DOMPERIDONE (MOTILIUM™) TABLETS

At the 33rd meeting on 9 June 2005, the Medicines Classification Committee considered an application to reclassify domperidone from prescription medicine to restricted medicine for the symptomatic relief of nausea and vomiting and for the treatment of symptoms of dysmotility-like dyspepsia.

The Committee concluded that the application as it stood was not acceptable for sale of domperidone as a restricted medicine and recommended that there be no change to the current prescription medicine classification. The Committee did, however, note the following:

> "In order to be acceptable for reconsideration, the Committee was of the opinion that the submission should: acknowledge that medication is not best practice for vomiting and not include this as an indication limit pack sizes to 20 tablets for limited duration and with a maximum daily dose of 40 milligrams contain draft labelling appropriate for OTC sale."

Janssen-Cilag Pty Ltd accepts these comments and would like the Committee to consider this revised application for reclassification of domperidone.

The application consists of the following documents:

1. Revised Part A (General Information)

2. Copy of the relevant minute from the 33rd MCC meeting

3. Draft labelling text for OTC MOTILIUM

4. Overseas example of packaging for OTC MOTILIUM (ex. Ireland)

5. Proposed Consumer Medicine Information for OTC MOTILIUM

6. Copy of the current approved MOTILIUM Data Sheet

7. Copy of the original application
   (As discussed with the MCC Secretary, rather than re-submitting the full documentation supplied in January 2005, only pages 1-35 of the original application have been provided. Copies of the 16 attachments to the original application are available on request)

Please note that in this application for OTC use of MOTILIUM:

- **The vomiting indication has been removed.**
- **The pack size has been limited to 20 tablets**
- **The duration of treatment has been limited to 48 hours.**
- **The maximum daily dose has been limited to 40 mg.**

PART A – GENERAL INFORMATION

International Non-proprietary Name:
Domperidone

Proprietary name:
MOTILIUM™

Name of company/organisation requesting reclassification:
Janssen-Cilag Pty Ltd

Dose form and strength for which a change is sought:
Tablets, 10 mg

Pack size and other qualifications:

- Maximum OTC pack size limited to 20 tablets
- Duration of OTC treatment limited to 48 hours
- Maximum OTC daily dose limited to 40 mg

Indications for which change is sought:

- Symptomatic treatment of nausea
- Treatment of the symptoms of dysmotility-like dyspepsia: sense of fullness, feeling of abdominal distension, eructation, flatulence and heartburn

Present classification of medicine:
Prescription Medicine

Classification sought:
Restricted (Pharmacist Only) Medicine

Classification status in other countries:

- Australia: prescription medicine
- UK: over the counter (OTC)
- USA: not marketed
- Canada: prescription medicine
- Belgium: OTC
- Ireland: OTC
- Italy: OTC
- Japan: OTC
- Netherlands: OTC
- South Africa: OTC
- Switzerland: OTC
- Other countries where domperidone is available OTC include: China, Russia, Slovakia, Malta, South Korea, and Romania

Extent of usage in NZ and elsewhere:
The unit sales volumes for MOTILIUM in New Zealand and Australia over the past 5 years are provided in the following table:

> ***[NB table containing commercially sensitive sales data withheld from the document placed on the Medsafe website, under the provisions of section 9(2)(b)of the Official Information Act 1982]***

Dates of original consent to distribute:
Consent to distribute MOTILIUM in New Zealand was given on 28 June 1984.
The product has been registered worldwide since 1978.

Labelling or draft labelling for the proposed new presentation:
A copy of the proposed labelling and the proposed CMI for OTC MOTILIUM is provided.

Proposed warning statements:
The relevant warning statements are contained in the proposed CMI for OTC MOTILIUM.

Other products containing the same active ingredient which would be affected by the proposed change:
None.

REVIEWER'S GUIDE

This application seeks the reclassification of domperidone 10 mg tablets from a Prescription Medicine to a Restricted (Pharmacist Only) Medicine when indicated for the symptomatic treatment of nausea and vomiting and for the treatment of symptoms of dysmotility-like dyspepsia.

The information contained in this application falls into three categories:

- General information (Part A)
- Information which is specifically related to nausea and vomiting (Part B1).
- Information which is specifically related to dyspepsia (Part B2).
- General information which is related to the medicine, irrespective of indication (Part B3).

To avoid repetition and overlapping of the above categories, the structure of the application is as follows:

	Executive Summary
	Response to the report prepared by Medsafe for consideration by the MCC in March 1999
Part A	General information
Part B1 – Nausea and vomiting	Information specifically related to nausea and vomiting
Part B2 – Dyspepsia	Information specifically related to dyspepsia
Part B3 – General	General information, irrespective of indication
	Conclusions
	Attachments 1 – 16

EXECUTIVE SUMMARY

Domperidone 10 mg tablets have been available on prescription in New Zealand since June 1984, under the trade name MOTILIUM™.

The classification of domperidone was reviewed at the 21st meeting of the Medicine Classification Committee (MCC) in March 1999. Domperidone was placed on the agenda for that meeting because it had been considered for reclassification to over the counter (OTC) status in the UK. The MCC recommended that there should be no change to the classification of domperidone. A copy of the relevant minute is provided in Attachment 1.

At that meeting, the MCC considered a report prepared by Medsafe (see Attachment 2). However, the MCC review was undertaken without a formal submission from Janssen-Cilag. As the sole sponsor of domperidone in New Zealand, we possess pertinent and up to date safety, usage and efficacy information and believe we can contribute greatly to the justification for domperidone to be reclassified to OTC status.

This application seeks the reclassification of domperidone 10 mg tablets from a Prescription Medicine to a Restricted (Pharmacist Only) Medicine when indicated for the symptomatic relief of nausea and vomiting and for the treatment of symptoms of dysmotility-like dyspepsia. We also wish to address the concerns raised during the 1999 review, as well as to challenge some of the comments made in the report prepared by Medsafe for consideration at the March 1999 meeting.

Domperidone has well established efficacy for nausea and vomiting and dyspepsia. For this reason we will not revisit the efficacy of the medicine in this application. However, as domperidone has been marketed for over 20 years, we would like to take this opportunity to provide the MCC with up to date safety information.

Acute non-specific nausea and vomiting (e.g. from 'food poisoning', communicable gastroenteritis, motion sickness[1] and hang-over) is established as a self-medication indication. Patients can be relied on to diagnose the disorder and in the majority of instances identify the most likely cause. In most cases the dehydration and malnutrition caused by the symptoms are of more concern than the cause, which is usually self-limiting. Importantly, early and convenient access to domperidone can reduce the amount of electrolytes lost and the possibility of dehydration.

With the product clearly labelled for the initial symptomatic treatment of acute nausea and vomiting, the general public will have convenient access to a very effective treatment. This will allow them, in most cases, to quickly return to normal activities.

[1] NB domperidone is not indicated for the prevention or treatment of motion sickness

Likewise, the general public is experienced in using OTC medicines to treat dyspepsia. For many years advertising and consumer education campaigns have highlighted the symptoms of dyspepsia to consumers, and it is now well accepted as a problem that is easily and safely treated with OTC medications.

Domperidone tablets have an excellent safety profile. Medsafe considers in its March 1999 report that domperidone is safer than metoclopramide and we also believe it is safer than prochlorperazine. Domperidone is also well tolerated. This is illustrated by the very low incidence of adverse reactions reported locally and internationally during the use of domperidone since the first international registration in Belgium in March 1978.

Domperidone has been marketed in New Zealand and internationally for over 20 years. During this time the safety and adverse reaction profile of the medicine has been clearly defined. The extensive knowledge gained about the product, which far exceeds the minimum standards for OTC consideration, means it is extremely unlikely that the medicine would behave in an unpredictable manner once reclassified to a Restricted (Pharmacist Only) Medicine.

Finally, the general public has a right of access to an effective and safe treatment for nausea and vomiting and dyspepsia that usually does not cause drowsiness or extrapyramidal symptoms, which are adverse reactions reported for some of the other currently available OTC treatments.

RESPONSE TO THE REPORT PREPARED BY MEDSAFE FOR CONSIDERATION BY THE MCC IN MARCH 1999

We are concerned with some of the statements made in the Medsafe report. Some adverse reactions to domperidone which are considered to be relatively rare seem to take undue prominence in the report. We therefore wish to take this opportunity to highlight particular examples and give our interpretation of their frequency, severity and hence relative importance.

We have reviewed the reports received by the Centre for Adverse Reactions Monitoring (CARM) in New Zealand and the Therapeutic Goods Administration (TGA) in Australia. As at 30 June 2003, CARM had only received 14 reports involving domperidone. Information on 13 of these reports is provided in the CARM printout dated 30 September 1999 (see Attachment 3) [NB an updated listing has been requested from CARM and will be provided when this becomes available]. In the printout of reports received up to 10 January 2005, TGA had only received 22 reports involving domperidone (see Attachment 5).

We have also reviewed the reports received by the company from around the world. The latest Periodic Safety Update Report (PSUR) for domperidone (see Attachment 6) covers the period from 2 January 2003 to 1 January 2004, and covers an estimated exposure to domperidone in this review period of approximately 86.5 million treatment courses.

The Medsafe report states that nausea and vomiting of unknown origin should not be treated with domperidone as the underlying cause may require further investigation and treatment. This is true of ongoing and reoccurring nausea and vomiting. The labelling and professional promotion of the product will confine the use of OTC domperidone to nausea and vomiting episodes that are acute and non-recurring in nature. The proposed Consumer Medicine Information (CMI; see Attachment 8) clearly directs patients to seek medical advice if symptoms persist for longer than 48 hours. In addition, we recommend that patients also seek medical advice should symptoms get worse, are not relieved or return. Furthermore, treating nausea and vomiting of unknown causes is no more harmful than for example treating pain of unknown cause with OTC analgesics.

The Medsafe report comments that "high doses of domperidone may lead to extrapyramidal effects and the possibility of cardiovascular effects." The limited pack size proposed in this application discourages the use of high doses. Importantly, at OTC doses it is not expected to cause extrapyramidal adverse reactions, drowsiness or cardiovascular effects.

The Medsafe report comments that "there is a possibility that epileptics may experience increase frequency and severity of seizures." The statement regarding epileptics is not representative of data in the company's possession and is not reflected in the CARM or TGA reports. None of the 13 cases reported to CARM, or the 22 cases reported to TGA

involves epilepsy or seizures. The PSUR records six cases of convulsion out of the estimated 86.5 million patients exposed to domperidone in the 1-year period to 1 January 2004. Three of the six cases had underlying medical conditions that provided reasonable alternative explanations for the reported events. A fourth did not provide sufficient information regarding planned or ongoing neurologic evaluation. The two remaining cases did not contain sufficient clinical information to make a reasonable causality assessment, although a possible role for domperidone could not be ruled out. Overall, these cases did not identify a new safety concern for domperidone.

Furthermore, the Medsafe report comments that "domperidone can interact with many other medications". The only relevant interactions associated with domperidone involve anticholinergic medicines, antacids, antisecretory agents and oral ketoconazole. Also, because domperidone has gastro-kinetic effects it could influence the absorption of concomitantly orally administered medicines, particularly those of sustained release or enteric-coated formulations. These interactions cannot be considered a significant risk to the OTC consumer due to domperidone's wide therapeutic index and perhaps were overstated in the Medsafe report.

However, the report is correct in stating that the patient may misdiagnose the cause of the nausea and vomiting in some circumstances. It is also true that this could lead to the inappropriate (or unnecessary) use of domperidone. Masking is possible as the symptoms may be ameliorated but the underlying cause could still be present and untreated. However, this possibility of masking is no greater in the case of domperidone than for any other OTC medicine. In general, the types of medicines available OTC do not actually cure their corresponding condition but simply alleviate the related symptoms. Therefore, amelioration of the symptoms occurs with the underlying cause still being present and untreated with the majority of OTC medicines. Furthermore, the danger of masking underlying gastrointestinal conditions cannot be considered any greater than for example that of OTC analgesics possibly masking tumours, muscle damage or degenerative bone disorders.

Where nausea and vomiting are caused by a more serious underlying condition, the symptoms will either persist or return after the completion of treatment. In this case, the product's labelling appropriately directs the consumer to seek medical advice. If self-medication begins inappropriately (or unnecessarily), this limited exposure to domperidone would not be a significant concern, because of the medicine's favourable safety profile.

The risk of misdiagnosis is small, and if misdiagnosis occurs and self-medication begins, the risk of negative consequences may be considered to be small.

The Medsafe report also comments that "domperidone can cause serious adverse effects if used inappropriately." We disagree with this statement, as domperidone has an excellent safety profile and is generally very well tolerated.

The Medsafe report also comments that "domperidone can (but does not readily) cross the blood- brain barrier and therefore can cause adverse central effects. There have been reports of dystonic reactions." It is important to reiterate that due to its unique structure, domperidone has very limited penetration of the blood brain barrier. The central:peripheral ratio for domperidone is approximately 1:300, compared with 1:45 for metoclopramide. This in practice means a very low incidence of central effects.

Finally, the Medsafe report comments that "heartburn is better treated with antacids or H_2 antagonists which are also available OTC." It has been established that H_2 antagonists are not effective in the treatment of dysmotility-like dyspepsia and that antacids are not effective in the treatment of either acid related or dysmotility-like dyspepsia (see later). Domperidone has demonstrated efficacy in the treatment of heartburn caused by motility problems. That is, H_2 antagonists should be used for acid related heartburn but domperidone is more appropriate for heartburn caused by motility problems.

PART A – GENERAL INFORMATION

International Non-proprietary Name:
Domperidone

Proprietary name:
MOTILIUM™

Name of company/organisation requesting reclassification:
Janssen-Cilag Pty Ltd

Dose form and strength for which a change is sought:
Tablets, 10 mg

Pack size and other qualifications:
Pack size of 10 or 20 tablets

Indications for which change is sought:

- Symptomatic treatment of nausea and vomiting
- Treatment of the symptoms of dysmotility-like dyspepsia: sense of fullness, feeling of abdominal distension, eructation, flatulence and heartburn

Present classification of medicine:
Prescription Medicine

Classification sought:
Restricted (Pharmacist Only) Medicine

Classification status in other countries:

- Australia: prescription medicine
- UK: over the counter (OTC)
- USA: not marketed
- Canada: prescription medicine
- Belgium: OTC
- Ireland: OTC
- Italy: OTC
- Japan: OTC
- Netherlands: OTC
- South Africa: OTC
- Switzerland: OTC
- Other countries where domperidone is available OTC include: China, Russia, Slovakia, Malta, South Korea, and Romania.

Note that the international regulatory status of MOTILIUM is provided as Appendix 1 of the PSUR document in Attachment 6.

Extent of usage in NZ and elsewhere:
The unit sales volumes for MOTILIUM in New Zealand and Australia over the past 5 years are provided in the following table:

[table containing confidential sales data withheld]

Dates of original consent to distribute:
Consent to distribute MOTILIUM in New Zealand was given on 28 June 1984.
The product has been registered worldwide since 1978.

Labelling or draft labelling for the proposed new presentation:
For information, a copy of the current (i.e. "Prescription Medicine") labelling for MOTILIUM is provided in Attachment 7. The "OTC" labelling for MOTILIUM would reflect the information in the proposed CMI document provided in Attachment 8.

Proposed warning statements:
The relevant warning statements are contained in the proposed CMI document for OTC MOTILIUM (see Attachment 8).

Other products containing the same active ingredient which would be affected by the proposed change:
None.

PART B1 – NAUSEA AND VOMITING

BENEFITS TO BOTH THE CONSUMER AND TO THE PUBLIC EXPECTED FROM THE PROPOSED CHANGE

Domperidone has an excellent safety profile and is well tolerated, making it an appropriate medicine to be reclassified to a Restricted (Pharmacist Only) Medicine. Reclassification of domperidone would provide appropriate and easier access to a safe treatment option for a common symptom complex. As a consequence, patients could have immediate access to a convenient and effective treatment for their condition.

In general, nausea and vomiting can be considered symptoms of conditions that are either acute, uncomplicated and self-limiting in nature, or symptoms of a serious underlying condition.

This application seeks to allow treatment of acute uncomplicated nausea and vomiting with OTC domperidone. At present, a patient wanting relief from acute nausea and vomiting without any obvious underlying conditions must present to a GP. This places an unnecessary burden on the health care system at a time when budgets are strained. Allowing the general public with the help of a Pharmacist to self-treat simple cases of acute nausea and vomiting with a safe and effective medicine such as domperidone will reduce the number of medical consultations and hence reduce demands on the healthcare system.

Some patients are unlikely to consult a doctor for simple acute nausea and vomiting. This is because they believe that the condition is not serious enough to warrant subjecting themselves to a visit to the local GP when they are feeling unwell and would prefer bed rest. The availability of OTC domperidone would greatly relieve the suffering of this subset of patients by providing more convenient access without compromising the patient's safety.

However, nausea and vomiting may be accompanied, for example, by blood in the vomitus, by fever or pain, or it may be ongoing or reoccurring. These concomitant symptoms may suggest a serious underlying condition. The proposed CMI for OTC domperidone (see Attachment 8) describes the symptoms of potentially serious underlying conditions. The OTC product labelling would recommend medical treatment and discourage use of the product without medical supervision when any symptoms suggestive of serious underlying conditions may be present. Such patients would be appropriately referred to a GP for further assessment. Should a patient not be comfortable reading a printed document, a Pharmacist is ideally placed to provide professional advice on the use of the product, or recommend referral to a GP.

With the product clearly labelled for the initial symptomatic treatment of acute nausea and vomiting, the general public would have convenient access to a very effective

treatment. This will allow them, in most cases, to return to normal activities quickly. Faster control and cure rates result in fewer days lost from work and therefore greater productivity in industry. In those cases where the treatment is not successful – that is if the condition has not resolved within 48 hours – the CMI and labelling advises the patient to consult a doctor.

Furthermore, changing domperidone to a Restricted (Pharmacist Only) Medicine will provide an opportunity for the public to gain a greater awareness of the benefits of this medicine, thus allowing more widely informed self-sufficient consumers.

In conclusion, the general public has a right of access to an effective and safe treatment for nausea and vomiting that does not usually cause drowsiness or extrapyramidal symptoms, which are adverse reactions reported for some of the other currently available OTC treatments.

EASE OF SELF-DIAGNOSIS OR DIAGNOSIS BY A PHARMACIST

Nausea

Feelings of nausea can occur in response to a variety of stimulus including; food, viral and bacterial infections, hunger, toxins, emotions (such as fear, stress, anxiety), disease and motion. Most of these are acute, uncomplicated and self-limiting conditions, which are suitable for OTC treatment. It is for these uncomplicated conditions that domperidone should be available to the patient without the need for medical consultation. The vast majority of adult members of the general public has experienced at least one of the above causes and hence is familiar with feeling nauseated.

Causes of nausea will be considered here in two sections: those easily self-diagnosed by the patient or Pharmacist, and those where the cause is unknown without further medical investigation.

In most circumstances it is easy to self-diagnose the cause of the nausea by looking at the acute history, for example recently consumed food, change to medication, high levels of anxiety or apprehension, or recent contact with gastroenteritis. The proposed CMI provides clear instructions for appropriate use of the medicine in these acute cases of nausea which are not caused by a more serious underlying condition.

However, reoccurring or prolonged episodes of nausea may suggest a serious underlying condition for which the product's CMI and labelling appropriately recommends seeing a doctor.

Vomiting

There are several possible causes of vomiting. All of these different causes may result in the complex sequence of physiological events which precede or accompany the act of

vomiting. These include nausea, salivation, yawning, and the coordinated respiratory, gastro-intestinal and abdominal muscular movements which result in retching and vomiting, accompanied by changes in body posture, cardiovascular function and psychological state[2].

The cascade of the events associated with vomiting makes it an experience easily identified by members of the general public. It is very unlikely that the patient will mistake the act of vomiting for something else. Although the act itself is not susceptible to misdiagnosis, the consumer may occasionally require some assistance with the diagnosis of the underlying cause.

By classifying domperidone as a Restricted (Pharmacist Only) Medicine, the Pharmacist would be available to discuss with the consumer any concerns held regarding the duration or severity of the episode, or the occurrence of concomitant symptoms. In addition, the proposed CMI provides clear descriptions of when the patient should seek further advice from their Pharmacist or GP. Also, by limiting the pack size to for example ten tablets, the patient with chronic symptoms would be forced to return to the pharmacy every two and half days, allowing the Pharmacist to intervene if required. The Pharmacist would be able to refer the patient with a chronic or reoccurring condition to a GP for a medical examination.

POTENTIAL FOR MASKING OTHER SERIOUS CONDITIONS

Nausea and vomiting are relatively common symptoms which may stem from, or be associated with, a wide variety of medical conditions. Many of these are acute, self-limiting conditions which can be readily treated by the patient with the advice of the Pharmacist.

Acute non-specific nausea and vomiting (e.g. 'food poisoning', communicable gastroenteritis, motion sickness and hang-over) is already established as a self-medication indication. Patients can be relied on to diagnose the disorder and, in the majority of instances, identify the most likely cause. In most cases the dehydration and malnutrition caused by the symptoms are of more concern than the cause, which is usually self-limiting. Importantly, early and convenient access to domperidone could reduce the amount of electrolytes lost and the possibility of dehydration.

Patients can also be relied upon to identify any obvious further symptoms (such as blood in vomitus, severe headaches, pains, fever or syncope) that may indicate a more serious illness requiring medical intervention. As a Restricted (Pharmacist Only) Medicine, the Pharmacist would be in the position to interview the patient about concomitant symptoms and inquire into the length and severity of the episode. Pharmacists are well trained to counsel patients on nausea and vomiting and are comfortable with intervening and directing patients to see their GP.

[2] Nausea and Vomiting: Mechanism and Treatment. Edited by CJ Davis, GV Lake-Bakaar and DG Grahame-Smith

In addition, appropriate patient information describing the indication symptoms as well as the contraindications, warnings and precautions for domperidone would facilitate self-diagnosis. The proposed CMI provides clear information and instructions to enable the patient to use the product correctly and allow them to recognise more serious symptoms which may require medical attention.

The report prepared by Medsafe for consideration by the MCC in March 1999 is correct in stating that the patient may misdiagnose the cause of the nausea and vomiting in some circumstances. It is also true that this could lead to the inappropriate or unnecessary use of domperidone. Masking is possible as the symptoms may be ameliorated but the underlying cause can still be present and untreated. However, the possibility of masking is no greater in the case of domperidone than for any other OTC medicine. In general, the types of medicines available OTC do not actually cure their corresponding condition but simply alleviate the related symptoms. With the majority of OTC medicines amelioration of the symptoms occurs with the underlying cause still being present and untreated. Furthermore, the danger of masking underlying gastrointestinal conditions cannot be considered any greater than for example OTC analgesics possibly masking tumours, muscle damage or degenerative bone disorders.

Where nausea and vomiting are caused by a more serious underlying condition, the symptoms will either persist or return after the completion of treatment. In this case the product's labelling appropriately directs the consumer to seek medical advice. If self-medication does begin inappropriately or unnecessarily, such limited exposure to domperidone would not be a major concern because of the medicine's favourable safety profile.

Hence, the risk of misdiagnosis is small, and if misdiagnosis does occur and self-medication begins, the risk of negative consequences may be considered to be small.

USE IN PREGNANCY

Use in pregnancy is of particular interest with domperidone because nausea and vomiting or morning sickness are conditions associated with pregnancy.

The MOTILIUM Data Sheet (see Attachment 9) states that domperidone "has only been taken by a limited number of pregnant women and women of childbearing age. This has not resulted in an increase in the frequency of malformation or other direct or indirect harmful effects on the foetus [see also Attachment 10]. A study in rats has shown reproductive toxicity at a high, maternally-toxic dose. The potential for humans is unknown. Therefore, MOTILIUM should only be used during pregnancy when justified by the anticipated therapeutic benefit."

According to the Australian categorisation of risk of drug use in pregnancy[3], domperidone is a Category B2 medicine, i.e. a drug "which has been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed".

One of the perceived risks of allowing anti-nauseants to be available without a prescription is the possibility of use by women yet to discover they are pregnant. Importantly, during the first two weeks of development, from conception to the first missed period, the embryo is considered to be resistant to any teratogenic effects of medicines. The critical period of embryonic development, when the organ systems develop, starts at about 17 days post-conception and is complete by 60-70 days[3]. After day 17 the majority of early term pregnant women have been alerted to the possibility of being pregnant due to a missed period. The proposed CMI and product labelling clearly state that the product should not be taken if the patient is, or thinks she may be, pregnant. These factors combined significantly decrease the chance of a pregnant woman taking domperidone. Importantly, the possibility of inadvertent short term exposure of domperidone in early pregnancy is not detrimental enough to deprive all other patients of the OTC availability of this useful medicine.

RELEVANT COMPARATIVE DATA FOR LIKE COMPOUNDS

Metoclopramide and prochlorperazine are two effective treatments for nausea and vomiting. Metoclopramide is classified as a Restricted (Pharmacist Only) Medicine when compounded with paracetamol in packs of not more than 10 tablets or capsules for the treatment of nausea associated with migraine. Prochlorperazine is classified as a Restricted (Pharmacist Only) Medicine when sold in packs containing not more than 10 tablets for the treatment of nausea associated with migraine.

Promethazine and dimenhydrinate as well as fructose and glucose combination products make numerous claims relating to nausea and vomiting. However domperidone has demonstrated efficacy in the treatment of nausea and vomiting from any cause.

Metoclopramide

Metoclopramide 5 mg is currently available OTC as a combination product with 500 mg paracetamol. This combination product, Paramax™, is indicated for the symptomatic treatment of migraine. It is also indicated for the treatment of pain accompanied by gastric stasis or nausea and vomiting.

[3] Prescribing Medicines in Pregnancy. 4th edition, 1999. An Australian categorisation of risk of drug use in pregnancy. Australian Drug Evaluation Committee. Commonwealth Department of Health and Family Services.

Although the indications for Paramax are quite different to those of domperidone and metoclopramide alone, the presence of metoclopramide in this product makes it an appropriate medicine for the purposes of comparison to domperidone.

Adverse effects

A listing of the 208 adverse reports received by CARM for metoclopramide (as at 30 June 2003) is provided in Attachment 4. The reports for metoclopramide differ significantly, in terms of number and severity of reactions, with the 14 reports for domperidone up to the same time point (see Attachment 3).

Metoclopramide is a dopamine antagonist with anti-emetic properties similar to those of domperidone and certain neuroleptic drugs. However, unlike domperidone metoclopramide readily crosses the blood-brain barrier and induces central anti-dopaminergic effects in 20% of patients. Various extrapyramidal reactions to metoclopramide, usually of the dystonic type, have been reported. These reactions include: spasm of the facial muscles; trismus; rhythmic protrusion of the tongue; a bulbar type of speech spasm of extraocular muscles; including oculogyric crises; unnatural positioning of the head and shoulders and opisthotonos. There may also be a generalized increase in muscle tone[4].

In contrast, extrapyramidal symptoms occur only in very rare instances when taking domperidone. Another distinction between metoclopramide and domperidone regarding this CNS adverse effect is its onset. Extrapyramidal symptoms have been reported with the long term use of domperidone, whereas with metoclopramide the majority of reactions occur within 36 hours of starting treatment. With both medicines these symptoms resolve after discontinuation of treatment. The delay in onset with domperidone gives the medicine a significant benefit over metoclopramide because it is only to be used short term or under medical supervision.

Due to metoclopramide's high level of CNS activity it causes drowsiness, which is a well documented adverse reaction. This impacts on the patient's ability to drive and operate machinery, carry out normal daily activities, and affects their general feeling of wellbeing.

Furthermore, restlessness, acute depression and diarrhoea have been reported in patients receiving metoclopramide, whereas restlessness and acute depression are not adverse reactions associated with domperidone. Elevated serum prolactin levels and galactorrhoea may occur during therapy with either metoclopramide or domperidone.

[4] Current Maxolon™ Data Sheet (Attachment 11).

Interactions

Domperidone and metoclopramide share the following interactions:

- Action on the gastrointestinal tract is antagonised by anticholinergics
- Absorption of any concurrently administered oral medication may be modified by their effect on gastric motility.

However, metoclopramide and phenothiazines should only be prescribed concurrently with care, since extrapyramidal symptoms may occur with both medicines. Care should also be used when prescribing metoclopramide for patients being treated with other centrally active medicines, such as anti-epileptic medicines.

Dosing with antacids and antisecretory drugs should be separated from dosing with domperidone by at least 2 hours. This is not necessary with metoclopramide.

Contraindications

Due to their pharmacology, neither metoclopramide nor domperidone should be used whenever stimulation of gastrointestinal motility might be dangerous, e.g. in the presence of gastrointestinal haemorrhage, mechanical obstruction or perforation.

Metoclopramide is contraindicated in patients with phaeochromocytoma and domperidone is contraindicated in patients with a prolactin-releasing pituitary tumour (prolactinoma).

Prochlorperazine

Prochlorperazine is classified as a Restricted (Pharmacist Only) Medicine. Its OTC indication is for treatment of nausea associated with migraine, however it is effective for other causes of nausea.

Adverse effects

Prochlorperazine, a phenothiazine, is an effective treatment for nausea and vomiting. Its mechanism of action differs from that of metoclopramide and domperidone. As with metoclopramide, prochlorperazine readily crosses the blood brain barrier and can cause extrapyramidal symptoms and drowsiness.

The following is a discussion of prochlorperazine 3 mg. Adverse reactions of prochlorperazine include dry mouth, insomnia, agitation and mild skin reactions. Other effects which have occurred with prochlorperazine and other phenothiazine neuroleptics include jaundice, blood dyscrasias and hyperprolactinaemic effects such as gynaecomastia. Neuroleptic malignant syndrome (hyperthermia, rigidity, autonomic dysfunction and altered consciousness) may occur with any neuroleptic.

Interactions

Alcohol, barbiturates and other sedatives: may intensify the CNS depressant actions of prochlorperazine. Respiratory depression may occur.
Antacids, anti-Parkinson agents and lithium: interfere with absorption of prochlorperazine.
Antihypertensive agents: prochlorperazine may exaggerate the hypotensive effect of most antihypertensive drugs, especially alpha-adrenoceptor blocking drugs.

Contraindications

Prochlorperazine should be avoided in patients with: liver dysfunction, prostatic hypertrophy, epilepsy, known hypersensitivity to phenothiazines, Parkinson's disease, narrow angle glaucoma, and existing blood dyscrasias.

Warnings and precautions

Hypotension, usually postural, may occur, particularly in elderly or volume depleted patients. Tardive dyskinesia may occur occasionally, although this is normally associated with higher doses than are recommended for Buccastem™. Nausea and vomiting as a sign of organic disease may be masked by the anti-emetic action of prochlorperazine[5].

Interestingly, additional information is contained in the Stemetil™ Data Sheet dated 23 March 1999 (see Attachment 12). Although Stemetil and Buccastem tablets are different strengths, it is not unreasonable to expect significant similarities between 3 mg and 5 mg prochlorperazine. For this reason it is important to highlight that 5 mg prochlorperazine is also contraindicated in patients with renal dysfunction, hypothyroidism, phaeochromocytoma and myasthenia gravis. Also, 5 mg prochlorperazine has been reported to cause hypotension, cardiac arrhythmias, including atrial arrhythmia, A-V block, ventricular tachycardia and fibrillation, and respiratory depression. Agranulocytosis may occur rarely and it is not dose related.

Summary — metoclopramide & prochlorperazine vs. domperidone

We agree with the statement made in the Medsafe report that domperidone is safer than metoclopramide. In contrast, we reject the view that domperidone is not as safe as prochlorperazine. Therefore, we do not accept the report's conclusion that domperidone should remain a Prescription Medicine "because there are several other products available OTC with better safety profiles (e.g. Buccastem)."

Unlike domperidone, prochlorperazine causes drowsiness, which is a significant adverse reaction in the OTC environment. It impacts on the patient's ability to drive and operate machinery, carry out normal daily activities, and affects their general feeling of

[5] Current Buccastem™ Data Sheet (Attachment 13).

wellbeing. All of these factors place domperidone at an advantage to prochlorperazine regarding safe use by the consumer.

Cyclizine

Cyclizine in oral preparations is classified as a Pharmacy Only Medicine.

Cyclizine is an antihistamine which is characterised by a low incidence of drowsiness. It is indicated for the prevention and treatment of nausea and vomiting caused by motion sickness, narcotic analgesics, general anaesthetics in the post-operative period and radiotherapy, especially for breast cancer since cyclizine does not elevate prolactin levels. Cyclizine may also be of value in relieving vomiting and attacks of vertigo associated with Menières disease and other forms of vestibular disturbance.

Like domperidone, cyclizine should be should be used with caution in patients with obstructive disease of the gastrointestinal tract. However, unlike domperidone, caution and appropriate monitoring should also be used when cyclizine is used in patients with glaucoma, males with possible prostatic hypertrophy and patients with severe heart failure.

Potential for abuse

The most significant disadvantage of cyclizine in the OTC setting is its potential for abuse. In some countries the availability of oral cyclizine formulations as an OTC medication has led to the misuse of cyclizine, predominantly by teenagers. The aim of abusers is to produce a state of disoriented exhilaration associated with hallucinations. Misuse may be by the oral or intravenous route. The concomitant misuse of cyclizine with large amounts of alcohol is particularly dangerous, since the anti-emetic effect of cyclizine may increase the toxicity of alcohol[6].

Promethazine

Promethazine is classified as a Restricted (Pharmacist Only) Medicine when sold in the manufacturer's original pack containing not more than 10 doses for the treatment of insomnia or anxiety. Promethazine is separately classified as a Pharmacy Only Medicine, except for promethazine theoclate when sold in a sealed container of not more than 12 tablets or capsules for the prevention of travel sickness and sold at a transport terminal or aboard a ship or plane (General Sale Medicine).

Promethazine is a sedating antihistamine which has several indications including the treatment of nausea and vomiting due to several causes. While its efficacy in the prevention of motion sickness is acceptable, its efficacy in the treatment of nausea and

[6] Current Valoid™ Injection Data Sheet (Attachment 14).

vomiting of other origins is lacking in comparison to domperidone, metoclopramide and prochlorperazine.

Adverse effects

The following adverse reactions have been reported for promethazine and domperidone:
Dry mouth, nausea, vomiting, diarrhoea, constipation, dizziness, urticaria, extrapyramidal symptoms (occurring at a significantly greater frequency than for domperidone) nervousness, and insomnia.

The following additional adverse reactions have been reported for promethazine:
Epigastric distress, loss of appetite, sedation, restlessness, lassitude, incoordination, fatigue, blurred vision, tachycardia, bradycardia, faintness, contact dermatitis (topical), photosensitisation, angioneurotic oedema, leucopenia, aplastic anaemia, thrombocytopenic purpura, jaundice, tinnitus, euphoria, convulsive seizures, oculogyric crises, excitation, catatonic like states, hysteria, tardive dyskinesia, marked irregular respiration, severe or life-threatening agranulocytosis.

Interactions

Promethazine may enhance the sedative effects of CNS depressants (including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives and neuroleptics). Promethazine may also interact with antimuscarinic drugs (atropine, tricyclic antidepressants).

Dimenhydrinate

Dimenhydrinate is classified as a Pharmacy Only Medicine, except when sold in a sealed container of not more than 12 tablets or capsules for the prevention of travel sickness and sold at a transport terminal or aboard a ship or plane (General Sale Medicine).

Dimenhydrinate has a significantly different mechanism of action than domperidone. Like promethazine, its efficacy in the prevention of motion sickness is acceptable. However, its efficacy in the treatment of nausea and vomiting of other origins is also lacking in comparison to domperidone, metoclopramide and prochlorperazine.

Adverse effects

The following adverse reactions have been reported for dimenhydrinate and domperidone:
dizziness, dry mouth, and nausea.

The following additional adverse reactions have been reported for dimenhydrinate:
drowsiness, lassitude, excitement and fixed drug eruption.

Interactions

Dimenhydrinate may enhance the effects of CNS depressant type drugs including alcohol, therefore concomitant usage should be avoided.

Fructose and glucose combination products

Fructose and glucose have an excellent safety profile, with the only limitation being their use in diabetic patients. While very safe, the combination product has limited efficacy in the treatment of nausea and vomiting. Its indication simply states that it "may be of assistance in the relief of nausea." It is not intended to treat vomiting.

CONCLUSIONS — NAUSEA AND VOMITING

Domperidone can be considered appropriate for sale to the general public as a Restricted (Pharmacist Only) Medicine for the symptomatic treatment of nausea and vomiting for the following reasons:

1. The general public can readily recognise the symptoms of nausea and vomiting.

2. The danger of masking underlying gastrointestinal conditions cannot be considered any greater than for example OTC analgesics possibly masking tumours, muscle damage or degenerative bone disorders.

3. Domperidone is well tolerated and has a very low incidence of adverse events reported locally and internationally during its extensive use since registration in Belgium in 1978 and New Zealand in 1984.

4. The consumer has a right to access of a convenient, effective and safe treatment option for acute uncomplicated conditions.

5. Domperidone will not present an increased danger to the consumer when used with advice from a Pharmacist, but without a medical consultation.

6. The proposed pack sizes and CMI/labelling are appropriate for the responsible and quality use of this medicine.

7. The extensive knowledge gained about the product, which far exceeds minimum standards for OTC consideration, means it is extremely unlikely that the medicine will behave in an unpredictable manner once reclassified to a Restricted (Pharmacist Only) Medicine.

8. Allowing less restrictive use of domperidone will not impact negatively on the safety of the community as a whole.

9. Domperidone is at least as safe and efficacious as other currently available Restricted (Pharmacist Only) Medicines for the treatment of nausea and vomiting and should be classified accordingly.

PART B2 – DYSPEPSIA

BENEFITS TO BOTH THE CONSUMER AND TO THE PUBLIC EXPECTED FROM THE PROPOSED CHANGE

The risk/benefit of domperidone is demonstrably favourable and in line with that of established OTC dyspepsia remedies, many of which are unclassified and available through grocery outlets. This risk/benefit is not likely to be adversely affected by domperidone being made available through pharmacies.

If this application is successful, it will be to the benefit of some OTC medicine users with this symptom complex of dysmotility-like dyspepsia. These sufferers will then be able to use a prokinetic agent instead of existing antacid mixtures, which is more logical and appropriate for this type of dyspepsia. Hence, domperidone is suitable for sale as a Restricted (Pharmacist Only) Medicine direct to the general public for the relief of symptoms associated with dysmotility-like dyspepsia.

EASE OF SELF-DIAGNOSIS OR DIAGNOSIS BY A PHARMACIST

The general public is experienced in using OTC medicines to treat dyspepsia. For many years advertising and consumer education campaigns have highlighted the symptoms of dyspepsia to consumers and it is now well accepted as a condition that is easily and safely treated with OTC medications.

The term dyspepsia encompasses several symptom complexes that often overlap. Three subgroups of dyspepsia have been defined. These are: ulcer like, reflux-like and dysmotility-like. In the first two categories patients recognise the symptoms of epigastric discomfort and heartburn whilst in the dysmotility group the predominate symptoms are fullness, nausea and bloating after meals.

Clearly, it is the symptoms that the patient recognises and the way these symptoms respond to treatment that are important when selecting an appropriate therapy. Symptoms that are related to gastric acid respond well to antacids and antisecretory drugs, while those associated with dysmotility do not. Conversely, clinical experience with prokinetic agents suggests that they are successful in relieving the dysmotility complex of symptoms. Therefore, in practice the sub group of patients with dyspepsia are at least partly defined by the way in which they respond to treatment. For this reason, an adequate description of the target symptoms is an acceptable way of defining the target population that would most benefit from a prokinetic agent.

Symptoms of dyspepsia are already represented in established indications for self-medication. A number of OTC pharmaceutical products, including Aludrox Plus™ suspension, Mucaine™, Mylanta™ and Mylanta II™ (Aluminium hydroxide, simethicone and magnesium hydroxide) specifically mention dyspepsia as part of their

labelling. A range of other OTC stomach remedies, including Roter™, Tums™ and Quickeze™ also describe their effectiveness in dyspepsia using consumer friendly terms such as feelings of stomach discomfort, including fullness, wind, heaviness, bloating and nausea. In addition, the H_2 antagonists, Apo-ranitidine™, Pepcid AC™ and Tagamet™ are available without prescription for the treatment of symptoms of acid related dyspepsia.

As evidenced by existing OTC products, it is clear that patients have a long established ability to correctly recognise the symptoms of dysmotility-like dyspepsia without medical supervision. Appropriate patient information describing the indication symptoms as well as contraindications, warning and precautions will facilitate quality use of this medicine. The proposed CMI (see Attachment 8) provides clear information and instructions to enable the patient to use the product correctly and exclude any conditions that may present in a similar way to dysmotility-like dyspepsia, but which are not suitable for treatment with domperidone.

Differential diagnosis

Dyspepsia is one of the most frequent complaints encountered in the general population. Epidemiological studies have reported prevalence rates that approach 25% annually if dyspepsia is restricted to those who have recurrent upper abdominal symptoms, and heartburn alone is excluded. Nevertheless, most people with dyspeptic symptoms do not seek medical attention and usually resort to OTC medicines, many of which are currently unclassified and available through grocery outlets.

Dysmotility-like dyspepsia is a heterogeneous disorder characterised by intermittent or chronic discomfort centred in the upper abdomen. Patients with this type of dysmotility-like dyspepsia often describe feelings of sickness and bloating, as well as stomach discomfort when eating, experienced as heaviness, fullness, trapped wind and belching. These symptoms often occur during or just after a meal. Arguably, the dysmotility symptom complex is less likely to indicate serious underlying disease than other dyspeptic symptoms such as heartburn and epigastric burning (see later).

The CMIs of currently approved OTC dyspepsia remedies such as H_2 antagonists (see Attachment 15 for ZANTAC™ CMI and Attachment 16 for PEPCIDINE M™ CMI) recognise that OTC consumers are able to differentiate the warning symptoms (such as unexplained weight loss and dysphagia) associated with more serious conditions. Since such a high proportion of patients are known to self-treat dyspepsia using OTC remedies, the availability of consistent and improved patient information in these newer products is likely to facilitate appropriate self-medication and encourage patients to consult with their GP when necessary.

Symptom duration is an important identifier of more serious disease. If symptoms respond to domperidone it is likely that treatment will be intermittent. The need to take any treatment for dyspepsia for longer than two weeks continuously suggests more

serious disease and a medical consultation is advisable. For this reason, we propose to limit continuous treatment to two weeks (consistent with the labels for newer dyspepsia treatments).

POTENTIAL FOR MASKING OTHER SERIOUS CONDITIONS

As discussed previously, dyspepsia is common complaint for which patients readily self-medicate. Due to the availability of other OTC medications for this indication, patients are already encouraged to recognise the signs and symptoms of the disorder and select an appropriate medication for themselves with or without the advice of a Pharmacist.

The risk of misdiagnosis of dysmotility-like dyspepsia is small, and if misdiagnosis does occur and self-medication begins, the risk of negative consequences is considered to be small. However, long term self management of 'gastric pain' is not encouraged. It is extremely difficult to differentiate between such pain and cardiac pain without proper medical examination.

Therefore, OTC domperidone is will not be labelled for treatment of upper abdominal pain, unlike the H_2 antagonists.

Overall

Appropriate patient information describing the indication symptoms as well as contraindications, warnings and precautions will facilitate self-diagnosis. The proposed CMI provides clear information and instructions to enable the patient to use the product correctly and allow them to recognise more serious symptoms that may require medical attention. Also Pharmacists are well positioned to intervene and refer these patients to their GP for full evaluation if necessary.

RELEVANT COMPARATIVE DATA FOR LIKE COMPOUNDS

H_2-Receptor antagonists — cimetidine, rantidine and famotidine

Currently there are three H_2 antagonists available to the consumer without a prescription – cimetidine, ranitidine and famotidine.

Cimetidine is classified as a Restricted (Pharmacist Only) Medicine, when sold in the manufacturer's original pack containing not more than 14 days supply. Ranitidine and famotidine are classified as Pharmacy Only Medicines, when sold in the manufacturer's original pack containing not more than 14 days supply.

All have slightly different approved indications but are basically used for short term symptomatic relief of indigestion, heartburn, dyspepsia, excess acid (hyperacidity), and prevention of these symptoms when associated with food and drink.

H_2 antagonists are currently the most effective OTC treatment for acid related dyspepsia. However, as discussed previously, they are not as effective as domperidone for the treatment of dysmotility-like dyspepsia.

Adverse effects

The following adverse reactions have been reported for cimetidine and domperidone:
Diarrhoea, headache, dizziness, skin rashes and gynaecomastia.

The following additional adverse reactions have been reported for cimetidine:
Tiredness, myalgia, reversible alopecia, hypersensitivity vasculitis and anaphylaxis, leukopenia (including agranulocytosis), thrombocytopenia, pancytopenia, aplastic anaemia, confusional states, small increases in plasma creatinine, hepatitis, fever, interstitial nephritis, pancreatitis, sinus bradycardia, tachycardia, heart block, hallucination and depression.

The following adverse reactions have been reported for ranitidine and domperidone:
Headache, nausea, constipation, diarrhoea, abdominal discomfort/cramps, dizziness, insomnia raised liver enzymes and rash.

The following additional adverse reactions have been reported for ranitidine:
Malaise, somnolence, vertigo, reversible mental confusion, depression, hallucinations, reversible effects on accommodation resulting in blurred vision, tachycardia, bradycardia, hypotension, AV block, asystole, interstitial nephritis and hepatotoxicity (with or without jaundice), thrombocytopenia, granulocytosis, neutropenia, aplastic anaemia, agranulocytosis or panycytopenia, sometimes with bone marrow hypoplasia or aplasia, arthralgia, myalgia, hypersensitivity reactions possibly resulting in urticaria, fever, angioneurotic oedema, bronchospasm, chest pain or anaphylactic shock and pancreatitis.

Regular supervision is recommended for patients taking NSAID concomitantly with ranitidine. Ranitidine may precipitate acute porphyric attacks and therefore should be avoided in patients with a history of acute porphyria.

The following adverse reactions have been reported for famotidine and domperidone:
Headache, dizziness, constipation, diarrhoea, dry mouth, nausea and/or vomiting, abdominal discomfort or distension, rash, pruritis, urticaria, insomnia and gynaecomastia.

The following additional adverse reactions have been reported for famotidine:
Anorexia, fatigue, liver enzyme abnormalities, cholestatic jaundice, anaphylaxis, angioedema, arthralgia, muscle cramps, reversible psychic disturbances including depression, anxiety disorders, agitation, confusion, hallucinations, toxic epidermal necrolysis, disorientation, decreased libido, paresthesia, somnolence, grand mal seizure, pancytopenia, leukopenia, thrombocytopenia and agranulocytosis.

Adverse reactions — summary

As evidenced above, the adverse reactions profiles of cimetidine, ranitidine and famotidine are all considerably less favourable than that of domperidone. That is, domperidone can be considered a safer medicine for short term treatment.

As previously discussed, domperidone is more efficacious than both antacids and H_2 antagonists in treating the dysmotility-like dyspepsia, and has a better adverse reaction profile than the H_2 antagonists that are already available without prescription or GP consultation. Therefore, we do not accept the conclusion of the Medsafe report that domperidone should remain a Prescription Medicine "because heartburn is better treated with antacids or H_2 antagonists which are also available OTC."

Interactions

Cimetidine

Cimetidine is well known for the several drug interactions it causes via the cytochrome P_{450} (microsomal) enzyme system. It is known to have caused clinically significant changes in the metabolism of some drugs by delaying their elimination and therefore increasing or prolonging blood concentrations of these drugs (for example, warfarin-type anticoagulants, phenytoin, theophylline, lidocaine and nifedipine). However, absorption of cimetidine is not significantly impaired by food or by concomitant administration of antacids at the usual recommended doses.

Ranitidine

Ranitidine does not interact with cytochrome P_{450} enzymes to any clinically significant degree when taken in recommended doses. However, sucralfate interferes with the absorption of ranitidine and should be given at least 2 hours after ranitidine.

Famotidine

Famotidine does not interact with the cytochrome P_{450} enzyme system. In addition, concomitant use of aluminium hydroxide/magnesium hydroxide at usual doses does not influence the pharmacodynamics or bioavailability of famotidine. Famotidine does not affect blood alcohol levels following oral ingestion of ethanol.

Domperidone

In vitro data suggest that the concomitant use of azole antifungals, macrolide antibiotics, HIV protease inhibitors and nefazodone with domperidone may result in increased plasma levels of domperidone. Domperidone is contraindicated in patients currently receiving oral ketoconazole. Since these potential interactions are not supported by clinical experience, they are unlikely to impact on the medicine's safety in the OTC environment. All interactions of domperidone can be adequately managed by following the proposed CMI.

Contraindications

As with domperidone and other medicines, cimetidine, rantidine and famotidine should not be used in patients with a known hypersensitivity to the medicine. In addition, cross sensitivity in the H_2 antagonist class of compounds has been observed. Therefore, once a patient experiences hypersensitivity to any of the H_2 antagonists, other medicines in this class cannot be taken by the patient.

Potential of H_2 antagonists to mask other serious conditions

Treatment with H_2 antagonists can mask the symptoms and allow transient healing of carcinomas of the stomach, thus delaying correct diagnosis of gastric cancer. The potential delay in diagnosis should be borne in mind in patients of middle age or older, with new or recently changed dyspeptic symptoms.

If patients have difficulty swallowing or if abdominal discomfort persists or becomes worse or new or additional dyspeptic symptoms develop, the underlying cause should be determined. Unlike the proposed indication for OTC domperidone, the H_2 antagonists are indicated for gastric pain. Long term self management of gastric pain is not encouraged. This is because it is extremely difficult to differentiate between such pain and cardiac pain without proper medical examination. Thus, the potential for domperidone to mask other serious underlying conditions is significantly lower than for the H_2 antagonists which are currently classified as Restricted (cimetidine) or Pharmacy Only (ranitidine and famotidine) Medicines.

General

As proposed with domperidone, therapy with H_2 antagonists should not exceed two weeks of continuous treatment without medical consultation.

<u>Antacids</u>

Antacids are frequently used by patients to self-treat all types of dyspepsia. However, of three randomised placebo-controlled studies that have been reported[7], all failed to show a significant effect of treatment, although there was improvement in both active and placebo treatment groups, reflecting the high placebo response in the condition. Therefore, although antacids have a more favourable safety profile, their efficacy in any type of dyspepsia is inadequate when compared to domperidone or H_2 antagonists.

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[7]

a) Gotthard R, Bodemar G, Brodin U, Jonsson K. Treatment with cimetidine, antacid or placebo in patients with dyspepsia of unknown origin. Scandinavian Journal of Gastroenterology, 23: 7-18, 1988

b) Nyren 0, Adami H, Bates S, Bergstrom R, Gustavsson S et al. Absence of therapeutic benefit from antacids or cimetidine in non-ulcer dyspepsia. New England Journal of Medicine, 314: 339-343, 1986

c) Weberg R, Berstad A. Low-dose antacids and pirenzepine in the treatment of patients with non-ulcer dyspepsia and erosive prepyloric changes. A randomised, double-blind, placebo-controlled trial. Scandinavian Journal of Gastroenterology, 23: 237-243, 1988

Optimal drug therapy of dysmotility-like functional dyspepsia

The symptoms of dysmotility-like dyspepsia have a high prevalence in the general population. However, as with other types of dyspepsia, only a small proportion of subjects with these symptoms require drug treatment. Medical treatment achieves at least partial relief of symptoms in the majority of patients.

It is logical and appropriate to use a prokinetic agent for patients with dysmotility-like symptoms. Domperidone has been widely used since its first international approval in Belgium in 1978 and New Zealand in 1984. Its clinical and post marketing safety database indicates that domperidone is effective and very well tolerated.

Treatment should be given for as short a period as possible. It is common to treat patents just until symptoms have resolved and then discontinue medication. Many patients with dysmotility-like dyspepsia have self-limiting symptoms, so intermittent treatment is often sufficient to achieve adequate control of the condition. Hence, the dosage in the proposed CMI and labelling of 10 mg up to three times daily and at night when required.

In general, if symptoms require treatment for longer than 2 weeks patients should be reevaluated. Hence, patients should be referred to their GP if they find they have to take domperidone continuously for more than 2 weeks.

CONCLUSIONS — DYSPEPSIA

Domperidone can be considered appropriate for sale to the general public as a Restricted (Pharmacist Only) Medicine for the treatment of the symptoms of dysmotility-like dyspepsia, for the following reasons:

1. The ability of the general public to recognise and appropriately treat the symptoms of the various types of dyspepsia is established with the use of other currently available OTC products. Domperidone will be used in an essentially similar manner to these products.

2. The potential for domperidone to mask other serious underlying conditions is significantly lower than for the H_2 antagonists, which are currently classified as Restricted or Pharmacy Only Medicines.

3. The danger of masking underlying gastrointestinal conditions cannot be considered any greater than for example OTC analgesics possibly masking tumours, muscle damage or degenerative bone disorders.

4. It is logical and appropriate to use a prokinetic agent for patients with dysmotility-like symptoms.

5. Domperidone is well tolerated and has a very low incidence of adverse events reported locally and internationally during its extensive use since registration in Belgium in 1978 and New Zealand in 1984.

6. The consumer has a right to access of a convenient, effective and safe treatment option for acute uncomplicated conditions.

7. Domperidone will not present an increased danger to the consumer when used with advice from a Pharmacist, but without a medical consultation.

8. The proposed pack sizes and CMI/labelling are appropriate for the responsible and quality use of this medicine.

9. The extensive knowledge gained about the product, which far exceeds minimum standards for OTC consideration, means it is extremely unlikely that the medicine will behave in an unpredictable manner once reclassified to a Restricted (Pharmacist Only) Medicine.

10. Allowing less restrictive use of domperidone will not impact negatively on the safety of the community as a whole.

11. Domperidone is as safe and efficacious as other currently available Restricted (Pharmacist Only) Medicines for the treatment of dyspepsia and should be classified accordingly.

PART B3 – GENERAL

LOCAL DATA AND SPECIAL CONSIDERATIONS RELATING TO NEW ZEALAND

Domperidone (MOTILIUM) 10 mg tablets have been available on prescription in New Zealand since June 1984. A copy of the current approved MOTILIUM Data Sheet is provided in Attachment 9.

The classification of domperidone was reviewed at the 21st meeting of the MCC in March 1999. Domperidone was placed on the agenda because it had been considered for reclassification to OTC status in the UK. As discussed above, the MCC review was undertaken without a formal submission from Janssen-Cilag. The MCC recommended that there should be no change to the classification of domperidone. A copy of the relevant minute is provided in Attachment 1.

Domperidone has well established efficacy for nausea and vomiting and dyspepsia. Domperidone also has an excellent safety profile.

INTERACTIONS WITH OTHER MEDICINES

Domperidone may interact with anticholinergic medicines as well as antacids and antisecretory agents, which should not be given simultaneously with domperidone because these medicines lower the bioavailability of domperidone. Since domperidone has gastro-kinetic effects it could influence the absorption of concomitantly orally administered medicines, particularly those of sustained release or enteric-coated formulations.

Interaction studies in healthy subjects have shown a marked inhibition of domperidone's first-pass metabolism by oral ketoconazole, as evidenced by an approximately three-fold increase in C_{max} and AUC of domperidone at steady state and a QTc prolongation of about 10-20 msec. Consequently, domperidone is contraindicated in patients currently receiving oral ketoconazole.

In vitro data suggest that the concomitant use of azole antifungals, macrolide antibiotics, HIV protease inhibitors and nefazodone with domperidone may result in increased plasma levels of domperidone. However, this is not supported by clinical experience.

CONTRAINDICATIONS

Domperidone should not be used:

- in patients with known hypersensitivity to domperidone
- in patients with prolactinoma (a prolactin-releasing pituitary tumour).
- in patients currently receiving oral ketoconazole

- whenever stimulation of gastrointestinal motility might be dangerous (such as in the presence of gastrointestinal haemorrhage, mechanical obstruction or perforation).

POSSIBLE RESISTANCE

None. The lack of possible resistance to domperidone means the usage of the medicine can increase without impacting negatively on the safety of the community.

THERAPEUTIC INDEX

The therapeutic index of domperidone is sufficiently wide to enable safe use by the consumer in the OTC environment.

ADVERSE EVENTS – NATURE, FREQUENCY, ETC.

Domperidone is well tolerated. This is illustrated by the very low incidence of adverse events reported locally and internationally during its extensive use since registration in Belgium in 1978 and New Zealand in 1984.

Domperidone tablets have an excellent safety profile. Medsafe considers in its March 1999 report that domperidone is safer than metoclopramide, and we also believe it is safer than prochlorperazine.

POST MARKETING EXPERIENCE

The latest Periodic Safety Update Report for domperidone (see Attachment 6) covers the period from 2 January 2003 to 1 January 2004, and covers an estimated exposure to domperidone in this review period of approximately 86.5 million treatment courses.

POTENTIAL FOR ABUSE

None. The lack of potential for abuse is of paramount importance with any OTC medicine. It is highly unlikely that consumers will self-medicate with domperidone for non therapeutic reasons, making it a safe medicine to be available without prescription.

POTENTIAL FOR MISUSE

The Medsafe report states that nausea and vomiting of unknown origin should not be treated with domperidone as the underlying cause may require further investigation and treatment. This is true of ongoing and reoccurring nausea and vomiting. As discussed previously, the labelling and professional promotion of the product will confine the use of OTC domperidone to nausea and vomiting episodes that are acute and non-recurring in nature. The proposed CMI clearly directs patients to seek medical advice if symptoms persist for longer than 48 hours. In addition, we recommend that patients also seek

medical advice should symptoms get worse, are not relieved or return. Furthermore, treating nausea and vomiting of unknown causes is no more harmful than for example treating pain of unknown cause with OTC analgesics.

POTENTIAL FOR COMMUNAL HARM

The availability of domperidone OTC will not lead to any community harm resulting from wider use of the medicine.

CONCLUSIONS

Domperidone can be considered appropriate for sale to the general public as a Restricted (Pharmacist Only) medicine for the symptomatic treatment of nausea and vomiting and for the treatment of the symptoms of dysmotility-like dyspepsia, for the following reasons:

GENERAL

1. Domperidone is well tolerated and has a very low incidence of adverse events reported locally and internationally during its extensive use since registration in Belgium in 1978 and New Zealand in 1984.

2. The consumer has a right to access of a convenient, effective and safe treatment option for acute uncomplicated conditions.

3. Domperidone will not present an increased danger to the consumer when used with advice from a Pharmacist, but without a medical consultation.

4. The proposed pack sizes and CMI/labelling are appropriate for the responsible and quality use of this medicine.

5. The extensive knowledge gained about the product, which far exceeds minimum standards for OTC consideration, means it is extremely unlikely that the medicine will behave in an unpredictable manner once reclassified to a Restricted (Pharmacist Only) Medicine.

6. Allowing less restrictive use of domperidone will not impact negatively on the safety of the community as a whole.

7. Domperidone is at least as safe and efficacious as other currently available Restricted (Pharmacist Only) Medicines for the treatment of nausea, vomiting and dyspepsia, and should be classified accordingly.

NAUSEA AND VOMITING

1. The general public can readily recognise the symptoms of nausea and vomiting.

2. The danger of masking underlying gastrointestinal conditions cannot be considered any greater than for example OTC analgesics possibly masking tumours, muscle damage or degenerative bone disorders.

DYSPEPSIA

1. The ability of the general public to recognise and appropriately treat the symptoms of the various types of dyspepsia is established with the use of other currently available OTC products. Domperidone will be used in an essentially similar manner to these products.

2. The potential for domperidone to mask other serious underlying conditions is significantly lower than for the H_2 antagonists, which are currently classified as Restricted or Pharmacy Only Medicines.

3. It is logical and appropriate to use a prokinetic agent for patients with dysmotility-like symptoms.

ATTACHMENTS

Attachment 1	Minute from the 21st meeting of the MCC held in March 1999
Attachment 2	Report on domperidone prepared by Medsafe for consideration by the MCC in March 1999
Attachment 3	Adverse reaction reports for domperidone received by CARM up to 30 June 2003, plus line summary details of reports received up to 30 September 1999 *[NB an updated listing has been requested from CARM and will be provided when this becomes available]*
Attachment 4	Adverse reaction reports for metoclopramide received by CARM up to 30 June 2003
Attachment 5	Adverse reaction reports for domperidone received by the Therapeutic Goods Administration (TGA) in Australia up to 10 January 2005
Attachment 6	Periodic Safety Update Report for domperidone (MOTILIUM™), period 02 January 2003 to 01 January 2004. Johnson & Johnson Pharmaceutical Research & Development, USA. 18 February 2004. *[NB copy of appendices available on request]*
Attachment 7	Current approved "Prescription Medicine" labelling for MOTILIUM
Attachment 8	Proposed Consumer Medicine Information for OTC MOTILIUM
Attachment 9	Current approved MOTILIUM Data Sheet, dated February 2003
Attachment 10	Postmarketing surveillance of exposure to domperidone during pregnancy. Janssen Research Foundation. 27 November 1997
Attachment 11	Current MAXOLON™ Data Sheet, dated 29 August 2001 (Pacific Pharmaceuticals Ltd)
Attachment 12	Current STEMETIL™ Data Sheet, dated 5 April 2000 (Aventis Pharma Ltd)
Attachment 13	Current BUCCASTEM™ Data Sheet, dated 11 July 2002 (Reckitt Benckiser Ltd)

Attachment 14 Current VALOID™ Injection, Data Sheet, dated 24 March 2004 (AFT Pharmaceuticals Ltd)

Attachment 15 Current ZANTAC™ Tablets Consumer Medicine Information, dated July 2004 (Glaxo Wellcome Ltd)

Attachment 16 Current PEPCIDINE M™ Consumer Medicine Information, dated October 2001 (Merck Sharp & Dohme Ltd)