

**Submission for  
Reclassification  
of  
Xenical®  
(Orlistat capsules 120mg)**

**To  
Pharmacist Only Medicine  
for  
Weight Control in Adults**

**December 2003**

**Prepared for: Medicines Classification Committee  
Ministry of Health**

**Prepared by: Roche Products (New Zealand) Limited**

**Executive Summary**

## **Part A**

Application is made by Roche Products (New Zealand) Limited to the Medicines Classification Committee for the reclassification of the medicine orlistat, the trade name of which is Xenical®, in New Zealand. Reclassification from Prescription Medicine to Pharmacist Only Medicine is sought for Xenical 120mg capsules, with no restriction on pack size. The proposed classification scheduling is:

Part I	Orlistat, except where included in Part II
Part II	Orlistat in oral preparations for weight control purposes containing 120mg or less of orlistat.

The proposed indication for this Pharmacist Only Medicine classification is:

***“Xenical is indicated for the treatment of obese adults with a body mass index (BMI)  $\geq$  30, and overweight adults with a BMI  $\geq$  27 in the presence of other risk factors, in conjunction with a mildly hypocaloric diet. Xenical is effective in weight control, including weight loss, weight maintenance and prevention of weight regain.”***

The first sentence of this proposed indication is identical to that currently approved in Australia. The second sentence has been derived from the current approved weight control indication for Xenical in New Zealand, and has been added as an important clarification of the therapeutic purpose of Xenical.

Xenical is a well-tolerated medicine that requires few warnings in order to be used safely. The following label warning statements are proposed for Xenical as a Pharmacist Only Medicine:-

- People taking medicines by mouth for diabetes should check with a doctor or pharmacist before taking Xenical.
- Do not use Xenical if your uptake of essential nutrients is lower than it should be (chronic malabsorption syndrome) or you have a blockage in your bile duct (cholestasis).
- People taking medicines containing cyclosporin, amiodarone or blood thinning agents (anticoagulants) should check with a doctor or pharmacist before taking Xenical.
- Xenical is not recommended for pregnant or breastfeeding women.

These proposed statements for the labelling are consistent with the Contraindications, Warnings and Interactions contained in the proposed Xenical Data Sheet.

Orlistat is currently approved in 93 countries world-wide, and at the time of this submission is a Prescription Medicine in all of these countries. However, a recommendation to reclassify orlistat to a Pharmacist Only Medicine was made in Australia by the NDPSC at the 39<sup>th</sup>

meeting in October 2003. The proposed scheduling in Australia is identical to that proposed above.

Xenical was approved for distribution in New Zealand on 2<sup>nd</sup> April 1998, and approximately 60,000 New Zealanders have been treated with Xenical since it was first introduced. World-wide almost 16 million people have been treated with Xenical.

Currently, no other products containing orlistat are available in New Zealand. As such, reclassification of Xenical will not affect other products in the New Zealand market.

## **Part B**

### **The Body Size of New Zealanders, and its Impact on their Health and Wellbeing**

Over half (52%) of the New Zealand population is overweight or obese. The body size of New Zealanders is increasing, with the mean Body Mass Index (BMI) of New Zealanders being 25.0 kg/m<sup>2</sup> in 1989, 26.1 kg/m<sup>2</sup> in 1997 and projected to be 27.4 kg/m<sup>2</sup> by 2011. For New Zealand's Maori population average BMI in 1997 was approximately 28.9 kg/m<sup>2</sup>, whereas by 2011 it is estimated to increase to 30.6 kg/m<sup>2</sup>. The BMI for the Maori population is increasing at a faster rate than that of non-Maori. By 2011 the 'average' New Zealander is likely to be considered overweight, and the prevalence of obese New Zealanders is likely to have increased substantially over current levels.

Body Mass Index is recognised as a risk factor for ischaemic heart disease, ischaemic stroke, diabetes and post-menopausal breast and colorectal cancer. Excess body fat is considered one of the most important *modifiable* risk factors for these diseases. Other diseases recognised as having a causal relationship with BMI are hypertensive heart disease, osteoarthritis, endometrial cancer, kidney cancer, back pain, menstrual disorders, infertility, dermatitis and gallstones. Ischaemic heart disease and diabetes have been shown to be the greatest risks to overweight or obese New Zealanders, both with a disproportionate impact on the Maori population. In 1997, 3154 deaths have been attributed to 'high' BMI – this represents approximately 11% of all deaths for that year.

A 1 kg/m<sup>2</sup> lower BMI is estimated to be associated with:

- a lower risk of type 2 diabetes of 32% in younger adults (25 – 34 years), dropping to a 17% lower risk in adults aged 75 years and over.
- a lower risk of ischaemic stroke of 13% in younger adults (25 – 34 years), dropping to a 4% lower risk in adults aged 75 years and over.
- a lower risk of ischaemic heart disease of 12% in younger adults (25 – 34 years), dropping to a 4% lower risk in adults aged 75 years and over.
- a 3% lower risk of colorectal cancer
- a 3% lower risk of breast cancer in post-menopausal women (aged 50 years and over).

Being overweight or obese is a significant cause of illness and death in New Zealand, and as such, costs to the individual and the health system are likely to be high. Any impact on reducing the prevalence or degree of being overweight or obese will provide significant benefits. A model that assumed intervention measures could reduce the forecast increase in BMI by 0.3 kg/m<sup>2</sup> in 2011, estimated that 385 deaths could be prevented each year from 2011, if this reduction in the increase in BMI could be achieved. It appears that New Zealand has a growing health problem, at least partially based on the body size of its population.

Depression and binge-eating disorder are more prevalent amongst obese people, and obese people tend to report feelings of low self-esteem. Additionally, overweight or obese people suffer from discrimination – they are less likely to be married, have lower household incomes, pay higher insurance premiums and may suffer public embarrassment with such things as public seating being too small. While possibly not immediate health concerns, these issues contribute to reduced enjoyment of life and may have a significant impact on some individuals.

### **The Need for Xenical to Become a Pharmacist Only Medicine**

Lowering BMI has the potential to go some way towards fulfilling 6 of the Government's 13 population health objectives – viz:

- improve nutrition
- reduce obesity
- increase the level of physical activity
- reduce the incidence and impact of cancer
- reduce the incidence and impact of cardiovascular disease
- reduce the incidence and impact of diabetes

Reducing the increase in mean population BMI is recognised as a multifactorial problem requiring a combination of environmental, social and behavioural interventions. It is also recognised that a many-pronged approach will be required.

Individual New Zealanders are also concerned about their weight. In addition to the number of people that are overweight or obese, the plethora of aids available to assist with losing weight, including diet programmes, herbal remedies/dietary supplements and meal replacements suggest a large amount of activity directed at weight loss. There is evidence to suggest that New Zealander's level of concern about their weight, and the numbers trying to lose weight, are increasing.

Removing barriers to the use of Xenical by obese individuals, and those that are overweight and have other risk factors, would contribute positively to the well-publicised desires of Government and individuals for weight control. One barrier to treatment with Xenical is the need to visit a doctor to obtain a prescription, with the inherent problems of making an appointment and so incurring a delay in treatment, transportation and cost. This barrier is present not only for initiating treatment, but also for continuing therapy.

Patients can be reluctant to discuss their overweight state with their doctor, fearing that they will not be taken seriously or treated with respect. Doctor's, also, can be reluctant to initiate

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discussing a patient's overweight state. Reclassification of Xenical to a Pharmacist Only Medicine would remove this reluctance between the doctor and patient to discuss the matter as the pharmacist – patient relationship is not as formalised as the doctor – patient relationship. Some patients may find it easier to consult a pharmacist.

Improving access to Xenical by reclassifying it as a Pharmacist Only Medicine will remove many of the barriers noted above. Furthermore, direct access to Xenical through reclassification to a Pharmacist Only Medicine provides to the patient opportunity to take greater control of their overweight state, therefore gaining better compliance so that the chance of successful weight management is increased.

Greater access to a clinically proven, safe and effective treatment for their condition, such as Xenical, is an important element in the armamentarium of motivated overweight and obese people wanting a self-care option.

The reclassification of pharmaceutical medicines from prescription to over-the counter status is known to substantially increase patient access and use. The Medicines Classification Committee has already shown willingness to apply this concept in its reclassification of nicotine patches and gum from Pharmacy Medicine to General Sales Medicine in May 2000. Allowing patients direct access to Xenical will lower health care costs by reducing visits to physicians and by reducing the long-term medical complications of obesity. Additionally, increasing access to Xenical is likely to improve the mortality and morbidity of New Zealanders, resulting in a clear public health benefit in addition to lowering public health costs.

## **The Suitability of Xenical as a Pharmacist Only Medicine**

Overweight or obese people can recognise their condition through their own observations, and likewise in many instances a pharmacist could confirm this diagnosis visually. If not, the pharmacist can, in a short time establish the patient's BMI and presence/absence of comorbidities and so confirm the patient's diagnosis. At the same time, by reviewing the proposed Xenical Pharmacist Only Medicine carton label with the patient, the pharmacist and patient together can determine the applicability of contraindications and warnings and so establish the patient's suitability for treatment with Xenical. Pharmacists are well-trained and experienced in making these kinds of decisions, and subsequently dispensing appropriate medications, referring to other health professionals and/or providing counselling as needed. Roche is confident that pharmacists have the ability to apply their training and experience to the distribution of Xenical as a Pharmacist Only Medicine. Consequently, use of Xenical as a Pharmacist only Medicine is expected to be safe and appropriate.

There is some question as to whether being overweight or obese can be considered as a minor or self-limiting problem. However, body weight reduction is frequently attempted in Western society. Many weight reduction programmes, courses and products are currently available to the general public and do not require the involvement of a health professional for commencement. Many weight loss treatments currently available lack clinical evidence of efficacy. Reclassification of Xenical to a Pharmacist Only Medicine would improve the current situation for these over-the counter customers. For the first time the overweight or obese consumer would have available an intensively-researched, clinically-proven, well-supported aid to the common practice of attempting to lose weight and keep it off through the use of over-the counter products.

In the same way that overweight and obese people can generally diagnose their own condition, so they can monitor their own condition and make decisions regarding switching from weight loss to weight maintenance, possibly with the assistance of pharmacists or other health care professionals that may be involved with their weight loss programme.

Pharmacist Only Medicines are not kept within public reach in pharmacy, must be obtained through consultation with a pharmacist, and the sale must be recorded on a register. All of these measures lessen the possibility of non-overweight individuals purchasing and using Xenical as a Pharmacist Only Medicine.

Although unlikely, should inappropriate use of Xenical by non-overweight individuals occur, it appears that benefits may still accrue to the individual as benefits of weight reduction have been demonstrated to BMI's as low as 20 kg/m<sup>2</sup>. Such use is likely to be self-limiting within a short period of time as it would quickly become obvious to the pharmacist that the individual constituted an inappropriate patient, and further supply of Xenical should not be provided.

Xenical must be taken in conjunction with a low-fat, mildly hypocaloric diet. Many sources of information are available to assist the consumer in maintaining such a diet, including the pack insert, the Xenical Support Programme, the patient's pharmacist or doctor, and possibly, with the recently developed structure of Primary Healthcare Organisations, practice nurses and dietitians.

People suffering from weight reduction syndromes such as anorexia nervosa, bulimia or laxative abuse may be tempted to try Xenical. However, many of these people would be identified as unsuitable for treatment by the pharmacist, and because of its mode of action Xenical does not represent a long-term threat to these people.

In clinical trials, Xenical has been demonstrated to be an effective aid to weight management. Outside the unique environment of clinical trials, the Xenical Support Programme is used to collect sample data on the weight loss of Xenical users who have registered with the programme in New Zealand. Trends that are apparent in Xenical clinical trials are also apparent in this Xenical Support Programme data – that the most weight is lost in the first 3 months, that more weight is lost by those people who stay on Xenical than by those that stop taking Xenical, and that there is on-going weight loss for those people that do not stay on Xenical (although not as great as if they had continued taking Xenical). By inference, the behaviour modifications made while taking Xenical of eating healthier food and/or more physical activity are maintained after the patient has stopped taking Xenical.

Thus, results obtained from using Xenical outside clinical trials in New Zealand (on average, 7.5 kg lost in 3 months) mirrors results obtained within clinical trials, confirming the overall efficacy of Xenical in weight management. This observation compares favourably with the situation for other over-the-counter weight loss products, as there is little data to support the efficacy or safety for either short or long term weight loss using these other agents.

Xenical is a medicine with few contraindications – they are chronic malabsorption syndrome, cholestasis and patients with a known hypersensitivity to the medicine. Roche will provide pharmacists with information on identifying the symptoms of these diseases, and should they be suspected an appropriate referral would be expected.

Xenical is not to be used in pregnancy and lactation, due to the absence of clinical data for these situations. Pharmacists have the ability to establish the presence of pregnancy or lactation as appropriate when reviewing the product labelling with the consumer.

Weight loss induced by Xenical can be accompanied by improved metabolic control in type 2 diabetics, which might allow or require reduction in the dose of oral glycaemic medication. Therefore, a warning as to this possibility is clearly listed on the back panel of the proposed carton label, and patients are instructed to check with a doctor or pharmacist before taking Xenical. Roche Products (New Zealand) Ltd will inform pharmacists of this effect. Weight reduction and decreased need for medication are both very positive health benefits, and so justify the increased monitoring and dosage adjustment that may be required.

Weight loss induced by Xenical (and the concurrent improvement in diet and/or increased physical activity) may also allow or require a reduction in dose levels of antihypertensive and/or antihypercholesterolaemic medicines. The proposed Xenical Consumer Medicine Information advises people to inform their doctors that they are taking Xenical. It is expected that these effects would be captured during routine patient monitoring by their doctors for these conditions, and at that time the doctor can instigate appropriate adjustments if required.

In clinical trials, adverse reactions to Xenical were largely gastrointestinal in nature and related to the pharmacologic effect of orlistat preventing the absorption of ingested fat. Commonly observed events were oily spotting, flatus with discharge, faecal urgency, fatty/oily stool, oily evacuation, increased defaecation and faecal incontinence. The incidence of these side effects increased as the fat content of the diet increased. These adverse

gastrointestinal reactions were generally mild and transient. They occurred early in treatment (approximately one third to one half occurred within the first week) and most patients experienced only one episode.

The proposed pack insert for Xenical as a Pharmacist Only Medicine details these side effects and how to minimise them, and the Xenical Support Programme is also available to counsel patients on the appropriate lifestyle measures to minimise these side effects. Additionally, Roche information to pharmacists includes advice on counselling patients to avoid these gastrointestinal adverse events.

Consumption of a low fat diet decreases the likelihood of experiencing adverse gastrointestinal events. These gastrointestinal side effects act as a feedback mechanism and may help patients to monitor and regulate their fat intake, and thereby contribute to their ultimate goal of losing weight.

In a long term clinical trial (four years), with the exception of gastrointestinal effects, the distribution of adverse events among all body systems was similar in both treatment and placebo groups.

Serious adverse events that may be associated with treatment are rare. They include hepatitis, allergic reaction and bullous eruption. All three of these side effects exhibit frank symptoms that would result in visiting a doctor for most cases, where treatment of the side effects and withdrawal of Xenical if appropriate can be effected.

New Zealand adverse event reports do not provide any basis for safety analysis or changes to the Xenical data sheet, and are consistent with the adverse events reported from clinical trials.

Given its poor systemic absorption, very wide therapeutic index and the absence of serious side effects, the risk of harm from overdose with Xenical is low. Orlistat is a well-tolerated medicine with a low toxicity profile. Additionally, Xenical is supplied in blister packaging, lowering the potential for overdose (particularly in small children) even further.

Xenical has a limited number of other medicines with which it may interact. – namely warfarin, cyclosporin and amiodarone – and so identifying possible interactions for Xenical is uncomplicated. This has been further simplified by clearly listing the possible interactions on the product label, so that the pharmacist and patient can identify any possible interactions and take appropriate action when reviewing the label together. Decreases in the absorption of vitamin D, E, and  $\beta$ -carotene have been observed when co-administered with Xenical. These vitamins should be taken at least two hours after the administration of Xenical or at bedtime. This information is clearly stated in the proposed Xenical Consumer Medicine Information and pack insert.

Given the mechanism of action and the lack of a systemic effect, and the low potential for abuse or inappropriate use of this medicine, the possibility of Xenical causing communal harm appears minimal.

In conclusion, Xenical is a safe and effective product that fits well into the profile of an over-the-counter medicine. Reclassification of Xenical to a Pharmacist Only Medicine is therefore a logical and appropriate step to provide greater consumer access to a clinically proven weight control product. Greater access to Xenical is expected to provide improved health status for Xenical users through lowering their BMIs. Public health benefits in the form of fewer doctor



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visits, and potentially a lower health burden through reduction of diseases associated with increasing BMI, are expected.