of ocular toxicity in the clinical setting was observed.

XXXXXXXXXX advised that the ADEC methodology of assessment is based on the European assessment methodology on statistical significance and not clinical significance and that it comes before the NDPSC after it was registered following a successful appeal to ADEC.

DECISION 2003/39 - 25

The Committee agreed to a new entry in Schedule 4 of the SUSDP for memantine on the basis that it is used to treat a medical condition that requires professional medical diagnosis, management and monitoring for side effects; and to harmonise scheduling with New Zealand.

Schedule 4 – New entry

MEMANTINE.

13.7 REVIEW OF NON-PRESCRIPTION ANALGESICS

PURPOSE

The Committee considered the Medicines Evaluation Committee's (MEC) package of warning statements for over the counter (OTC) analgesics for inclusion in Appendix F of the SUSDP.

This item is related to substances and items discussed at items 1.8.1.3.2 Paracetamol, 1.8.1.3.3 Aspirin and 12.2 Ibuprofen, and also the sub items referred to below.

BACKGROUND

A review of non-prescription analgesics, prepared by David Newgreen in February 1998, made a series of recommendations to address health and safety concerns regarding OTC analgesics, which related to matters within the NDPSC's terms of reference.

The May 2000 NDPSC meeting considered the Newgreen Report and the TGA's response. In February 2003, the TGA published the Review of Non-prescription Analgesics - an Update as a "draft for comment". This document was finalised by the MEC in April 2003 and referred to the NDPSC for consideration of the recommended changes to the SUSDP Appendix F warning statements for OTC analgesics.

The 38th (June 2003) meeting was provided with a copy of the Review of Non-prescription Analgesics – An update, April 2003 (April 2003 Update). Members noted that four of the recommendations of the April 2003 Update (numbers 9, 10, 11 and 13) and three of the Newgreen Report recommendations (numbers 6.5, 6.7 and 6.8) related to labelling requirements for analgesics that are required by the SUSDP. Additionally, members were aware that the responsibility for regulating label-warning statements was to be transferred from the NDPSC to the TGA in July 2005. The MEC had asked the NDPSC to implement OTC analgesic warning statement changes in the interim period. Members understood that the MEC's proposed package of warning statements for inclusion in Appendix F of the SUSDP are intended to replace the current SUSDP Appendix F warning statements for non-prescription analgesics, except for WS 36 with respect to aspirin.

Gazettal of the proposed MEC warning statements prior to the 38th NDPSC meeting resulted in a number of public submissions being received. The MEC considered these public submissions and provided advice and revised wording to the June 2003 meeting. It was pointed out that the public had not had the opportunity to comment on the revised wording recommended by the June 2003 MEC meeting and accordingly, the Committee agreed that it would not be able to resolve this issue at that meeting and referred the revised changes back to the MEC to enable it to undertake consultation with industry and provide a unified response to the NDPSC for consideration at the October 2003 meeting.

DISCUSSION

The Committee noted that MEC considered the June 2003 NDPSC recommendation at its August 2003 meeting. MEC's response to the NDPSC response including recommended analgesic warning statements was provided to members.

Members were informed that all pre-October 2003 meeting public submissions relating to this matter had been referred to MEC for comment. Public submissions were received from XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX and XXXXXXXXXX.

MEC considered these public submissions at its October 2003 meeting and a summary of the considerations is at Attachment 4. The issues addressed by MEC were discussed by the Committee.

The XXXXXXXXXX member was concerned about the reasons for adopting the analgesic WS in Appendix F at this time when the TGA was going to transfer warning statements for medicines from the SUSDP to a labelling order in the near future. The Chair advised that inclusion in the SUSDP would allow earlier implementation of the WS and a seamless transition to the new labelling order.

The Committee noted that a number of pre-meeting respondents sought a 12 month transition time to allow time for labels to be updated.

The XXXXXXXXXX member raised the issue that the NDPSC decision, if adopted at this meeting, would require changes to be implemented at State and Territory level by 1 May 2004. It was suggested that there be an additional 12 month transition to allow the changes to come into effect as of 1 May 2005 to avoid undue industry hardship.

The XXXXXXXXXX representative also advised that companies were concerned with statements that were prescriptive by the TGA as opposed to words that carried the same intent. Members discussed the proposition of using performance based labelling as proposed by XXXXXXXXXX.

The Committee noted the pre-meeting submission from XXXXXXXXXX which was concerned with the lack of precision in the proposed warning statement 102, "*Unless a doctor has told you don't take this [medicine] for more than a few days at a time"* but accepted that there was no better alternative. Another pre-meeting submission considered that the current statement on XXXXXXXXXX of "*Do not exceed the recommended dose or use for more than 48 hours without seeking medical advice*", adequately meets the intention of the new recommendations, is more restrictive and better promotes safe use. The NDPSC noted the view of the MEC that the new statement is consistent with this one, therefore the NDPSC proposed no change to revised warning statement 98.

Members noted that some public submissions raised concerns that warning statement 99 may be alarmist and considers that performance testing of the statement may be appropriate before inclusion and the use of the word 'overdose'.

XXXXXXXXXX advised that performance based labelling was a matter for the TGA and the new Trans Tasman Therapeutic Products Regulatory Agency.

OUTCOME

The Committee agreed to transitional arrangements for implementing the new analgesic warning statements, which would come into effect on 1 May 2005. See Items 13.7.1 Paracetamol; 13.7.2 Aspirin; 13.7.3 Ibuprofen; 13.7.4 Naproxen and 13.7.5 Mefenamic acid for specific decisions.

13.7.1 PARACETAMOL

PURPOSE

The Committee considered the Medicines Evaluation Committee's (MEC) package of warning statements for over the counter (OTC) paracetamol for inclusion in Appendix F of the SUSDP.

BACKGROUND

See Item 13.7 Review of non-prescription analgesics.

DISCUSSION

The Committee discussed the concerns raised in public submissions about the inclusion of the PIC phone number in the proposed new warning statement number 99. Members agreed to include the Appendix E section regarding PIC in the introduction section of Appendix F to allow some flexibility.

DECISION 2003/39 - 26

The Committee agreed to the inclusion of the MEC proposed new label warning statements for paracetamol in Appendix F the SUSDP and the consequential amendments to the Schedule 2 entry for paracetamol. It was also agreed that the effective date would be 1 May 2005.

SCHEDULE 2 – AMENDMENT

PARACETAMOL – amend entry to read:

PARACETAMOL for therapeutic use **except**:

(a) when included in Schedule 4;

(b) in individually wrapped powders or sachets of granules each containing 1000mg or less of paracetamol as the only therapeutically active constituent other than effervescent agents, when:

(i) in a primary pack containing not more than 12 such powders or sachets;

(ii) (A) labelled with the statement (permitted until 30 April 2005):

WARNING - This medication may be dangerous when used in large amounts or for a long period; or

CAUTION - This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. Prolonged use without medical supervision could be harmful; or

(B) labelled with the statements (mandatory from 1 May 2005):

Adults: Keep to the recommended dose. Don't take this medicine for longer than a few days at a time unless advised to by a doctor;

Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor;

If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 131 126; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage;

Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist; and

(iii) not labelled for the treatment of children 6 years of age or less; or

(c) in tablets or capsules each containing 500mg or less of paracetamol as the only therapeutically active constituent other than effervescent agents, when:

(i) packed in blister or strip packaging or in containers with child-resistant closures;

(ii) in a primary pack containing not more than 25 such tablets or capsules;

(iii) (A) the primary pack is labelled with the statement (permitted until 30 April 2005):

WARNING - This medication may be dangerous when used in large amounts or for a long period; or

CAUTION - This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. Prolonged use without medical supervision could be harmful; or

(B) labelled with the statements (mandatory from 1 May 2005):

Adults: Keep to the recommended dose. Don't take this medicine for longer than a few days at a time unless advised to by a doctor;

Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor;

If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 131 126; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage;

Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist; and

(iv) not labelled for the treatment of children 6 years of age or less.

APPENDIX F, INTRODUCTION – NEW ENTRY

Poisons Information Centre Telephone Numbers

Companies should use the poisons information centre telephone number(s) appropriate to the country(ies) of sale for the product, that is Australia or New Zealand or both. These

are 13 1126 for Australia and 03 4747 000 for New Zealand. A new free-call number (0800 764 766) is being introduced in New Zealand. Use of the old number (03 4747 000) shall be phased out by May 2005.

Companies wishing to use a poisons information centre telephone number other than the national telephone numbers for Australia and New Zealand in warning statement No. 99 in Part 1 of this Appendix must meet the following criteria:

1. The poisons information service whose number is used must be attended by adequately trained staff for 24 hour emergency poisons information; and

2. Calls must be logged and submitted for incorporation into the official collection of poisoning data.

APPENDIX F, PART 1 – NEW ENTRIES

97. *Adults:* Keep to the recommended dose. Don't take this medicine for longer than a few days at a time unless advised to by a doctor.

98. *Children and adolescents:* Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.

99. If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 131 126; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage.

100. Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.

APPENDIX F, PART 3 – AMENDMENT

Paracetamol – amend entry to read:

Paracetamol (a)	34 or 35 (permitted until 30 April 2005) or
(b).....	97 and/or 98, 99, 100 (mandatory from 1 May 2005)

13.7.2 ASPIRIN

PURPOSE

The Committee considered the Medicines Evaluation Committee's (MEC) package of warning statements for over the counter (OTC) aspirin for inclusion in Appendix F of the SUSDP.

BACKGROUND

See Item 13.7 Review of non-prescription analgesics.

DISCUSSION

The Committee discussed the overlap between the two pregnancy warning statements as raised by XXXXXXXXXX. Members noted that MEC had advised that both warnings are appropriate as the warning statement *"Don't use this product in the last 3 months of pregnancy"* is a contraindication while the other warning statement *"Unless a doctor has told you to, don't use this product if you are pregnant"* is a caution.

The XXXXXXXXXX member was of the view that the proposed pregnancy warning statements may be 'diluting' the message on pregnancy contained in the relevant analgesic consumer medicine information leaflets.

DECISION 2003/39 - 27

The Committee agreed to the inclusion of the MEC proposed label warning statements for aspirin in Appendix F of the SUSDP and to the consequential amendment to the Schedule 2 for aspirin (this can be found under Item 1.8.1.3.3). It was also agreed that the effective date would be 1 May 2005.

Appendix F, Part 1 - Warning Statements – New Entry

101. Don't use [this product / name of the product]:
If you have a stomach ulcer
In the last 3 months of pregnancy *[This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea]*
If you are allergic to (name of substance) or anti-inflammatory medicines.

102. Unless a doctor has told you to, don't use [This statement this product / name of the product]:
For more than a few days at a time
With other medicines containing aspirin or other anti-inflammatory medicines
If you have asthma

In children under 12 years of age
If you are pregnant.

103. See a doctor before taking [this product / name of the product] for thinning the blood or for your heart. *[This statement may be omitted in products for inhibition of platelet aggregation or with additional active ingredients.]*

APPENDIX F, PART 3 – AMENDMENT

Aspirin – Amend entry to read:

Aspirin	
(a) for inhibition of platelet aggregation.	36
(b) in sustained release preparations containing 650 mg or more of aspirin.	36
(c) except as above.	.....(i) 37 and 38 and
	.....(ii) 34 or 35 or 36 (permitted until 30 April 2005) or
	.....(iii) 101, 102, 103 and 37 (mandatory from 1 May 2005)

13.7.3 IBUPROFEN

PURPOSE

The Committee considered the Medicines Evaluation Committee's (MEC) package of warning statements for over the counter (OTC) ibuprofen for inclusion in Appendix F of the SUSDP.

BACKGROUND

See Item 13.7 Review of non-prescription analgesics.

DISCUSSION

The Committee considered that the issues concerning the MEC proposed warning statements raised under the general item 13.7 “Review of non-prescription analgesics” and its sub-items 13.7.1 “Paracetamol” and 13.7.2 “Aspirin” as well as under item 12.2 “Ibuprofen” had allowed for adequate discussion.

DECISION 2003/39 - 28

The Committee agreed to the inclusion of the MEC proposed label warning statements for ibuprofen in Appendix F of the SUSDP. It was also agreed that the effective date would be 1 May 2005.

APPENDIX F, PART 1 – NEW ENTRY

104. Unless a doctor has told you to, don't use [this product / name of the product]:
For more than a few days at a time
With other medicines containing (name of substance) or other anti-inflammatory medicines
If you have asthma
If you are pregnant *[This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea]*.

APPENDIX F, PART 3 – AMENDMENT

Ibuprofen – amend entry to read:

Ibuprofen (a)	34 or 35, 71 (permitted until 30 April 2005) or
(b)	101, 104 (mandatory from 1 May 2005)

13.7.4 NAPROXEN

PURPOSE

The Committee considered the Medicines Evaluation Committee's (MEC) package of warning statements for over the counter (OTC) naproxen for inclusion in Appendix F of the SUSDP.

BACKGROUND

See Item 13.7 Review of non-prescription analgesics.

DISCUSSION

The Committee considered that the issues concerning the MEC proposed warning statements raised under the general item 13.7 "Review of non-prescription analgesics" and its sub-items 13.7.1 "Paracetamol" and 13.7.2 "Aspirin" had allowed for adequate discussion.

DECISION 2003/39 – 29

The Committee agreed to the inclusion of the MEC proposed label warning statements in Appendix F of the SUSDP. It was also agreed that the effective date would be 1 May 2005.

APPENDIX F, PART 3 – AMENDMENT

Naproxen – amend entry to read:

Naproxen

(a)	in preparations for the treatment of dysmenorrhoea	(i) 34 or 35 (permitted until 30 April 2005); or (ii) 101, 104 (mandatory from 1 May 2005).
(b)	in other preparations;	(i) 34 or 35, 71 (permitted until 30 April 2005); or (ii) (101, 104 (mandatory from 1 May 2005).

13.7.5 MEFENAMIC ACID

PURPOSE

The Committee considered the Medicines Evaluation Committee's (MEC) package of warning statements for over the counter (OTC) mefenamic acid for inclusion in Appendix F of the SUSDP.

BACKGROUND

See Item 13.7 Review of non-prescription analgesics.

DISCUSSION

The Committee considered that the issues concerning the MEC proposed warning statements raised under the general item 13.7 “Review of non-prescription analgesics” and its sub-items 13.7.1 “Paracetamol” and 13.7.2 “Aspirin had allowed for adequate discussion.

DECISION 2003/39 - 30

The Committee agreed to the inclusion of the MEC proposed label warning statements for mefenamic acid in Appendix F of the SUSDP. It was also agreed that the effective date would be 1 May 2005.

APPENDIX F, PART 3 – AMENDMENT

Mefanamic acid – amend entry to read:

Mefanamic acid (a)	34 or 35 (permitted until 30 April 2005) or
(b)	101, 104 (mandatory from 1 May 2005)

13.8 IBUPROFEN

PURPOSE

The Committee discussed the MEC request to clarify the rationale behind the current proposal to revise the AGRD 2 guideline for ibuprofen to restrict concentrations of oral liquid ibuprofen preparations in Australia to 100mg/5mL or 200mg/5mL.

BACKGROUND

The November 2000 TTHWP meeting made a recommendation (33/7) that NZ MOH adopt the revised wording of the SUSDP amendment for ibuprofen that sets an upper daily dose for divided and undivided preparations for ibuprofen; and relaxes the concentration requirements for ibuprofen liquid preparations, but retains a 4g total content of ibuprofen in these packs.

The February 2001 NDPSC meeting endorsed this recommendation and referred it to NZ Medsafe. In May 2002 MCC considered TTHWP recommendation 33/7 and agreed that:

- the maximum daily dose for pharmacy-only solid dose and liquid ibuprofen should not exceed 1200 milligrams.
- the maximum pack size for pharmacy-only liquid preparations should not exceed 4g of total ibuprofen content.
- packs of undivided preparations for pharmacy-only sale should be in concentrations only of 100mg in 5ml or 200mg in 5ml of ibuprofen
- That the NDPSC adopt the MCC recommendation limiting the concentrations of liquid ibuprofen permitted in pharmacy-only (S2) medicines.

The May 2002 MCC meeting minutes stated that the purpose of reclassifying liquid ibuprofen to pharmacy-only medicine is to allow for paediatric doses that are not intended for chronic use.

The October 2002 NDPSC meeting agreed to gazette the consideration of scheduling of ibuprofen for consideration at the February 2003 meeting which received pre-meeting comment that objected to the inclusion of a dose limit for the Schedule 2 entry for ibuprofen. This was made on the basis that New Zealand has included the dose limit for ibuprofen in the NZ regulatory guidelines and not in the First Schedule to the NZ Medicines Regulations. XXXXXXXXXX felt it is more appropriate to include this level of detail in the Australian guidelines for the registration of medicines (AGRD vol 2). This approach is considered consistent with the current paracetamol guideline in the AGRD.

The Committee noted that there was harmonisation on pack size. New Zealand, however, had adopted dose limitations into their regulatory guidelines and NZ MCC were recommending harmonisation on strengths. Accordingly, the Committee agreed that the Schedule 2 entry for ibuprofen remained appropriate and that the scheduling of ibuprofen would remain unharmonised at this time, furthermore the Committee asked the Secretariat to draw MEC's attention to the dose limit in the NZ Regulatory Guidelines and recommended that MEC consider including similar requirements in the AGRD vol 2.

DISCUSSION

The Committee noted the response from MEC in June 2003 referring the issue back to NDPSC to clarify the rationale behind the current proposal to restrict the strength of OTC liquid ibuprofen preparations in Australia.

The Committee understood that NZ Medsafe, for practical means, decided to include the strength, pack size and dose requirements for OTC ibuprofen in their Regulatory Guidelines rather than the First Schedule of the Medicines Regulations.

Members noted that current ibuprofen guideline in the AGRD Volume 2 (now called the Australian Regulatory Guidelines for OTC Medicines (ARGOM) lists the dosage recommendations for ibuprofen. However, the ibuprofen ARGOM did not include a section on product strength.

OUTCOME

The Committee agreed that MEC be advised that the NDPSC did not include the strength limits for OTC liquid ibuprofen to allow for Trans-Tasman harmonisation and schedules and that MEC should consider harmonising their guidelines with New Zealand.

13.9 HYOSCYAMUS NIGER

PURPOSE

The Committee considered a cut-off to exempt preparations containing *Hyoscyamus niger* to harmonise with NZ.

BACKGROUND

The 38th (June 2003) NDPSC meeting considered a recommendation of the 28th (November 2002) NZ MCC to amend the cut-off in Appendix G of the SUSDP for atropine (100µg), hyoscine (10µg) and hyoscyamine (10µg) to 300µg/L to harmonise with New Zealand. The Committee agreed to amend the cut-offs in Appendix G for atropine to 300µg, hyoscine to 150µg and hyoscyamine to 100µg to reflect the relative potencies. NZ Medsafe was advised that harmonisation of the scheduling outcome for atropine had been achieved and that Australia would remain unharmonised on the cut-off to exempt hyoscine and hyoscyamine at this time.

The 29th (May 2003) MCC meeting considered a submission from XXXXXXXXXX seeking reclassification of *Hyoscyamus niger* from pharmacy only medicine to general sale medicine when in packs containing 300µg[1] or less of total solanaceous alkaloids. This submission resulted from the recommended cut-offs in Appendix G not allowing general sale status for a *Hyoscyamus niger* product.

The 29th MCC meeting agreed to classify *Hyoscyamus niger* as a general sale medicine when in packs containing 30 micrograms or less of total solanaceous alkaloids. The MCC decision was made on the grounds that the 30µg total solanaceous alkaloid content per pack was within the general principles of the herbal framework adopted in NZ that a general pack should contain not more than one hundredth of the lowest fatal dose.

DISCUSSION

The Committee considered XXXXXXXXXX submission to the NZ MCC and their pre-meeting submission to the NDPSC which proposed that the SUSDP be amended to allow for an exemption for preparations containing 30 micrograms or less of total solanaceous alkaloids per pack to harmonise with NZ.

Members discussed previous harmonisation activities for atropine, hyoscine and hyoscyamine and the XXXXXXXXXX member was concerned that the decision, if agreed, would endorse the general principle of the herbal framework adopted in NZ that a general pack should contain not more than one hundredth of the lowest fatal dose. Members agreed that the decision should be agreed on harmonisation.

A member questioned the relevance of the Appendix G entry for hyoscyamine. It was noted that Appendix G level for hyoscyamine was less than the level for the general sale.

OUTCOME

The Committee agreed to foreshadow, on the grounds of harmonisation, an amendment to the Schedule 2 entry for *Hyoscyamus niger* to exempt preparations containing 30 micrograms or less of total solanaceous alkaloids from the requirements of scheduling.

Foreshadowed for consideration at the February 2004 meeting

[1] The value "300µg" was corrected to read "30µg" at the June 2004 NDPSC Meeting (Item 1.5.2)

Schedule 2 – Amendment

HYOSCYAMUS NIGER – amend entry to read

HYOSCYAMUS NIGER for oral use:

(a) in undivided preparations containing 0.03 per cent or less of total solanaceous alkaloids when labelled with a dose of 0.3 mg or less of total solanaceous alkaloids and a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids; or

(b) in divided preparations containing 0.03 mg of total solanaceous alkaloids or less per dosage unit when labelled with a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids,

except in a pack containing 30 micrograms or less of total solanaceous alkaloids.

Schedule 4

HYOSCYAMUS NIGER – amend entry to read

HYOSCYAMUS NIGER **except**:

(a) when included in Schedule 2; or

(b) in a pack containing 30 micrograms or less of total solanaceous alkaloids.

14. PROPOSED CHANGES/ADDITIONS TO THE STANDARD FOR THE UNIFORM SCHEDULING OF DRUGS AND POISONS.

14.1 SUSDP, PART 4

14.1.1 ORLISTAT

The Committee considered an application seeking to reschedule orlistat for the treatment of obesity from Schedule 4 to Schedule 3 of the SUSDP.

BACKGROUND

Orlistat is a potent, specific and reversible long-acting gastric and pancreatic lipase inhibitor that limits the breakdown of triglyceride and the absorption of dietary fat. It is used in conjunction with dietary modification in the management of obesity.

XXXXXXXXXX markets XXXXXXXXXX containing 120 mg per capsule of orlistat for the treatment of obese patients with a Body Mass Index (BMI) of ≥30 and overweight patients with a BMI ≥27 in the presence of other risk factors, in conjunction with a mildly hypocaloric diet. Orlistat was first considered by the August 1999 NDPSC meeting and included in Schedule 4 of the SUSDP. The June 2002 NDPSC meeting initially considered a submission from XXXXXXXXXX seeking to reschedule orlistat for the treatment of obesity from S4 to S3, at which the Committee decided that the existing S4 scheduling remained appropriate. The Committee's decision was based on the following:

- The Committee was not satisfied that the safety profile of orlistat was consistent with Schedule 3 medicines, given the wide range of contraindications and potential adverse outcomes associated with obesity.
- The Committee agreed that thorough pre-screening and assessment by medical professional for co-morbidities associated with obesity was essential to determine the patient's suitability for orlistat therapy and reduce the potential for adverse effects.
- The Committee was of the view that making orlistat for the treatment of obesity Schedule 3 medicine would impart the wrong public health message that therapeutic intervention is the first-line treatment for obesity or over-weight conditions, and could expose the public to unnecessary risks. It was stated that consumers should be encouraged to undertake the appropriate lifestyle changes as a first option to achieve safe and long-term weight loss.

A second submission from XXXXXXXXXX to reschedule orlistat for the treatment of obesity from S4 to S3 was submitted to the February 2003 NDPSC meeting, which included a proposal to list orlistat in Appendix H of the SUSDP. However, the Committee agreed that the concerns raised at the June 2002 meeting had essentially remained unresolved and the decision to retain orlistat in Schedule 4 was reconfirmed. The following reasons were provided:

- In the absence of medical assessment of progress and regular monitoring for co-morbidities of patients undergoing pharmacotherapy with orlistat, long-term OTC treatment of this condition was undesirable on public health terms.
- The issue relating to the need for dietary supplementation with fat-soluble vitamins during treatment of orlistat and its overall effect on nutrition remained unresolved.
- Community pharmacists were not equipped to screen for co-morbidities associated with obesity (diabetes etc) and deal with potential adverse effects, and they were not set up to handle the high level of counselling and on-going support required to successfully manage obesity.

The Committee pointed out that any further rescheduling proposal should provide sufficient evidence to support the claim that orlistat is efficacious, safe and appropriate for long term weight loss outside the controlled environment of clinical trials.

DISCUSSION

The Committee noted that XXXXXXXXXX made a new application to reschedule orlistat for the treatment of obesity from S4 to S3. The following points were submitted:

There is no safe and effective over the counter medication available to help the subset of patients who may require pharmacological intervention but do not wish to visit a doctor. On the other hand, consumers have unrestricted access to many unproven OTC medicines for weight loss.

A full study report (XXXXXXXXXX study) of the trial conducted over a 4-year period was submitted to the meeting which confirmed the long term efficacy of orlistat in terms of weight loss and weight maintenance. Also, the study demonstrated that XXXXXXXXXX was more effective than diet and exercise alone and had the effect of delaying the onset of type 2 diabetes and decreasing the hazard of diabetes mellitus by 37.3% compared to placebo. The level of counselling used in the above study was similar to that provided by weight reduction dieticians or in many of the commercial weight reduction programs, i.e. visit once every 2 weeks for the first 25 weeks and then every 4 weeks.

Orlistat has reasonable efficacy in the uncontrolled setting (outside the clinical trial setting) as shown in the findings of the two studies: 1.) An Australian survey of 2131 patients who voluntarily enrolled into the XXXXXXXXXX patient support program (the real world of community use of the product under prescription), and 2.) a post-marketing efficiency study from Germany.

It was claimed that there was no evidence of either vitamin deficiency or bone disease in the 4-year XXXXXXXXXX study.

Pharmacists are well-equipped and trained to provide the required level of counselling and on-going support to consumers, and are well-placed to direct patients to their GP for a health check, where necessary.

- Appendix H brand advertising of XXXXXXXXXX would not again be sought until such time that it was fully supported by the community and pharmacy professional groups.

The Committee noted that the following points were highlighted in the report evaluating the sponsor's rescheduling application:

- The company provided a number of letters of endorsement from leading physicians working the in area of the treatment of obesity. All were in favour of

the rescheduling and their comments were consistent in their appraisal of orlistat and many had addressed the issues raised by the committee.

- There was a wide range of unscheduled products on the market whose efficacy was not evaluated by the TGA and for which many extravagant claims were made. The company in its submission identified a wide range of OTC Listed products including – "XXXXXXXXXX", "XXXXXXXXXX", "XXXXXXXXXX", "XXXXXXXXXX", "XXXXXXXXXX", "XXXXXXXXXX", "XXXXXXXXXX", as well as some food products and weight management programs. Some of the experts have also indicated that a range of very low calorie food products are also available and that these carry some of the same side effects and potential complications as XXXXXXXXXX and are currently available without prescription.
- The product has been shown to be effective and safe in long term studies of up to 4 years. Apart from the 1 and 2 year studies that have been presented previously, the 4-year XXXXXXXXXX study that was briefly presented in the last submission was re-submitted with a summary of the trial and some of the details. The XXXXXXXXXX study compared orlistat added to a moderately hypocaloric diet and moderate increase in exercise to the diet and exercise alone. The results for orlistat were statistically significantly better than placebo at 12 months ($p<0.001$) and at 4 years ($p<0.001$) for percent losing $\geq 5\%$ and $\geq 10\%$. The hazard ratio indicates that orlistat treatment significantly decreased the hazard of diabetes mellitus relative to placebo. The evaluator agrees that the study has given evidence for the long term efficacy, and the effect on development of type 2 diabetes. The counselling visit to a dietician scheduled every 2 weeks for the first 25 weeks and then every 4 weeks for the remainder of the 4 years, which was considered to be similar to that provided by weight reduction dietician or many commercial weight reduction programs.
- The efficacy of the product in the unsupervised setting is difficult to demonstrate but 2 studies are presented which suggest that the efficacy is similar to that which was considered acceptable for nicotine replacement therapy.
- The safety of XXXXXXXXXX appears acceptable for a Schedule 3 product. In response to the Committee's previous concerns over the issues of the fat soluble vitamins and the potential for metabolic bone disease, the company has presented extensive data from the 4-year XXXXXXXXXX study, and demonstrated that neither complications are likely to be a problem with orlistat. Furthermore, data from the company and the experts suggests that the Australian patients are likely to take the drug average for 3 months, which may be partially attributed to the cost XXXXXXXXXX /month). There is potential misuse by inappropriate dietary modification and/or patients eg overweight anorexia nervosa suffers, since the drug does not lead to sudden or excess weight loss. The relationship between GI side effects and fat intake reinforces to the patient the need for fat reduction in the diet.

- The Committee has previously expressed the view that patients should be prescreened for comorbidities before being prescribed the drug. This view was not supported by any of the Experts.

- The data presented addressed the issues raised by the Committee and demonstrated that the product met the criteria for Schedule 3 in terms of safety and efficacy, and for the use intended.

The Committee noted all pre-meeting submissions listed in Attachment 5. The main arguments in support the rescheduling proposal contained in pre-meeting submissions were summarised as follows:

- Obesity is a major public health concern that is currently under-treated. Consumers need greater access to effective weight loss products.
- Orlistat is an effective treatment for obesity, has a favourable safety profile and meets the criteria for inclusion in S3.
- Since obesity is linked to both the onset of pre-diabetes, Type 2 diabetes, and increased complications from Type 2 diabetes. Improvement of individual and community access to orlistat with its support programs will further enhance the outcome of quality education programs for diabetes.
- Its S3 scheduling will provide long term benefits to public health, reduced costs to the health system, and unproved health outlooks and general wellbeing.
- Australian environment is ideal for first OTC experience of orlistat – OTC medicine supply with access to pharmacist assessment and advice in Australia is different from that in the US.
- Pharmacists are well equipped to safely and effectively administer orlistat in the S3 setting and are well placed to provide counselling and advice in many aspects including the combination of lifestyle changes and pharmacological intervention on weight management. In fact, several weight management programs / protocols (Weight Wise Program, Your Weight Your Way, Weight Control Pharmacy Self Care Card) have been developed by the pharmacy profession. The community pharmacy network is well placed to screen for conditions and monitor potential adverse effects, and has the capabilities to assist a customer to identify and select an approach that will be effective for them, and prevent misuse.
- Although treatment with orlistat decreased the mean 25-hydroxy vitamin D, vitamin E and vitamin K1 levels, the mean levels of all vitamins assessed at any time during the 4-year treatment period of the XXXXXXXXXX study remained well within the normal reference ranges. The orlistat Consumer Medicine Information provides an ideal opportunity to discuss the latest evidence regarding the need for fat soluble vitamin supplementation.

The Committee noted the main arguments opposing the rescheduling proposal contained in public submissions:

- More Australian experience should be accumulated with its long-term use before its down scheduling, although orlistat appears to have a fairly benign side effect profile compared with most S4 drugs.
- The preferred first-line treatment for obesity is non-pharmacologic therapies. The S3 scheduling of orlistat may cause wrong public perception for early pharmacotherapy.
- Before a patient embarks on a course of treatment with orlistat, a full medical assessment is necessary, with particular reference to the possibility of diabetes.
- Potential misuse by people with eating disorders, and consequent vitamin deficiencies.
- Unacceptable GI symptoms induced by orlistat combined with a high dietary fat intake.

The Committee noted that orlistat has a relatively good safety profile. In the 1-4 year clinical trials submitted by the sponsor, the product caused a low incidence of severe adverse / side effects which generally required no medical intervention, and with no evidence of significant effects on either vitamin levels or bone disease. It was noted that the sponsor provided a number of letters from physicians who were working in the area of the treatment of obesity who were in favour of the rescheduling.

The Committee accepted the view that most obese patients did not loose body weight through diet and/or exercise alone, and use of orlistat in conjunction with lifestyle changes was more effective and more efficient in patients, including those with non-insulin dependent diabetes mellitus who were under medications. A member questioned orlistat's real efficacy as an OTC product compared to that described in the clinical trials. It was stated that patients generally drop the therapy after 3 to 6 months probably due to unsatisfactory outcome, and high cost. Another member expressed concern regarding the need for treatment related dietary behaviour reinforcement which seemed a key issue for the efficacy of the product. Hence, a reasonable expectation for a gradual and long-term weight loss and the requirement for its use in conjunction with exercise and dietary changes should be indicated in the product information.

Members discussed the potential risk for misuse and overdose of the product. It was noted that increased dose did not increase the efficacy for weight loss, and the product could not be used as an alternative for dietary modification. Furthermore, its relatively low gastrointestinal tolerability was likely to discourage abuse. The likelihood of inappropriate use would be minimised by the requirement for initial counselling by a pharmacist.

The Committee recognised that with good training and extensive experience in weight loss programs, pharmacists were able to appropriately handle patient requirement for S3 availability of this product. Its inclusion in S3 would enhance the accessibility of the product.

Member agreed that a distinction be made between the product for diabetes containing orlistat (XXXXXXXXXX) should remain in S4, and that only orlistat-containing weight loss products (XXXXXXXXXX) for obesity were being considered for rescheduling to S3.

Members noted that the applicant did not apply for inclusion of the product in Appendix H. However, in a disease-awareness advertising campaign, obesity patients were encouraged to talk to their doctors / pharmacists for weight loss. The Committee agreed that since no drug was mentioned in the advertisement, it was not considered to breach the code.

DECISION 2003/39 - 31

The Committee agreed to include orlistat for the treatment of obesity in Schedule 3 of the SUSDP. The decision was made on the following grounds:

- Safety profile of orlistat based on the a low incidence of adverse effects;
- Orlistat was reasonably efficacious for gradual and long term weight loss when used in conjunction with exercise and dietary restriction;
- Obesity is a disease which can be easily recognised by consumers;
- Pharmacists in Australia have good training and experience in providing advice and consultation in relation to management of weight loss and treatment of obesity;
- Orlistat for use in weight loss has low potential for abuse or overdose.

Schedule 3 - New entry

ORLISTAT in oral preparations for weight-control purposes containing 120 mg or less of orlistat.

Schedule 4 - Amendment

ORLISTAT **except** when included in Schedule 3.

14.1.2 PARACETAMOL / CAFFEINE

PURPOSE

The Committee considered an application seeking to include paracetamol 500 mg when combined with caffeine XXXXXXXXXX in a tablet when in a 50 tablet pack in Schedule 2.

BACKGROUND

Paracetamol is a p-aminophenol derivative that inhibits analgesic and antipyretic effects without anti-inflammatory activity. Paracetamol is currently in Schedule 4 when combined with aspirin, caffeine, or salicylamide or any derivative of these substances. It is in S2 for all other therapeutic uses except when in small packs which are unscheduled. Caffeine is currently an unscheduled substance, which is allowed to be included in a number of foods and beverages at concentrations of up to 320 mg/L in formulated caffeine beverages.

In the 1960s – 70s in Australia, analgesic combinations containing aspirin, phenacetin (paracetamol from 1975) and caffeine, or aspirin, salicylamide and caffeine were found to be associated with a high risk of analgesic abuse and consequent analgesic nephropathy. Combinations of any two or more or paracetamol, aspirin, salicylamide, caffeine or any derivatives of these substances were rescheduled from over the counter products to prescription-only products following a recommendation from XXXXXXXXXX in 1977.

XXXXXXXXXX sought an amendment to the SUSDP to include in Schedule 2, XXXXXXXXXX which contain a fixed dose of paracetamol 500 mg and caffeine XXXXXXXXXX. The product is in a pack containing 50 tablets (25 grams paracetamol and XXXXXXXXXX caffeine). The proposed indication was “for the temporary relief of self-limiting pain conditions and the reduction of fever”.

DISCUSSION

The Committee noted the following main points had arisen in the application and a pre-meeting submission by the applicant:

- The combination of paracetamol and caffeine is currently available OTC in small pack sizes in a number of other markets for various periods, including the UK (15 years), New Zealand (3 years), and has an excellent safety profile.
- The rationale for combining paracetamol with caffeine is that it provides superior analgesia with a faster onset of action compared to paracetamol alone. There is substantial evidence that caffeine potentates the action of minor analgesics.
- The amount of caffeine present in a single dose (two tablets) is XXXXXXXXXX, which is similar to that in a medium strength cup of coffee (100mg).
- The association between combination analgesic abuse and analgesic-associated nephropathy (AAN) shown in the data review from 1962 to 1972, was related to the triple combination products (aspirin, phenacetin and caffeine [XXXXXXXXXX], or aspirin, salicylamide and caffeine [XXXXXXXXXX]. However, a prospective review (Kidney International 2000) in renal medicine concluded that sufficient evidence is absent to associate non-phenacetin combined analgesics (paracetamol and caffeine) with nephropathy, and that new studies should be done to provide appropriate data for resolving this question.
- Currently there are no combined caffeine analgesic products on the Australian market, although products containing a single ingredient, paracetamol 500mg (XXXXXXXXXX and others) or caffeine 100mg (XXXXXXXXXX), are available and exempt from scheduling.
- There is a need for access to a product that produces faster, more effective pain relief than paracetamol alone. Schedule 2 access to the combination product would provide pharmacists with a new option with which to aid patients with acute pain, particularly headache and migraine. This would be particularly important for those patients for whom non-steroidal anti-inflammatory agents are contraindicated.

The Committee noted that the evaluation report stated the following:

- The co-administration of caffeine with paracetamol increases both the rate of onset and the size of the analgesic effect, although the mechanism of this effect remains unknown. A meta-analysis (Laska et al 1984) indicated that paracetamol alone would have to be given in a 37% higher dose to achieve the same effect as the combination, and the onset of action was also significantly more rapid. Further clinical trials in tension headache have demonstrated a statistically significant superiority of paracetamol 1000 mg with caffeine 130 mg (2 tablets in a single dose) over paracetamol alone (Migliardi et al 1994).

There is also evidence from animal experiments that caffeine has direct antinociceptive effects (Sawynok and Yaksh 1993).

- Despite extensive epidemiological and experimental investigation, there is no evidence that a paracetamol-caffeine combination is associated with analgesic-associated nephropathy (AAN). A descriptive review (Whelton 1999) of drug-induced renal toxicity states that caffeine is not an independent nephrotoxin. In addition, there is little evidence, either experimental or epidemiological, that paracetamol alone is capable of inducing analgesic nephropathy (Blantz 1996). A position statement from the National Kidney Foundation (USA, 1996) states that there is experimental evidence indicating that very large doses of paracetamol (0.5-1.0 g/kg for weeks to months) can cause renal papillary necrosis, but that there is only a weak association between habitual use of paracetamol and end-stage renal failure. Although this paper recommends against the use of compound analgesic preparations (eg. aspirin + paracetamol), insufficient data were available on the effects of paracetamol + caffeine to make a recommendation in relation to this combination. More recent reviews of the literature on analgesic-caffeine combinations (Bach et al 1998; Feinstein et al 2000) conclude that there is no compelling evidence to support the argument that caffeine induces craving for, or misuse of, analgesic formulations in the majority of users.

- Caffeine is a widely available unscheduled substance with a well-understood toxicological profile and a wide therapeutic index. Paracetamol has a moderately narrow therapeutic index, is well tolerated when used therapeutically, but has significant hepatotoxicity when taken in overdose (usually intentional). The potential toxicity of the combination from overdose is similar to that of paracetamol alone, which can cause serious hepatotoxicity at relatively small overdoses (12 g in 24 tablets or more), and 50 tablets has the potential to cause lethal hepatotoxicity if consumed as a single dose. The total dose of caffeine present in a full pack of 50 tablets could also cause serious toxicity if ingested as an overdose, but has a low risk of lethality. However, since overdosage of caffeine is likely to produce nausea and vomiting, this could help to protect a patient from fully absorbing the paracetamol.

- A risk-benefit comparison of the proposed combination product with paracetamol alone suggests that the combination has similar risks and increased benefit.

- There is sufficient safety information in relation to this specific combination of paracetamol and caffeine, to overturn the 1977 XXXXXXXXXX recommendation that any analgesic combination including caffeine should be included in Schedule 4 due to potential analgesic nephropathy.

The Committee noted the pre-meeting submission received from XXXXXXXXXX who did not support the proposal of S2 scheduling. XXXXXXXXXX expressed concerns on: (1) the uncertainty of caffeine enhancing the analgesic action of paracetamol; (2) the experience of the high incidence of analgesic nephropathy in Australia in the 1970s; (3) the addition of a sought-after stimulant may encourage the excessive or improper consumption of paracetamol. Hence, there seemed little justification for amending the schedule entries.

Members questioned the rationale for the combination of paracetamol with caffeine, although the sponsor claimed that caffeine potentiated the action of paracetamol by increasing both the rate of onset and the size of the analgesic effect. A member pointed out that a dose of caffeine > 250 mg/day might cause cardiovascular effect, whereas the total amount of caffeine in a daily dose of 8 tablets was XXXXXXXXXX. Members further discussed whether it was necessary to add caffeine to paracetamol for reducing headache, how robust the data were from the study (Laska et al 1984) which showed enhancement of the analgesic effect of paracetamol, and whether paracetamol in this tablet (500 mg) was enough for reducing fever.

Members extensively discussed the public health benefit and potential risk for down-scheduling of the combined analgesic preparations with caffeine. Caffeine was a substance to which people had daily broad/extensive exposure. Some degree of dependency/addiction to caffeine, probably rebound headache following withdrawal, might lead to excess use, or abuse of the caffeine-containing product. This mechanism might be related to enhanced utilisation of combination analgesics and analgesic-associated nephropathy in the past. Since the original S4 setting for the combination of analgesic and caffeine was based on the concern on analgesic nephropathy in Australia, epidemiological evidence for negative renal problems was not solid enough to allow for down-scheduling. Hence, the benefit gained by adding caffeine into paracetamol, if any, was offset by its risk.

Members were informed that it was recommended by TGA that all complementary medicine products containing caffeine should be indicated in the label. This product should also be labelled similarly if the down-scheduling was to proceed.

OUTCOME

The Committee agreed that the current scheduling of paracetamol and caffeine remains appropriate. XXXXXXXXXX containing a fixed dose of paracetamol 500 mg and caffeine XXXXXXXXXX "for the temporary relief of self-limiting pain condition and the reduction of fever" was not included in Schedule 2 of the SUSDP for the following reasons:

- There was inadequate evidence provided to demonstrate that the combination of caffeine and paracetamol was safe.

- Caffeine had potential toxic/side effects at high doses, but no convincing therapeutic benefit.
- The stimulating nature of caffeine might encourage excessive use or abuse of the product.

14.1.3 FLUTICASONE

PURPOSE

The Committee considered rescheduling fluticasone propionate for the short-term (3-6 months) prophylaxis or treatment of allergic rhinitis in adults and children aged 12 years and over.

BACKGROUND

Fluticasone propionate is a semi-synthetic trifluorinated glucocorticoid that has local anti-inflammatory activity and a potency of about twice that of beclomethasone dipropionate.

XXXXXXXXXX (fluticasone propionate) was approved for registration in Australia on 13th January 2000, as a Schedule 4 product. It was rescheduled to S3 status in November of 2000 for short-term prophylaxis or treatment of seasonal allergic rhinitis and launched as a non-prescription product in July 2001 (under the brand name XXXXXXXXXX). The S3 indications were amended in November 2001 to include perennial allergic rhinitis.

XXXXXXXXXX submitted an application to reschedule intranasal fluticasone propionate from Schedule 3 to Schedule 2 for the prophylaxis and treatment of allergic rhinitis, including hayfever, in adults and children aged 12 years and over, when supplied in packs containing 120 doses or less.

DISCUSSION

The Committee noted the following points highlighted in the application:

- Intranasal corticosteroid sprays, such as fluticasone, have high efficacy, and are more effective in control symptoms of allergic rhinitis than do antihistamine tablets which are S2 products and indicated for the treatment of this disease, and are considered to be first line therapy by many specialists in the allergy field.
- The good safety profile of intranasal fluticasone propionate with minimal risk of systemic side effects is demonstrated by extensive worldwide and local experience in the treatment of allergic rhinitis.
- Fluticasone propionate has a comparable safety and efficacy profile to the other intranasal corticosteroids, beclomethasone, budesonide and mometasone which have been rescheduled to S2.

- The product has similar properties to other topically active steroids, but has extremely low oral bioavailability (<1.0%) than others, and thus an improved therapeutic index (ratio).
- Hayfever and many perennial allergies are easily self-diagnosed by their characteristic nasal symptoms and its seasonal nature.
- Fluticasone has been available as a non-prescription medicine in Australia for 2-years and almost 4 years in New Zealand. Post marketing surveillance confirms that the product did not pose safety concerns more than other corticosteroids sold as S2 products.

The Committee noted the main points summarised in the evaluation report on the submission:

- Due to its very low bioavailability, there is little evidence of significant systemic adverse events with fluticasone intranasally, in particular no suppression of hypothalamic-pituitary axis function following dosing up to 800 μg/day for 4 weeks. There have been no cases of abuse or overdose.
- Periodic Safety Update Report (PSUR), data received and updated by XXXXXXXXXX of XXXXXXXXXX, indicates that there were XXXXXXXXXX patient-years of exposure to intranasal fluticasone propionate from 1 September 2002 to 31 December 2002. In addition to respiratory (epistaxis and nasal septal perforation) and eye disorders (cataract and glaucoma), there was one case of acute adrenal crisis following receiving an unspecified dose of intranasal fluticasone, and budesonide concomitantly. Generally, there appeared to be no worrisome or otherwise previously unrecognised adverse events or increase in frequency of the expected adverse event profile.
- The product fulfils the relevant criteria for S2 listing, including its safe by in use with a wide therapeutic index and a low incidence of adverse effects; available pharmacist advice or counselling if necessary; easily recognised indications (minor ailments or symptoms) by consumer; low potential for abuse or inappropriate use; and low likelihood of masking serious disease.

Members noted the pre-meeting comment from XXXXXXXXXX opposing the rescheduling of intranasal fluticasone to S2, and raising the concerns on the potency of this steroid, a potential risk of overdose or cumulative exposure, and consequent adverse effects.

Members considered the extremely low bioavailability (< 1%) of fluticasone, and the aqueous nasal spray for short-term use (3-6 months) in prophylaxis or allergic rhinitis showing low potential for adverse effects (sneeze, running nose), rare cases in suppression of hypothalamic-pituitary axis function, and its low potential for overdose or abuse. The Committee agreed to reschedule intranasal fluticasone propionate from Schedule 3 to Schedule 2, and removal from Appendix H.

DECISION 2003/39 - 32

The Committee agreed to include intranasal fluticasone propionate in Schedule 2 for the prophylaxis and treatment of allergic rhinitis in adults and children aged 12 years and over, when supplied in packs containing 120 doses or less, and removal from Appendix H. The decision was based on:

- Its safety in use with a wide therapeutic index and a low incidence of adverse effects;
- Available pharmacist advice or counselling if necessary;
- Use for minor ailments or symptoms which can be easily recognised by the consumer;
- Its low potential for abuse or inappropriate use; and
- Its low likelihood of masking serious disease.

Schedule 2 – New Entry

FLUTICASONE in aqueous nasal sprays delivering 50 micrograms or less of fluticasone per actuation when the maximum recommended daily dose is no greater than 400 micrograms and when packed in primary pack containing 200 actuations or less, for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years and over.

Schedule 3 – Amendment

FLUTICASONE - delete entry.

Schedule 4 – Amendment

FLUTICASONE – amend entry to read:

FLUTICASONE **except** when included in Schedule 2.

Appendix H – Amendment

Fluticasone – delete entry.

14.1.4 KAVA (*PIPER METHYSTICUM*)

PURPOSE

The Committee considered scheduling of kava (*Piper methysticum*) which contains kavalactones as the active constituents.

BACKGROUND

Piper methysticum (kava) is a member of the pepper family (Piperaceae), and has a wide distribution throughout the Pacific. Kava has been used in traditional medicine to treat venereal disease, gout, rheumatism, diarrhoea, asthma, and to calm nervous children and induce women's breast milk flow. Pharmacologically, kava is described as having an anxiolytic effect, is a muscle relaxant and has anticonvulsant and spasmolytic activity. It is a sedative and can depress the limbic system. Its effects appear to be mainly due to the activity of the compounds in the lipid soluble resin – the kavalactones. The pharmacological properties of kava are comparable to those of benzodiazepines, although kavalactones bind very weakly to GABA-A and benzodiazepine receptors. More recently, kavalactones have been extracted for therapeutic products by volatile solvent extraction.

During 1988 to 1990, the Committee considered scheduling of kava and agreed to include kava in Schedule 4 in order to prevent its widespread consumption in XXXXXXXXXX. The S4 entry was deleted by the August 1992 Meeting, due to the introduction of a Kava Control Act in XXXXXXXXXX, and there being no need to schedule kava in other States. During 1997 and 1998, the re-scheduling of kava was returned to the Committee for consideration since therapeutic preparations containing kava were marketed in Australia and had been included as listable products on the Australian Register of Therapeutic Goods (ARTG). However, the Complementary Medicines Evaluation Committee (CMEC) advised that therapeutic products containing kava could be controlled adequately through the listing and registration systems, rather than by poison scheduling. The recommendation was that kava would be a listable substance in products containing up to 125 mg of kavalactones per dose, with a recommended daily dose of no more than 250 mg, or a maximum amount of dried rhizome per tea bag of 3 g. Products containing in excess of these amounts would be required to go through the registration rather than the listing process, and would require evidence of efficacy as well as safety. Hence, a foreshadowed S4 decision was not progressed by the Committee at the May 1998 NDPSC Meeting.

Concerns were raised internationally in 2001 over liver toxicity associated with kava-containing medicines, which was involved in 82 adverse reaction reports including 4 deaths. In July 2002, the Adverse Drug Reactions Advisory Committee (ADRAC) received a report of the death, from complications of liver failure, of a woman in Australia who had been taking a kava-containing medicine for four months. As a consequence, the TGA, acting on the advice of CMEC and ADRAC, instigated a voluntary recall of medicines containing kava. Kava has also been authorised/voluntarily withdrawn from the market in Canada, UK, Germany and Singapore.

The TGA invited industry to provide evidence that kava is safe for human consumption before making a final decision on any change to the regulatory status of kava. During 2003 the OCM completed a safety evaluation of kava containing medicines, which was reviewed by XXXXXXXXXX. XXXXXXXXXX was requested to review the safety of kava (*Piper methysticum*) and to make a recommendation to CMEC on whether or not kava is suitable for use as an ingredient in listed medicines.

DISCUSSION

The Committee noted the evaluation report provided by XXXXXXXXXX to the CMEC which highlighted the following points:

Toxicology studies on kava have been limited mainly to acute and subchronic studies in mice and rats. The LD50 was estimated between 800 to 1000 mg/kg for the oral intake of the different kavalactones investigated. While the dosage in the therapeutic industry is typically up to 250 mg/day of kavalactones (4.2 mg/kg/day for a person with body weight of 60 kg), and it can vary considerably (up to 3800 mg/hour) when kava is consumed as a drink.

Absorption of kavalactones via the gastrointestine is poor and variable. Kavalactones appear to be hydroxylated by the cytochrome P-450 system (CYP enzymes) and are eliminated by the kidneys and in the faeces. CYP enzyme deficiency may possibly be a risk factor with respect to kava hepatotoxicity. There is the possibility that genetic polymorphism of the CYP enzymes may underlie the potential for kava hepatotoxicity even at low dose rates. Increased liver enzymes (GGT, ALT, AST and/or ALP) were observed in some human cases. Kava might: (a) have additive effects with benzodiazepines, (b) antagonise central dopaminergic mechanisms and (c) intensify the effects of alcohol.

Internationally, there have been 82 reports of liver toxicity associated with the use of kava-containing medicines including 4 deaths. The severity of the liver damage varies from abnormal liver function tests to liver transplantation. The TGA review of these case reports indicates that there are a number of the cases where the association of the kava-containing medicine with the adverse event has been rated as possible. However, there do not appear to be any trends between either the adverse event or the severity of the adverse event and age/sex of the patient, product, dose or product form. On 30 July 2002, the ADRAC received a report of the death, from complications of liver failure, of a woman in Australia who had been taking, among other medicines, a kava-containing medicine for four months. The use of a kava-containing medicine was the only factor in the woman's medical history that could be identified as a possible cause of her liver failure.

XXXXXXXXXX recommended options to CMEC for regulation of kava which were:

> (1). The TGA does not allow *Piper methysticum* to remain an ingredient in listed medicines; or
>
> (2). The TGA allows *Piper methysticum* to remain an ingredient in listed medicines, with label warnings or advisory statements, restriction to practitioner dispensing only, restriction to certain extraction methods, restriction to certain plant parts, and/or only allow kava in the form of the throat sprays or topical formulations.

Additionally XXXXXXXXXX also suggested that the scheduling of *Piper methysticum* may also be an option. It was pointed out that scheduling would result in the removal of kava as a listable ingredient, and thus kava-containing products would have to be registered.

The Committee noted that the 41st Meeting of CMEC considered XXXXXXXXXX recommendations concerning the suitability of kava for use as an ingredient in listable medicines. The CMEC made a number of recommendations including Recommendation 41.3. The Committee agreed with the CMEC Recommendation 41.3 that products containing *Piper methysticum* must be Registered prior to their supply, other than:

(i) Aqueous dispersions of whole or peeled rhizome of *Piper methysticum*;
(ii) Aqueous extracts of whole or peeled rhizome of *Piper methysticum*;
(iii) Dried whole or peeled rhizome of *Piper methysticum*;
(iv) Products for topical application to the skin; and
(v) Homoeopathic preparations more dilute than a thousand fold dilution of a mother tincture;

which may be included in Listed medicines under certain conditions.

Aqueous dispersions and extracts of whole or peeled rhizome of *Piper methysticum*as as well as dried whole or peeled rhizome of *Piper methysticum*as were considered by CMEC to be suitable for use as ingredients in Listed medicines for oral use, subject to the following conditions:

(a) the preparation does not contain, for its recommended daily dose, more than 250 mg of kavalactones; and
(b) if the preparation is in a tablet or capsule – the amount of kavalactones does not exceed 125 mg for each tablet or capsule; and
(c) if the preparation is in a tea bag – the amount of dried whole or peeled rhizome does not exceed 3 g for each tea bag; and
(d) if the preparation contains more that 25 mg of kavalactones per dose – the label on the goods includes the following warnings (or words to the same effect):
    - Not for prolonged use. If symptoms persist, seek advice from a healthcare practitioner.
    - Not recommended for use by pregnant or lactating women; and
    - May harm the liver.

Such preparations were also considered by CMEC to be suitable for use as ingredients in Listed medicines for the topical application to the rectum, vagina and by spray to the throat.

CMEC further recommended that *Piper methysticum*as may be used as an ingredient in Listed medicines for topical applications to the skin.

Additionally, it was pointed out that the NDPSC was requested by the Non Prescriptions Medicine Branch to:

- note the recommendations of the CMEC;
- consider the need for possible restrictions on the supply of kava containing products containing other than what is stipulated in the CMEC Recommendations, which are extemporaneously compounded and dispensed by health care practitioners;
- consider the need for possible restrictions on the regulation of alcoholic extracts of kava that are supplied to health care practitioners in bulk as starting materials for extemporaneously compounding; and
- note that TGA does not regulate sole traders in States and Territories, raw material suppliers and personal importers. Therefore, there remains the potential for supply of non-aqueous extracts of kava.

The Committee noted an article entitled "Sit-down drink"published in Sydney Morning Herald on 16 September 2003. It was reported in the article that a researcher at the Menzies School of Health Research believes that kava is a strong muscle relaxant and may disturb normal heart function, a factor that may exacerbate a pre-existing heart disease. It was also reported that this researcher had found no indicators of long-term liver damage in kava users in Arnhem Land. He did, however, find reversible changes in liver function.

Members were aware of that kava has a long history of traditional use as a beverage or medicine. In recent years, solvent extraction methods have been employed, either an ethanol:water or acetone:water mixture to produce therapeutic products containing a total kavalactone content of 30% to 70%, respectively. There were 84 products on the ARTG which contain *Piper methysticum*, the majority was extracts (95%) and the rest was dry herb.

The Committee noted that prior to the voluntary withdrawal of kava-containing medicines in Australia, the maximum recommended daily dose permitted for Listed medicines was 250 mg of kavalactones with a maximum amount per tablet or capsule of 125 mg and a maximum amount of dried rhizome per tea bag of 3 g. In a clinical trial under recommended therapeutic doses (mostly 60 – 240 mg/day kavalactones for 1-4 weeks), a good efficacy in reduction of anxiety was achieved, while little / mild adverse effects (stomach complaints, restlessness, tiredness, drowsiness), rather than liver toxicity, were involved.

Members further noted that elevated liver enzymes (GGT, ALP-alkaline phosphatase, but a normal ALT level) were associated with heavy drinkers/users of kava. The toxicity might be related to some mechanisms including induction of liver enzymes, an immunoallergic mechanism, or a genetic polymorphism of the CYP enzymes. In the review of case reports, severe liver toxicity which led to liver transplant or death, occurred in individuals taking extracts of alcohol or acetone, and mostly in females. There appeared no dose-response relationship in the toxicity. Members noted that the

method of extraction played an important role in toxicity. The hepatotoxicity of extracts varies significantly, with water extract being the least hepatotoxic and the organic solvents (ethanol, acetone and hexane) being the most hepatotoxic.

Members were informed that kava came to XXXXXXXXXX in XXXXXXXXXX about 20 years ago as a peaceful alternative to alcohol, and became popular with Aboriginal communities. In 1998, XXXXXXXXXX government banned kava. The XXXXXXXXXX member mentioned that XXXXXXXXXX now controlled kava through the Kava Management Act (administered by XXXXXXXXXX). From last year, the XXXXXXXXXX Government allowed restricted supply under licence to some communities, and one person could buy 800 g a week. It was also pointed out by the XXXXXXXXXX member that kava had been restricted in XXXXXXXXXX for several years, and was only allowed to be used with a special licence, for ceremonial purposes or for clinical trials. No listed medicines containing kava were allowed in XXXXXXXXXX.

Members were informed that New Zealand currently did not restrict kava, and it was sold as food, drink or dietary supplements which was equivalent to listable products in Australia. The Committee was advised that XXXXXXXXXX was currently undertaking a review of kava in food, and urged the Secretariat to seek advice from XXXXXXXXXX regarding the outcome of the review.

Members noted the current international regulatory status of kava products. Restrictive regulatory action on voluntary withdrawals from the market have occurred in Canada, UK, Germany and Singapore. The USA and South Africa have issued consumer and professional advisory notices regarding the safety of kava.

OUTCOME

The Committee considered the need for possible restrictions on the regulation of alcohol/acetone extracts of kava that were supplied to health care practitioners in bulk as starting materials for extemporaneously compounding.

The Committee agreed that there was a risk of liver toxicity with use of non-aqueous extracts of kava plants at high doses, and that a schedule entry to minimise this risk without affecting the current usage of listed complementary products should be made following the review of the listed products on the ARTG.

14.2 SUSDP, PART 5

14.2.1 APPENDIX F – CONSIDERATION OF WARNING STATEMENTS FOR S2 PRODUCTS

PURPOSE

The Committee considered a proposal to amend Appendix F, Part 3 entries for acetic acid, chloroform, ether, sodium fluoride and carbon tetrachloride to include Schedule 2 substances.

BACKGROUND

An editorial review of Appendix F, Part 3 highlighted a number of entries that required amendments to include Schedule 2 substances.

DISCUSSION

The Committee thought it appropriate to defer consideration on this item until a list of all affected products could be determined.

OUTCOME

The Committee agreed to defer this agenda item to the February 2004 meeting to allow time for the Secretariat to prepare a list of all products that would be affected by the proposed amendments. The Committee also agreed to foreshadow the proposed amendments.

14.2.2 APPENDIX G

14.2.2.1 MERCURY

PURPOSE

The Committee considered the scheduling of mercury.

BACKGROUND

A request was received to clarify whether 10 ppm of mercury for human therapeutic use is exempt from scheduling under the general exemption in Part 1 – Interpretation of the SUSDP.

The tolerable limit for total mercury, set at the 16th meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and maintained after reconsideration at the 22nd JETCFA meeting, was 0.3 mg per person per week, equivalent to 5 µg/kg bw/week. This limit has also been adopted by Food Standards Australia and New Zealand.

DISCUSSION

The Committee was informed that the general exemption in Part 1 – Interpretation of the SUSDP for substances at concentrations of less than or equal to 10 mg/kg or 10 mg/L did not apply to mercury. This was because mercury was also included in Schedule 7.

Furthermore, it was highlighted that mercury was not currently listed in Appendix G suggesting that a safe limit for the use of mercury in dilute preparations for therapeutic use had yet to be determined.

Based on the weekly tolerable limit for mercury through the food pathway, it was proposed that an entry for mercury be included in Appendix G of the SUSDP at a level of 5 μg.

OUTCOME

In the absence of better evidence regarding a safe limit for the use of mercury in dilute preparations, the Committee agreed to foreshadow the inclusion of mercury in Appendix G at the level of 5 micrograms.

Foreshadowed for consideration at the February 2004 meeting

Appendix G – new entry

MERCURY	5 micrograms

15. MATTERS REFERRED BY THE AUSTRALIAN DRUG EVALUATION COMMITTEE (ADEC)

15.1 NEW SUBSTANCES

15.1.1 PIMECROLIMUS

PURPOSE

The Committee considered the scheduling of pimecrolimus, a new medicine.

BACKGROUND

Pimecrolimus is an ascomycin macrolactam derivative related to tacrolimus and sirolimus and acts by inhibiting the transcription of early cytokines and pro-inflammatory mediators from T cells and mast cells.

DISCUSSION

The Committee noted the April 2003 ADEC minutes.

The Drugdex monograph on pimecrolimus reported that topical pimecrolimus was indicated for the treatment of atopic dermatitis in adults and children over 2 years of age. Additionally, a section in the Patient Instructions for XXXXXXXXXX included a warning that the medicine should not be used on children under 2 years of age.

The Committee agreed that a restriction regarding the use of pimecrolimus on infants under 2 years of age was required at this stage. However, in view of the issues raised at the April 2003 ADEC meeting, the NDPSC Member asked that ADEC clarify its recommended indication for use on infants 3-23 months of age.

The Committee noted that pimecrolimus was classified as a prescription medicine in New Zealand.

DECISION 2003/39 - 33

The Committee agreed to include pimecrolimus in Schedule 4 of the SUSDP on the grounds that the safe use of this medicine required ongoing patient management and monitoring by a medical professional.

Schedule 4 - New entry

PIMECROLIMUS.

15.1.2 ARIPIPRAZOLE

PURPOSE

The Committee considered the scheduling of aripiprazole, a new medicine.

BACKGROUND

Aripiprazole is an atypical antipsychotic agent indicated for the treatment of schizophrenia.

DISCUSSION

The Committee noted the April 2003 ADEC minutes and the approved Product Information for XXXXXXXXXX.

The Committee also noted that aripiprazole was not a classified medicine in New Zealand.

DECISION 2003/39 - 34

The Committee agreed to include aripiprazole in Schedule 4 of the SUSDP on the grounds that the condition bring treated necessitated appropriate medical diagnosis and the safe use of this medicine required patient management and monitoring by a medical professional.

Schedule 4 - New entry

ARIPIPRAZOLE.

15.1.3 ANAKINRA

PURPOSE

The Committee considered the scheduling of anakinra, a new medicine.

BACKGROUND

Anakinra is a recombinantly XXXXXXXXXX which antagonises the effect of the IL-1 cytokine in inflammatory joint disease. The recommended dose is Xmg/kg once daily by XXXXXXXXXX XXXXXXXXXX.

DISCUSSION

The Committee noted the April 2003 ADEC minutes and the approved Product Information for XXXXXXXXXX.

The Committee also noted that anakinra was classified as a prescription medicine in New Zealand.

DECISION 2003/39 - 35

The Committee agreed to include anakinra in Schedule 4 of the SUSDP on the grounds that the condition bring treated necessitated appropriate medical diagnosis and the safe use of this medicine required patient management and monitoring by a medical professional.

Schedule 4 - New entry

ANAKINRA.

15.1.4 EZETIMIBE

PURPOSE

The Committee considered the scheduling of ezetimibe, a new medicine.

BACKGROUND

Ezetimibe is a new chemical entity representing a new class of agents for the treatment of hypercholesterolaemia. Ezetimibe acts to reduce absorption of dietary cholesterol from the intestine. However, the pharmacological mechanism and site of action of the drug has not been elucidated and therefore it is not clear whether the drug works at the site of the brush border, although it is thought to act locally in the intestines.

DISCUSSION

The NDPSC noted the minutes of the April and June 2003 ADEC meetings and the approved Product Information for XXXXXXXXXX.

The NDPSC also noted that ezetimibe was classified as a prescription medicine in New Zealand.

DECISION 2003/39 - 36

The NDPSC agreed to include ezetimibe in Schedule 4 of the SUSDP on the grounds that the condition bring treated necessitated appropriate medical diagnosis and the safe use of this medicine required patient management and monitoring by a medical professional.

Schedule 4 - New entry

EZETIMIBE.

15.1.5 GEFITINIB

PURPOSE

The Committee considered the scheduling of gefitinib, a new medicine.

BACKGROUND

Gefitinib acts via receptor tyrosine kinase inhibition. Gefitinib inhibits the effects of epidermal growth factor. [Sentence deleted]. Gefitinib inhibits this part of the receptor and as a result inhibits the transmission of intracellular signals responsible for cell survival and proliferation. Several solid tumours, including non small cell lung cancer, are known to over-express EGFR.

DISCUSSION

The Committee noted the Drugdex monograph on gefitinib, which reported that the FDA had classified gefitinib as Pregnancy Category D (studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the foetus. However, the benefits of therapy may outweigh the potential risk). The Committee agreed that inclusion of gefitinib in Appendix D was not warranted as it has a standing policy of not including anti-cancer agents in Appendix D of the SUSDP on the basis of their mode of action.

The Committee noted that gefitinib was classified as a prescription medicine in New Zealand.

DECISION 2003/39 - 37

The Committee agreed to include gefitinib in Schedule 4 of the SUSDP on the grounds that the condition bring treated necessitated appropriate medical diagnosis and the use of this medicine required patient management and monitoring by a medical professional.

Schedule 4 - New entry

GEFITINIB.

15.1.6 FENOFIBRATE

PURPOSE

The Committee considered the scheduling of fenofibrate, a new medicine.

BACKGROUND

Fenofibrate is an analogue of XXXXXXXXXX and is used in the treatment of hyperlipoproteinemias.

DISCUSSION

The Committee noted the minutes of the April 2003 ADEC meeting.

The Committee also noted that fenofibrate was not a classified medicine in New Zealand.

DECISION 2003/39 - 38

The Committee agreed to include fenofibrate in Schedule 4 of the SUSDP on the grounds that the condition bring treated necessitated appropriate medical diagnosis and the use of this medicine required patient management and monitoring by a medical professional.

Schedule 4 - New entry

FENOFIBRATE.

15.2 FOR INFORMATION (SUBSTANCES ALREADY SCHEDULED)

15.3 OTHER ADEC MATTERS FOR CONSIDERATION

15.3.1 PANCREATIC ENZYME EXTRACT

PURPOSE

The Committee considered scheduling of pancreatic enzyme extract.

BACKGROUND

Pancreatic enzyme extract products are marketed in Australia to treat pancreatic insufficiency and non-specific gastrointestinal conditions. Products containing more than 20,000 BP units of lipase are classified as prescription medicines, while those containing 20,000 BP units or less of lipase can be supplied without prescription. These products include lipase, amylase and protease in varying concentrations, and are used to treat pancreatic exocrine insufficiency including cystic fibrosis, chronic pancreatitis, post pancreatectomy, gastrointestinal by-pass surgery and ductal obstruction. Other non-prescription pancreatic enzyme products, often combined with other complementary medicines, are indicated for use to prevent dyspepsia, to assist digestion, and to prevent flatulence.

In June 2002, the French Health Product Safety Agency (FHPSA) initiated action to limit the marketing of pancreatic enzyme extracts in France to the treatment of exocrine pancreatic failure, due to the potential for porcine parvovirus (PPV) contamination of the products. The FHPSA decided that while the risk/benefit balance justified the continued marketing of such products for serious medical conditions associated with exocrine pancreatic failure, the risk/benefit balance did not justify the continued marketing of the products for less serious conditions. Since 1995, the US FDA has required sponsors of products "labelled, represented or promoted for OTC use in the treatment of exocrine insufficiency" to undergo the same evaluation as prescription drugs, while there are also relevant products marketed as "nutritional supplements". In the UK, it appears that porcine pancreatic enzyme products are approved only for use in pancreatic insufficiency.

DISCUSSION

The Committee noted that the following points were highlighted in XXXXXXXXXX and relevant information provided:

Contamination of Australian marketed pancreatic enzyme products with PPV cannot be ruled out based on the data supplied by the Sponsors.

There is no evidence that the presence of PPV in oral pancreatic extracts intended for human use results in human infection. Although there is a theoretical risk that the PPV could be transmitted to humans, there is no evidence that this would result in disease. However, it is possible that PPV might be a marker for other porcine viruses in pancreatic extracts with the potential to infect humans and cause disease.

The available data suggest that the benefits associated with treatment of pancreatic exocrine insufficiency with porcine pancreatic enzymes outweigh the potential risk of PPV contamination of these products.

The risk-benefit ratio for the use of porcine pancreatic enzymes for conditions unrelated to pancreatic insufficiency (eg. dyspepsia), or as complementary medicines is too high,

and consideration will need to be given to cancelling their listing. In fact, in the absence of any proven benefits, there is a potential risk, however small.

The Product Information (PI) and Consumer Medicine Information (CMI) documents for all porcine pancreatic enzyme extract products should contain relevant information on PPV. Sponsors should be advised to vigorously pursue satisfactory viral inactivation methods.

The XXXXXXXXXX recommended that the use of these products should be restricted to indications for conditions characterised by pancreatic exocrine enzyme insufficiency. The risk-benefit ratio was unfavourable for the use of these products for complementary medicine indications. Hence, those products indicated for conditions other than pancreatic exocrine enzyme insufficiency should be withdrawn.

Members noted that XXXXXXXXXX investigated the potential PPV contamination of porcine pancreatic enzyme products, and recommended necessary regulations based on risk-benefit analysis. The Committee agreed with XXXXXXXXXX recommendations: 1). the benefits associated with treatment of pancreatic exocrine insufficiency (including cystic fibrosis, chronic pancreatitis, post pancreatectomy, gastrointestinal by pass surgery and ductal obstruction) with porcine pancreatic enzymes outweighs the potential risk of PPV contamination, and these products should be included in Schedule 4 and supplied on prescription only. 2). the risk-benefit ratio was unfavourable for the use of porcine pancreatic enzyme-containing products for complementary medicine indications, and hence should be withdrawn.

The Committee noted that on the current Australian market, pancreatic extracts used as essential medication for patients with pancreatic exocrine insufficiency included those containing > 20,000 BP units of lipase (XXXXXXXXXX and XXXXXXXXXX) for supplying on prescription only, and others containing ≤ 20,000 BP units of lipase (XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX) for supplying without prescription. Members were informed that these non-prescription products with lower lipase (≤ 20,000 BPU) were mainly used in patients with cystic fibrosis (CF) to avoid unwanted secondary effects induced by overdose. Hence, the CF patients would be affected and disadvantaged by the inclusion of these products in S4. The Committee asked the XXXXXXXXXX representative to advise XXXXXXXXXX of the foreshadowed consideration on this issue in the February 2004 Meeting.

The Committee also noted that the S4 inclusion would affect some complementary medicine products containing pancreatic enzyme which were indicated for use to prevent dyspepsia, to assist digestion, and to prevent flatulence. The Secretariat was requested to inform the XXXXXXXXXX of the foreshadowed consideration of regulatory actions proposed by XXXXXXXXXX at the next NDPSC meeting, and to seek relevant comments.

A member informed that in addition to complementary medicine products, there were also some OTC products containing pancreatic enzyme which would be affected by S4

inclusion. The Committee agreed that gazetting the item for consideration in the February 2004 Meeting would allow for public comments.

OUTCOME

The Committee agreed to foreshadow the inclusion of pancreatic enzymes in Schedule 4 with no cut-off to lower schedules for the following reasons:

Contamination of Australian marketed pancreatic enzyme products with PPV and potential risk of human infection cannot be ruled out.

The available data suggest that the benefits associated with treatment of pancreatic exocrine insufficiency with porcine pancreatic enzymes outweighs the potential risk of PPV contamination of these products.

The risk-benefit ratio for the use of porcine pancreatic enzymes for conditions unrelated to pancreatic insufficiency, as OTC products or complementary medicines is too high, and those products should be withdrawn.

Foreshadowed for consideration at the February 2004 meeting

Schedule 4 - Amendment

PANCREATIC ENZYMES – amend entry to read:

PANCREATIC ENZYMES

16. OTHER MATTERS FOR CONSIDERATION

16.1 AMINOLEVULINIC ACID

PURPOSE

The Committee considered the scheduling of aminolevulinic acid.

BACKGROUND

The scheduling of the methyl ester of aminolevulinic acid, methyl aminolevulinate, an antineoplastic agent, was considered by the Committee at the June 2003 Meeting and was include in Schedule 4 on the grounds that the condition being treated required medical diagnosis, patient management and monitoring by a medical professional.

The Secretariat received a public inquiry seeking advice on whether aminolevulinic acid was a derivative of methyl aminolevulinate under the provision specified in Part 1-Interpretation, Paragraph 2(c) which states that “unless the contrary intention appears a reference to a substance in a Schedule or an appendix to this Standard includes every salt, active principle or derivative of the substance, including esters and ethers, and every salt

of such an active principle or derivative." The matter was referred to the Committee for an interpretation.

DISCUSSION

Members were advised that aminolevulinic acid is a natural biological substance produced by all humans. It was noted that the substance was available in other countries as a therapeutic agent with sufficient toxicity to warrant scheduling if it were to be marketed in Australia.

The Committee did not consider that aminolevulinic acid was a derivative of methyl aminolevulinate and as such was not included in Schedule 4. Furthermore, in the absence of any products containing aminolevulinic acid on the Australian market and information on its use, the Committee considered it appropriate to wait until a submission for registration containing a full data package was received before considering the scheduling of aminolevulinic acid.

OUTCOME

The Committee agreed that aminolevulinic acid should remain unscheduled at this time.

16.2 IBUPROFEN AND CODEINE

PURPOSE

The Committee considered correspondence from XXXXXXXXXX concerning XXXXXXXXXX.

BACKGROUND

XXXXXXXXXX purchases made by a consumer of XXXXXXXXXX, a Schedule 3 product, from several pharmacies. XXXXXXXXXX is a combination of ibuprofen (200 mg) with codeine phosphate (12.8 mg).

OUTCOME

The Committee noted the correspondence from XXXXXXXXXX.

16.3 1,4-BUTANEDIOL, GAMMA AMINOBUTYRIC ACID, GAMMA BUTYROLACTONE, GAMAHYDROXYBUTYRALDEHYDE AND RELATED ANALOGUES

PURPOSE

The Committee considered correspondence from XXXXXXXXXX concerning 1,4-butanediol and related analogues.

BACKGROUND

The scheduling of 1,4-butanediol, gamma aminobutyric acid, gamma butyrolactone, gamma hydroxybutyraldehyde and related analogues and metabolic precursors was considered at the June 2003 Meeting. The Committee agreed to recommend to XXXXXXXXXX that the following substances be considered for inclusion in the XXXXXXXXXX Code-of-Conduct under Category 1:

1,4-BUTANEDIOL.
4-AMINO-BUTANOIC ACID.
4-HYDROXY-BUTANOIC ACID NITRILE.
4-HYDROXYBUTANAL.
2-HYDROXYTETRAHYDROFURAN.
2-PYRROLIDONE.
4-HYDROXY PENTANOIC ACID.
4-HYDROXY PENTANOIC ACID LACTONE.

XXXXXXXXXX advised that their Code of Practice for Supply Diversion into Illicit Drug Manufacture had been amended to include the substances listed above.

OUTCOME

The Committee noted that correspondence received from XXXXXXXXXX. Members were appreciative of the speed with which XXXXXXXXXX actioned the Committee's request.

17. MATTERS REFERRED BY THE MEDICINES EVALUATION COMMITTEE (MEC)

17.1 DROMETRIZOLE TRISILOXANE

PURPOSE

The Committee considered the scheduling of drometrizole trisiloxane.

BACKGROUND

XXXXXXXXXX sought approval for drometrizole trisiloxane to be used as a UV filter in listed sunscreen products. MEC noted that drometrizole derivatives had been used widely in polymer photo-protection for the past 40 years and their photochemistry has been extensively studied. Drometrizole trisiloxane had been on the accepted list of UV filters in the European Union since September 1998, at a concentration of up to 15% in sunscreen products.

DISCUSSION

The Committee noted the following points raised in the MEC minutes:

- Drometrizole trisiloxane exhibits low acute toxicity (LD_{50} >2000 mg/kg) in acute oral and dermal toxicity studies in rats and mice. These results were attributed to the very low systemic exposure following oral and dermal administration. Intraperitoneal administration to rats produced moderate to low toxicity, with LD50 values of 563 mg/kg in female and 2000 mg/kg in male rats, and 1200 and 2000 mg/kg in female and male mice, respectively. No obvious reason for the pronounced sex difference observed with both species was noted. There were no changes of toxicological significance in repeat dose oral toxicity studies in rats at up to 1000 mg/kg/day and mice. Testing at higher dosages was thought to be unnecessary since kinetic data showed that increasing the dose did not lead to a relative increase in exposure.
- The reproductive toxicity NOEL was estimated to be 1000 mg/kg/day, based on studies on rats and rabbits. While one study showed an equivocal result for developmental changes in chinchilla rabbits, this was thought to be an aberration as there was no evidence of similar results in the repeat study with rabbits or in rat studies.
- *In vitro* studies using bacterial and mammalian cell systems and *in vivo* studies in mice showed no evidence of genotoxicity. However, information regarding whether drometrizole trisiloxane can penetrate cells to interact with genetic material is not available.
- While a carcinogenicity bioassay was not provided in the MEC submission, two expert commentaries were provided as justification for the absence of this test. The XXXXXXXXXX XXXXXXXXXX concluded that, based on the available information in support of the application, the likelihood of drometrizole trisiloxane being carcinogenic would be low to negligible.
- Toxicokinetic data in rabbits, mice and rats indicates that the systematic exposure following oral or dermal administration of drometrizole trisiloxane is very low (< 1%). Metabolism of the parent molecule is limited or unlikely, with no sex differences or likely accumulation observed in rats. An *in vitro* test for percutaneous absorption using human skin *ex vivo* found that approximately 0.8% of the amount applied to the skin was absorbed. Two studies measuring *in vitro* percutaneous absorption using human skin reported values of less that 0.5% and 0.32%.
- Drometrizole trisiloxane is not an ocular irritant in rabbits and was not found to be a skin irritant nor a sensitising agent in the animal models studied. It was not phototoxic or photosensitising in guinea pigs at concentrations up to 85%.
- Human studies indicated that drometrizole trisiloxane is not a skin sensitiser in normal and atopic agents. It is not phototoxic and did not induce photoallergenic reactions in humans. A sunscreen containing XXXXXXXXXX drometrizole

trisiloxane did not show comedogenic potential and was deemed unlikely to have an adverse effect on normal human skin.

The Committee agreed that the low toxicity of the drometrizole trisiloxane warranted exemption from scheduling requirements.

The Committee considered whether it was appropriate for all new active substances for use in sunscreen products being considered by the TGA to be referred to the NDPSC for consideration of scheduling. A member advised that the Committee should continue to review new active substances of this type so as to maintain consistency. Furthermore, it was felt that the review of new sunscreens was warranted on the basis that they are applied to large areas of the skin thus resulting in a large exposure despite having a low toxicity. A member advised that the review of all new active sunscreen substances was unlikely to cause a significant increase in workload for the NDPSC. The Committee agreed that all new active substances for use in sunscreens reviewed by the TGA should be referred to the Committee.

DECISION 2003/39 - 39

The Committee agreed to exempt drometrizole trisiloxane from scheduling on the basis of low toxicity and included it in Appendix B under category 6.4 – sunscreen.

Appendix B – New Entry

DROMETRIZOLE TRISILOXANE ……..October 2003……..a……..6.4

18. MATTERS REFERRED BY THE MEDICINES CLASSIFICATION COMMITTEE (MCC) OF NEW ZEALAND

18.4 SEDATING ANTIHISTAMINES/CODEINE

PURPOSE

The Committee considered the scheduling of combined antihistamine preparations containing other active ingredients, including paracetamol, codeine and pseudoephedrine.

BACKGROUND

In Australia, primary entries for antihistamines were in S4, sedating oral antihistamines in S3 and non-sedating antihistamines including compounded non-sedating antihistamines in Schedule 2 (S2). In contrast, all antihistamines in New Zealand (NZ) were included in Part III (S2). The inclusion of single active sedating antihistamine products in S3 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) was based on concerns that such products were inappropriately used for sedation, particularly of infants and children.

The June 2003 NDPSC meeting endorsed TTHWP Decision 8/8 with the following proposed amendments, and referred this decision to NZ for consideration:

- Antihistamines and preparations with the potential for serious abuse be included in S4/Part 1;
- Single-active preparations of sedating antihistamines be included in S3/Part II; and
- Single-active preparations of non-sedating antihistamines and specified combination preparations of antihistamines be included in S2/Part III.

DISCUSSION

Following the June 2003 meeting, the NDPSC received an inquiry from NZ-MCC, seeking clarification regarding the intent of TTHWP Decision 8/8. It was highlighted that the amendments relating to Decision 8/8 would reclassify a significant number of existing oral sedating antihistamine products in combination with analgesics such as paracetamol from S2 to S3, in NZ. In addition, NZ also raised the issue that there were S2 products registered in both NZ and Australia containing a combination of sedating antihistamines, paracetamol and codeine.

Data on combination products containing paracetamol, codeine and antihistamines registered on the ARTG were provided to members, which confirmed NZ's advice. Members also noted that the existing entries in the SUSDP for codeine did not allow codeine preparations compounded with antihistamines outside of S4 and similarly, the Schedule entries for sedating antihistamines did not allow preparations compounded with analgesics in S2. However, these provisions in the SUSDP were not reflected in the status of many combination products registered on the ARTG.

The Committee was notified that certain combination products containing codeine, paracetamol and sedating antihistamines were allowed under S2 in some States and Territories including XXXXXXXXXXX, which may have implications on uniformity of the regulation of such products between the jurisdictions.

Members were advised that consideration of the scheduling of antihistamines as recommended by NDPSC at the June 2003 meeting had been gazetted and included on the agenda of the November 2003 NZ Medicines Classification Committee (MCC) meeting.

The Committee agreed to foreshadow consequential amendments to the SUSDP for consideration at the February 2004 meeting to align the SUSDP with current regulation of antihistamines in the jurisdictions including NZ, and taking into account the following points:

- maintain the status quo of existing day and night cough/cold/flu preparations containing sedating antihistamines for night time doses and labelled as S2; and

- remove the specificity from existing sedating antihistamine entries in the SUSDP to allow the inclusion of wider range of substances in combination antihistamine preparations, where considered appropriate at registration.

OUTCOME

The Committee agreed to foreshadow the following amendments to the SUSDP in order to align scheduling with the registration status of products while maintaining consistency with the recommendations of TTHWP Decision 8/8:

- All oral preparations containing non-sedating antihistamines, ie. single-active and compounded preparations combined with other S2 substances be included in S2;
- Allow oral combination preparations containing sedating antihistamines and other S2 substances formulated for night time dosing in S2.
- Oral sedating antihistamines combined with a S2 decongestant such as pseudoephedrine be allowed as S2.
- S2 codeine to be allowed in combined oral preparations containing an antihistamine in S2.
- All other oral sedating antihistamines be included in S3 except when included in Schedule 2.

Foreshadowed for consideration at the February 2004 meeting

Schedule 2 - Amendments

(sedating antihistamines - brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, diphenylpyraline, doxylamine and triprolidine):

[SUBSTANCE] – amend entry to read:

[SUBSTANCE] in combination preparations for oral use when:

(i) compounded with a decongestant; or

(ii) in a pack containing [substance] in a night time dose,

except in preparations for the treatment of children under two years of age.

TRIMEPRAZINE – amend entry to read:

TRIMEPRAZINE in combination preparations for oral use when:

(i) compounded with a decongestant and not labelled for the treatment of children under two years of age; or

(ii) in a pack containing trimeprazine in a night time dose and not labelled for the treatment of children under two years of age,

except when included in Schedule 3.

(sedating antihistamines with indications other than for oral use):

PHENIRAMINE – amend entry to read:

PHENIRAMINE:

(a) in eye drops;

(b) in combination preparations for oral use when:

(i) compounded with a decongestant; or

(ii) in a pack containing pheniramine in a night time dose,

except in preparations for the treatment of children under 2 years of age.

THENYLDIAMINE – amend entry to read:

THENYLDIAMINE:

(a) in nasal preparations for topical use;

(b) in combination preparations for oral use when:

(i) compounded with a decongestant; or

(ii) in a pack containing thenyldiamine in a night time dose,

except in preparations for the treatment of children under two years of age.

(amendment to allow codeine in combination with antihistamine)

CODEINE – amend entry to read:

CODEINE when:

(a) compounded:

(i) with a single non-opiate analgesic substance in tablets or capsules each containing 10 mg or less of codeine when:

(A) packed in blister or strip packaging or in a container with a child-resistant closure; and

(B) in a primary pack containing 25 or less dosage units; or

(ii) with a single non-opiate analgesic substance in individually wrapped powders each containing 10 mg or less of codeine when in a primary pack containing 25 or less dosage units; or

(iii) with one or more other therapeutically active substances:

(A) in divided preparations each containing 10 mg or less of codeine; or

(B) in undivided preparations containing 0.25 per cent or less of codeine; and

(b) labelled with a recommended daily dose not exceeding 60 mg of codeine.

19. INITIAL REVIEW/FORMAL OPINIONS (PHARMACEUTICALS)

22.1.1 3,4-METHYLENEDIOXY-N,A-DIMETHYLPHENYLETHYLAMINE (MDMA)

The Committee was advised that the nomenclature for 3,4-methylenedioxy-N,a-dimethylphenylethylamine (MDMA) in Schedule 9 of the SUSDP may be incorrect.

A member advised that the World Health Organization chemical name for MDMA based on the WHO list (Part One – Psychotropic Substances under International Control), is (+/-)-N,α-dimethyl-3,4-(methylenedioxy)phenylethylamine. There was no INN for this illicit drug.

OUTCOME

The Committee agreed to foreshadow consideration of the following amendment at the February 2004.

Foreshadowed for consideration at the February 2004 meeting

Schedule 9 – Amendment

3,4-METHYLENEDIOXY-N,α-DIMETHYLPHENYLETHYLAMINE – amend entry to read:

(+/-)-N,α-DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE *(MDMA).