



Bayer HealthCare
Consumer Care

**Rescheduling Application
for**

**Canesten[®]
Clotrimazole
Vaginal Products**

January 2006

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EXECUTIVE SUMMARY

Bayer New Zealand Limited proposes that the Canesten range of antifungal products for vaginal thrush should be rescheduled in New Zealand from Pharmacist Only Medicines to Pharmacy Medicines. The proposal includes vaginal cream products, vaginal pessary products and a combination vaginal pessary and topical cream product. A similar proposal HAS BEEN submitted to the NDPSC in Australia and will be considered at its February 2006 meeting.

Clotrimazole in vaginal presentations IS already classified less restrictively, compared to New Zealand, in a number of countries, including the USA (equivalent to General Sales) and Canada (equivalent to Pharmacy Medicine). Of key interest is recent reclassification in the United Kingdom, where in 2004 and 2005 two combination products became equivalent to General Sales Medicines.

Clotrimazole was first synthesized in 1967, and is now used extensively as a highly effective antifungal agent in New Zealand and throughout the world. Systemic absorption of topically applied clotrimazole is extremely low, and any absorbed drug is rapidly metabolised by the liver. Due to this favourable pharmacokinetic profile, the range and incidence of side effects experienced with clotrimazole are very small, and interactions with other medicines are unknown. Furthermore, clotrimazole is relatively safe for use in pregnancy, and is a Category A medicine in Australia. There are a number of other clotrimazole products in New Zealand besides Canesten.

In order to facilitate the switch to Pharmacy Medicine, Bayer proposes to change the labelling to performance-based labelling and to rewrite the product Consumer Medicine Information and pack inserts to maximise consumer comprehension and compliance for these medicines. Additional warnings are envisaged to cover the situation where multiple occurrences of vaginal thrush may be symptomatic of a more serious underlying disease.

Vulvovaginal thrush is a common condition that causes a distressing range of recognisable symptoms, including itching, burning, soreness and redness of the vulva along with a white odourless vaginal discharge. While definitive diagnosis of the condition can only be made with the aid of laboratory findings, for many patients a delay in treatment is unacceptable, and often treatment is initiated immediately. If such treatment is not effective, this observation is subsequently used as a diagnostic tool. Clotrimazole for vaginal use has been a Pharmacist Only Medicine in New Zealand since 1992, with the recommendation to see a doctor if it is the first infection – thus, the ability of the consumer to recognise thrush, having experienced it once, is well-established.

With approximately 13 years experience in New Zealand as a Pharmacist Only Medicine, clotrimazole is well-suited to be considered for a Pharmacy Medicine classification. Such a classification would provide the consumer with greater access to the medicine and greater ability to review the range and select a product that meets their personal requirements. Additionally, all other indicators being favourable, classification to Pharmacy Medicine would release pharmacist's from the need to participate in every clotrimazole sale for vaginal thrush, conveying a public benefit by allowing them time to focus on higher needs customers.

Clotrimazole for vaginal use fulfils the criteria for a Pharmacy Medicine – it is suitable for self-treatment of a minor ailment, symptoms are capable of being monitored by the consumer, it has an extremely low abuse potential, a low and well-characterised incidence of adverse effects, the only contraindication is allergy, interactions with other medicines are unknown, and there is a low risk of compromising the medical management of other diseases.

Inappropriate use is an area that warrants discussion as misdiagnosis is a potential problem. Bayer has addressed this issue through labelling, providing the consumer not only with symptoms of vaginal thrush, but also with a list of symptoms that are not usually associated with vaginal thrush. The labelling stresses that if symptoms do not start to resolve within 4 days the patient should see a doctor. Pharmacy Assistants can effectively support the labelling message. Thus, the outcome of any condition misdiagnosed by the consumer is likely to be a delay in diagnosis and treatment of 4 days – while possibly uncomfortable, the potential for harm to the consumer is slight.

The risk of masking a serious disease also warrants further discussion. Recurrent thrush can be a symptom of more serious disease, such as diabetes or immunosuppression. Bayer intends to address this possibility through Consumer Medicine Information, the pack insert and Pharmacy Assistant training. All of these communication channels can be used to effectively refer the consumer back to the pharmacist, or a doctor, if vaginal thrush is recurrent.

Bayer proposes a four stage programme to facilitate the transition of Canesten products for vaginal use to Pharmacy Medicines – improve the labelling, improve the Consumer Medicine Information and consequentially the pack insert, training for Pharmacy Assistants and make information available to consumers to promote appropriate use of the product.

Clotrimazole is already well-established in New Zealand as Pharmacy Medicine for topical application, and indeed is a General Sales Medicine for some indications. Bayer believes that the product is entirely suitable to become a Pharmacy Medicine for vaginal use as well.

PART A

This submission to the New Zealand Medicines Classification Committee is to seek rescheduling of the following products:-

A1. Name of the Medicine

The International Non-Proprietary Name of the medicine is clotrimazole.

The proprietary or brand name is Canesten®. Canesten is an umbrella brand name that covers a number of antifungal products. This application is specifically related to Canesten Clotrimazole products for vaginal use. The registered trade names of the Canesten vaginal products are:-

Canesten Clotrimazole Thrush Treatment 6 Day Cream
Canesten Clotrimazole Thrush Treatment 6 Day Pessary
Canesten Clotrimazole Thrush Treatment 3 Day Cream
Canesten Clotrimazole Thrush Treatment Once (vaginal cream)
Canesten Clotrimazole Thrush Treatment Once (pessary)
Canesten Clotrimazole Thrush Treatment Once Pessary + Cream

A2. Name of the Company

This submission is made by:-

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A3. Dose Forms, Strengths and Pack Sizes

This rescheduling submission applies to two different dose forms of Canesten Clotrimazole Thrush Treatment – vaginal cream and vaginal pessaries.

Both of these dose forms are presented in different strengths:-

Vaginal Cream

Available strengths are 10 mg/g (1% cream), 20 mg/g (2% cream) and 100 mg/g (10% cream).

Vaginal Pessaries

Available strengths are 100 mg pessaries and 500 mg pessaries.

Additionally, a combination product of one 500 mg pessary and a 10 g tube of topical clotrimazole 1% cream is available, and this combination product would also be affected by the proposed classification change.

All of these products are marketed in pack sizes that represent one course of treatment. No products are marketed in pack sizes of more than one treatment, and there is no intention to develop such pack sizes.

In summary, the following Canesten products are proposed for reclassification:-

- Canesten Clotrimazole Thrush Treatment 6 Day Cream,***
clotrimazole 10 mg/g vaginal cream, one tube of 35 g cream
plus six applicators
- Canesten Clotrimazole Thrush Treatment 6 Day Pessary,***
clotrimazole 100 mg pessary, six pessaries plus one applicator
- Canesten Clotrimazole Thrush Treatment 3 Day Cream,***
clotrimazole 20 mg/g vaginal cream, one tube of 20 g cream
plus 3 applicators
- Canesten Clotrimazole Thrush Treatment Once,***
clotrimazole 100 mg/g vaginal cream, one tube of 5 g cream
plus one applicator
- Canesten Clotrimazole Thrush Treatment Once,***
clotrimazole 500 mg pessary, one pessary plus one applicator
- Canesten Clotrimazole Thrush Treatment Once Pessary + Cream,***
clotrimazole 500 mg pessary plus clotrimazole 10 mg/g topical
cream, one pessary and one applicator plus one tube of 10 g
cream

A4. Indications

All of the Canesten products proposed for reclassification have the same approved indication – namely:-

“Canesten provides effective treatment of vaginal thrush infections.”

For the combination product, in which a topical cream product is also available, the approved indication is:-

“Canesten provides safe and effective treatment of candidal infections of the vagina and vulvovaginal, and sexual partner.”

The only purpose of these vaginal products is treatment of vaginal thrush. For the proposed reclassification definition of the indication and definition of the administration route effectively amount to the same thing.

A5. Classification

The current classification of clotrimazole, taken from the Medsafe Web site on 13 December 2005, is:-

Clotrimazole, except when specified elsewhere in this Schedule	Prescription
Clotrimazole; for vaginal use	Restricted
Clotrimazole; for dermal use except in medicines for tinea pedis only	Pharmacy Only
Clotrimazole; for dermal use in medicines for tinea pedis only	General Sale

The classification sought for clotrimazole is:-

<i>Clotrimazole, except when specified elsewhere in this Schedule</i>	<i>Prescription</i>
<i>Clotrimazole; for vaginal use, and dermal use except in medicines for tinea pedis only</i>	<i>Pharmacy Only</i>
<i>Clotrimazole; for dermal use in medicines for tinea pedis only</i>	<i>General Sale</i>

Clearly, the proposed change applies only to vaginal use of the medicine, and as previously discussed applies only to the treatment of vaginal and vulvovaginal thrush. The proposed change is a less restrictive classification of the medicine – justification for this less restrictive classification is provided in Part B of this submission.

Note that a submission proposing effectively the same down-scheduling of clotrimazole in Australia was made to the NDPSC in October 2005 and is due to be considered at their February 2006 meeting. Bayer Australia Limited has received an evaluation report of the submission made to NDPSC, and has responded to the evaluation report. Copies of the NDPSC evaluation report and the company response are provided in Appendix 1. The NDPSC evaluation report relies heavily on a paper by Ferris DG et al – Appendix 1 also provides a copy of this paper, and subsequent Letters to the Editor expressing concern regarding the study design and recruitment methods, and questioning the validity of the results and conclusions drawn.

A5.1 Classification Status in Other Countries

Clotrimazole vaginal preparations are available globally, mostly as general sales or OTC medicines. The table on the next page presents the legal classification of clotrimazole vaginal preparations in selected countries.

Status of Clotrimazole in Vaginal Preparations in Selected Countries

Country	Current Classification	Year of Switch from Prescription
Australia	Schedule 3 (Pharmacist Only Medicine)	1994
New Zealand	Restricted Medicine (Pharmacist Only Medicine)	1992
USA	OTC for 1% cream and 200mg pessaries (equates to General Sales Medicine in New Zealand)	1990
Canada	Schedule III (equates to Pharmacy Only Medicine in New Zealand)	1994
Austria	OTC - up to 0.5g per dose	2003
Belgium	OTC	
Denmark	OTC	1996
Finland	OTC - up to 2% cream and pessary	1994
France	OTC - maximum dose 200mg, up to 1.2g per pack	
Germany	OTC	1994
Ireland	OTC - vaginal candidiasis only	
Portugal	OTC	1995
Sweden	OTC	1994
UK	OTC (equates to a Pharmacy Medicine in New Zealand). General Sale – 500 mg pessary + 2% cream for treatment of vulvovaginal candidiasis. General Sale – 10% vaginal cream + 2% external cream	1992 2004 2005(?)
Switzerland	OTC for recurrent therapy of vaginal fungal infections - 2% cream, 1 x 500 mg or 3 x 200 mg pessary	1998

Table adapted from AESGP/WSMI publications <http://www.aesgp.be> status 18 October 2004 and data on file.

In the United Kingdom, vaginal products generally are classified as pharmacy medicines, with the designation 'P'. However MHRA have recently approved the general sale (GSL) of two combination packs. The first was a combination of a single 500 mg dose pessary and 2% cream (marketed as Canesten Combi). More recently a second combination being a 10% internal cream and 2% external cream (marketed as Canesten Complete) was granted GSL status. These GSL products can be sold in supermarkets as well as pharmacies without a pharmacist being present. Appendix 2 to this submission contains documentation of the decision to reclassify the combination pessary plus cream in the UK – the relevant Expert Statement, MCA briefing document, meeting report, reclassification summary and MHRA letter dated 17 July 2003 are provided. Additionally, the UK switch approval letter is provided.

These figures demonstrate that since 1990 there has been a world-wide trend towards less restriction of clotrimazole treatments for vaginal thrush, and in many instances this trend has embraced classifications where the customer can self-select and purchase the product without the intervention of a healthcare professional.

A6. Extent of Usage

A6.1 Usage in New Zealand

Accurate sales data for Canesten products in New Zealand is not available before 2002, due to a computer systems change. Sales volumes from 2002 onwards are:-

Sales ex-Manufacturer (units)

Product	2002	2003	2004	2005 (est. total)
Canesten Once Cream 5g Canesten 3 Day Cream 20g Canesten 6 Day Cream 35g Canesten Once Pessary 500mg Canesten 6 Day Pessary 100mg Canesten Once Pessary + Cream	C O N F	D E N T I	A L	
TOTAL				

Each unit sold represents a complete thrush treatment. Thus, in 2004 approximately [CONFIDENTIAL] occurrences of vaginal thrush were treated with a Canesten product in New Zealand, and over the last 4 years approximately [CONFIDENTIAL] occurrences were treated. New Zealand has considerable clinical experience with these products.

While Bayer considers changing the classification of clotrimazole may have some effect on the relative usages of different thrush treatment products, the overall usage of vaginal thrush treatment is not expected to increase appreciably. The symptoms of thrush are distressing and cause considerable discomfort. In the majority of cases women experiencing symptoms will seek some sort of therapy for rapid relief. Thus, the incidence of untreated vaginal thrush is likely to be small, and the potential to increase the overall market size for vaginal thrush treatments limited.

A6.2 Usage World-Wide

World-wide, the number of treatments with a Canesten product for the period September 2004 – August 2005 is almost 50 million (see Periodic Safety Update Report – Appendix 7). Clearly, Canesten is a very widely used product, and much of this usage would have derived from an over-the-counter purchase, with or without the involvement of a health professional.

A6.3 Regulatory Status

Clotrimazole is an antifungal agent synthesised in 1967 by Bayer AG in a systematic investigation of imidazole compounds. In 1973 clotrimazole was brought on to the market initially in the United Kingdom and then in Germany.

Today clotrimazole is sold under the tradename Canesten in over 100 countries, in the United States of America under the tradename Mycelex[®] and in Japan as Empecid[®]. A full tabulation of the marketing authorisation status of clotrimazole products can be found in the PSUR appended.

A7. Labelling

All of the Canesten Clotrimazole Thrush Treatment products that are the subject of this submission are currently available on the New Zealand and Australian markets. The products in each market are identical, and in all cases the labelling is Trans-Tasman i.e. the same label is used for both countries. Should this

submission for rescheduling of the Canesten Clotrimazole Thrush Treatment products to Pharmacy Only Medicines be successful, Bayer plans to change the current labelling format to performance-based labelling.

Performance-based labelling has been accepted in both Australia and New Zealand as an effective medium to communicate the usage of, and precautions required for, medicines. It now represents the “gold standard” of labelling, and this proposed upgrade of the Canesten vaginal products’ labelling is expected to improve consumer’s comprehension of the labels, and subsequently maximise safe and effective use of these products. An important feature of the proposed performance based labelling is that the symptoms of vaginal thrush are included more prominently on the carton, allowing the consumer better self-assessment of their symptoms before purchasing the product.

Mock-ups of the proposed product cartons follow on the next pages.

**Canesten Clotrimazole Thrush Treatment 6 Day Cream Proposed
Carton**

**Canesten Clotrimazole Thrush Treatment 6 Day Pessary Proposed
Carton**

**Canesten Clotrimazole Thrush Treatment 3 Day Cream Proposed
Carton**

**Canesten Clotrimazole Thrush Treatment Once Cream Proposed
Carton**

**Canesten Clotrimazole Thrush Treatment Once Pessary Proposed
Carton**

**Canesten Clotrimazole Thrush Treatment Once Pessary + Cream
Proposed Carton**

A8. Proposed Warnings

Anticipating that the proposed classification is accepted in both New Zealand and Australia, Bayer proposes to maintain Trans-Tasman labelling. Thus any labels with the new classification must satisfy both countries' requirements

All applicable warning statements or wording with similar intent as required by Appendix F of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) for Australia will be included on both the outer carton labels and the pack inserts. These are:

- seek medical advice before first course of treatment
- see a doctor if you are pregnant or diabetic
- see a doctor if no better after 4 days
- see a doctor if problem returns

Additionally, when clotrimazole was first rescheduled to a Pharmacist Only Medicine in 1992, it was a condition of this (then) new classification that the product would only be presented in pack sizes of one course of treatment. This condition has been maintained, even though it is no longer part of the schedule, and Bayer plans to maintain it on through the proposed reclassification to Pharmacy Medicine.

Currently, the various Canesten vaginal product's pack inserts are replicas of the product Consumer Medicine Information published on the Medsafe Web site. As part of the proposal to reschedule these products to Pharmacy Medicines, Bayer intends to update the current Consumer Medicine Information and pack inserts, tailoring them to further facilitate the purchaser's safe and effective use of the products.

In addition to the required SUSDP warnings listed above, the current CMI/pack insert also contains the following safety information:-

- a list of symptoms that are not normally signs of thrush (to facilitate the purchaser's differential diagnosis)
- a warning regarding prior allergies
- a warning if the patient is under 18 years of age
- a warning if the patient is breast-feeding
- a warning if the is a local reaction to the treatment
- a warning regarding reduction of effectiveness of latex products

The updated CMI/pack inserts will maintain all of this safety information, and further information will be added as considered necessary. For example, further symptoms not usually signs of thrush were recently added to the current Consumer Medicine Information – namely pain when passing urine, fever or chills and foul smelling and/or unusual coloured discharge.

Drafts of the proposed updated pack inserts are provided as Appendix 3 to this submission. However, they are working documents and not intended to be taken as finalised. Bayer is actively seeking expert advice on the proposed labelling and pack inserts to further optimise the instructions to the patient. The section “*Some situations which can increase susceptibility to thrush are...*”, which details risk factors, will be updated to include other concomitant medicines and include symptoms of diabetes (as recurrent thrush can be a symptom for the undiagnosed or poorly controlled diabetic).

A9. Other Products

In addition to the Canesten range of products that are the subject of this submission, there are a number of other clotrimazole products for vaginal administration currently sold in the New Zealand market. These are:-

Brand Name	Strength and Pack Size	Sponsor Company
Clocreme	Vaginal cream 1% 35g	Pacific
Clotrimaderm	Vaginal cream 1% 45g Vaginal cream 2% 25g	AFT
Clomazol	Vaginal cream 1%	Multichem
Clotrihexal	Vaginal tablet 100mg Vaginal tablet 200mg Vaginal tablet 500mg	Hexal

PART B

B1. Vaginal Thrush

Thrush is the common name given to fungal (usually *Candida spp.*) infections. The word thrush is often used by the general public to mean vaginal thrush, and encompasses *Candida spp.* infections of the vulva and vagina (vulvo-vaginal candidiasis).

Candida spp. are a common pathogen to colonise humans, although they are not considered normal body flora. Often such colonisation is asymptomatic. However, in predisposing circumstances the level of colonisation can increase dramatically, symptoms can develop and the host is considered to have an infection (infection = colonisation plus disposition).

In the case of an acute vaginal infection, the patient suffers itching in the genital region, which turns to burning. The vulva and vaginal walls can become red and inflamed, often with visible white patches. A white to yellowish, odourless, crumbly discharge is often, but not always (especially in the early stages), present. Dysuria (pain on urination) and dyspareunia (pain during or after intercourse) may occur consequentially. The itching/burning sensation is often intense and exacerbated by scratching. The infection can be extremely uncomfortable and distressing for the patient (4, 14).

The symptoms of vulvovaginal candidiasis are itching, burning, soreness and redness of the vulva. Other possible symptoms are vulvar pain and dyspareunia (pain during sexual intercourse). Sufferers of candidal vulvitis usually recognise it as 'thrush', and can suffer the same symptoms on each occasion. Research amongst sufferers reveals that the itching and burning are the most distressing aspect of the conditions from which patients seek urgent relief.

Vaginal candidiasis presents clinically as white, odourless vaginal discharge, or may be relatively asymptomatic. Vaginal and vulval candidiasis frequently co-exist. It is generally accepted that both conditions should be treated simultaneously to prevent reoccurrence of vulval candidiasis due to untreated candidal infection in the vagina. In patients with chronic recurrent disease the symptoms usually subside spontaneously with the menses, but recur a few weeks later. However severe infection can be protracted with annoying discomfort; chronic symptoms can lead to frustration and depression, and can

lead to sexual and marital problems which can negatively impact the patient's quality of life (4).

B1.1 Predisposing Causes of Vaginal Thrush

As previously mentioned, colonisation by *Candida spp.* plus disposing factors are required for symptomatic vaginal thrush to occur. The average incidence of pathogenic yeasts in the vagina is approximately 10% for healthy non-pregnant premenopausal women and 5 – 10% for healthy post-menopausal women. *Candida albicans* is the most commonly occurring yeast (approximately 70%), followed by *Candida glabrata* (approx. 13%) and other *Candida species* (approx. 12%).

The principal predisposing factors are (3):-

- high circulating oestrogen levels (oral contraceptives, IVF treatment, pregnancy, hormone replacement therapy, obesity).
- medical intervention, such as douching, antibiotic therapy, immunosuppression, cytotoxic drugs, radiotherapy.
- metabolic disorders such as diabetes mellitus, Cushing's disease or Addison's disease
- diseases that weaken the immune system such as leukaemia or AIDS
- mechanical irritation (tight clothing, intercourse)
- diet rich in carbohydrates, especially sugar.

In these cases where predisposing factors to the disease exist, the incidence of pathogenic yeasts in the vagina can rise to 30% and more. Additionally, the presence of predisposing risk factors tends to be accompanied by an increase in the percentage of *Candida albicans* at the expense of other species, especially *Candida glabrata*.

Three out of four women suffer from a yeast infection at least once in their lives and approximately 40 to 50% will experience a second attack. A smaller proportion of women, estimated to be less than 5%, have chronic recurrent vulvovaginal candidiasis (3,4).

B1.2 Diagnosis of Vaginal Thrush

The symptoms and signs of vaginal and vulvovaginal candidiasis are not specific enough to make a definitive diagnosis possible, based solely on a patient's history or on genital examination (1). Therefore, positive diagnosis of vaginal and vulvovaginal candidiasis can only be made after performing these recommended laboratory tests:

- confirmation of a normal vaginal pH (4.0 - 4.5)
- prepare a wet mount of the vaginal discharge for identification of yeast cells and mycelia and to rule out other diagnoses (the "clue cells" of bacterial vaginosis and motile trichomonads of trichomoniasis).
- examine a 10% KOH preparation of the vaginal discharge. This has a higher sensitivity for identification of yeast. A gram-stained preparation may also be used. Yeasts are gram-positive.
- if microscopic studies are negative and the index of suspicion for vaginal or vulvovaginal candidiasis continues to be high, send a swab sample for fungal culture. Microscopy is negative for yeast in as many as half of the patients with culture-proven vaginal and vulvovaginal candidiasis that will respond to antifungal therapy.

Vulvovaginal candidiasis is generally classified as either uncomplicated or complicated (1). Such classification is useful, as longer treatment durations are generally recommended for complicated disease compared to uncomplicated disease. The possibility of uncontrolled diabetes mellitus or immunodeficiency should be considered in women with recurrent infection.

Classification of Vulvovaginal Candidiasis

Uncomplicated	Complicated
Sporadic/infrequent infection	Recurrent infection
Mild to moderate infection	Severe infection
Candida albicans as likely cause	Non-albicans infection
Women without immunosuppression	Women with uncontrolled diabetes mellitus, immunosuppression, or debilitation; pregnant women

In clinical practice, if a patient presents with uncomplicated thrush-like symptoms most doctors, faced with a patient in considerable discomfort and anxious for a solution, will treat for candidiasis (10). In most instances, waiting for laboratory results would be unacceptable to the patient. Thus, treatment for vaginal thrush is initiated, and if the treatment is subsequently not effective this lack of efficacy is then used as a further diagnostic tool.

B1.3 Treatment of Vaginal Thrush

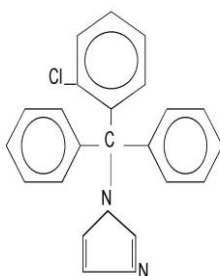
Effective antifungal agents have been available for the treatment of vaginal thrush for many years (12) (section B2 provides a summary for clotrimazole). The most common of these involve a topical (intravaginal, plus possibly a vulval) treatment (creams or pessaries), while some systemic treatments are also available.

The suitability of topical antifungal agents as OTC medicines is well-established – the Canesten range of vaginal products has been classified as Pharmacist Only Medicines in New Zealand since 1992. Recently, a systemic treatment of vaginal thrush has also been reclassified to Pharmacist Only Medicine, further reinforcing that a doctor's diagnosis and determination of the appropriate treatment is not considered necessary for this common disease. As discussed in Section B1.2, a doctor cannot provide a definitive diagnosis without laboratory testing and often will use antifungal treatment to aid clinical diagnosis – thus, whether it is the patient or the doctor that initiates antifungal treatment, it is likely that the final outcome for the patient will be the same.

B2. Canesten Clotrimazole Thrush Treatment

Clotrimazole was synthesised by Bayer AG in 1967 in a systematic investigation of imidazole compounds.

Clotrimazole is 1-(o-chloro- α, α - diphenylbenzyl) imidazole, $C_{22}H_{17}ClN_2$ with a molecular weight of 344.84



B2.1 Physico-Chemical Properties

Clotrimazole is a colourless, crystalline, weakly alkaline substance, with a melting point of 141° - $145^{\circ}C$. It is soluble in acetone, chloroform and ethanol and practically insoluble in water. It forms stable salts with both organic and inorganic acids. It is not photosensitive but is slightly hygroscopic, and may be hydrolysed in acid media.

B2.2 Pharmacology

Clotrimazole is a broad-spectrum antifungal agent that inhibits the growth of most fungi pathogenic to man, including, *inter alia*, *Trichophyton* species, *Microsporium* species, *Aspergillus* species and *Candidal* species. *In vitro* investigations have also shown it to be active against strains of *Staphylococcus aureus*, *Streptococcus pyogenes*, *Proteus vulgaris*, and *Salmonella* spp. (2).

B2.3 Pharmacodynamics

The site of action of clotrimazole, like that of the polyene antifungal agents, appears to be the cell membrane to which it is preferentially bound. In contrast to the polyene antifungal agents, the action of clotrimazole has been shown to be less dependent upon the sterol content of fungal cell membranes. It has been proposed that the mechanism of action involves an interaction with the phospholipid layer of cellular membranes causing alterations in membrane permeability. Permeability changes result in loss of essential precursors, metabolites, and ions, thus inhibiting macromolecular synthesis. Loss of intracellular potassium could cause acidification of the cell interior and eventual activation of autolytic enzymes.

Clotrimazole brings about inhibition of fungal ergosterol biosynthesis, which involves numerous intermediate stages. Ergosterol is an essential constituent of the cell membrane of fungi. If ergosterol synthesis is completely or partially inhibited, the cell is no longer able to construct an intact cell membrane. This leads to the death of the fungus.

Compared to other azole derivatives the Minimal Inhibitory Concentrations (MIC) tested *in vitro* show that yeasts and dermatophytes are highly susceptible to clotrimazole. *In vitro* MIC's for clotrimazole for yeasts and selected pathogens is given in the table below.

Minimal inhibitory concentrations (MIC) *in vitro* of clotrimazole for yeasts and other gynaecological relevant pathogens (adapted from data on file)

	Species of Fungus	MIC in µg clotrimazole/mL
Yeasts	<i>Candida albicans</i>	0.02 – 1 - 4
	<i>Candida krusei</i>	1
	<i>Candida tropicalis</i>	1
	<i>Candida pseudotropicalis</i>	0.08 - 0.1 - 0.5
	<i>Candida utilis</i>	1
	<i>Candida parapsilosis</i>	1
	<i>Candida glabrata</i> etc.	1 – 4 - 12
	<i>Rhodotorula rubra</i>	>1
Bacteria	<i>Staphylococcus aureus</i>	1 - 3
	<i>Streptococcus pyogenes</i>	0.75 – 30
	<i>Bacteroides</i>	2.16
	<i>Gardnerella vaginalis</i>	4 - 64
Trichomonas	<i>Trichomonas vaginalis</i>	100

B2.4 Pharmacokinetics

The concentrations of active substance in the plasma of volunteers following the application of 50g of ¹⁴C 1% vaginal cream after 8 - 24 hours corresponded to 10 ng/ml.

Following vaginal administration of 500 mg of 10% Canesten cream, plasma concentrations after 2 - 120 h were < 3 µg/ml, and following vaginal administration of 100 mg of 2% cream, plasma concentrations were < 5 µg/ml after 2 - 120 h. Since only very small amounts of active substance are absorbed and it is metabolised very quickly ($t_{1/2}$ = 1 - 2 hours), concentrations in blood plasma are always very low, if detectable.

The vaginal availability of clotrimazole from pessaries has also been investigated. After 24 hours, samples of vaginal fluid from 8 volunteers administered with one 500 mg pessary gave an average of 68.1 mg/mL clotrimazole (2.05 mg/mL after 72 hours). In contrast the blood plasma concentrations of clotrimazole in the volunteers remained below the detection limit of 0.01 µg/mL. Further studies with a 500 mg pessary indicated plasma concentrations of < 1 - 10 µg/mL after 2 - 72 hours.

Thus, clotrimazole is absorbed vaginally to a very small extent, and that which passes into the circulation undergoes rapid and extensive hepatic metabolism, the products of which are renally excreted. It can thus be concluded, given the above results, that systemic exposure from the clotrimazole vaginal preparations is low and that risk as a consequence of over application is unlikely.

B2.5 Toxicology

The following is a summary from the animal studies, which coupled with the long history of clotrimazole use, demonstrate a superior margin of safety for the use of clotrimazole in humans. Despite intensive searches in accepted databases, data published in recent articles do not deviate from the results of the studies documented in this overview. More recent investigations support the data obtained in older studies. Thus newer studies do not alter the overall risk - assessment of clotrimazole drawn from studies conducted in the 1980's and 1990's.

B2.5.1 Acute Toxicology

The acute toxicity of clotrimazole was investigated in 6 animal species. Following single oral administration, the compound was slightly toxic with LD50 values of 923 mg/kg body weight (b.w.) in male mice, 761 mg/kg b.w. in female mice, 708 mg/kg b.w. in male rats, 718 mg/kg b.w. in female rats, between 1000 to 2000 mg/kg in male and female rabbits, greater than 2000 mg/kg b.w. (with emesis) in male and female dogs, greater than 2000 mg/kg b.w. (with emesis) in male and female cats, and about 250 mg/kg b.w. in male guinea pigs. A single oral administration of the test article to newborn male and female rats resulted in moderate toxicity with LD50 values of 95 - 114 mg/kg b.w.

B2.5.2 Repeat-Dose Toxicology

Sub chronic oral toxicity studies of 13 weeks duration were run in rats and dogs. Chronic oral toxicity studies run for 18 and 12 months were conducted in rats and dogs respectively.

Up to 3 Months

In the rat 3-month study, doses of 25, 50, 100 or 200 mg/kg/day b.w. were administered by gavage to five groups of n = 10 male and n = 10 female Wistar rats. Doses up to and including 25 mg/kg/day b.w. were tolerated over the study period. Body weight gains were significantly reduced in high dose males. Erythrocytes, haemoglobin, and haemocrit were significantly decreased after 12 weeks in male rats receiving 100 mg/kg/day b.w. and above. The mean corpuscular volume (MCV) of high dose males was significantly increased at 12 weeks. In females the only significant change seen after 12 weeks was an elevation in MCV at the 200 mg/kg/day b.w. dose level. There were however, significant reductions in erythrocyte counts and haemoglobin levels and elevations in MCV seen in 100 and 200 mg/kg/day b.w. females at the interim period of 4 weeks.

There was also a significant reduction in leukocyte concentration in high dose females after 4, but not 12 weeks. At necropsy, male and female liver weights were significantly increased over control at all dose levels. Adrenal weights in males in the 200 mg/kg/day group and females in the 100 and 200 mg/kg/day groups were also significantly increased when compared to the controls. Histopathologically, liver cells of male and female rats receiving 100 or

200 mg/kg/day were enlarged. Cell enlargement and vacuolization were seen in the zona reticularis of the adrenal cortex. Liver enlargement is explainable, at least in part, as hyperfunctional enlargement related to enzyme induction.

In the dog 13 week study, encapsulated clotrimazole doses of 50, 100 or 200 mg/kg b.w. were administered orally 5 days per week to four groups of n = 2 male and n = 2 female beagle dogs. Dose dependent vomiting, loose stools and anorexia were frequently seen. Change from a single dose to 2 divided doses daily alleviated but did not eliminate signs of intolerance. Treatment elicited progressive increases in plasma alkaline phosphate activity over the course of the study. High- and mid-dose dogs showed low-grade increase in activities of liver-specific transaminases. Liver weights of high dose animals were clearly the highest of any study group. Adrenal weights of mid-and high-dose dogs were statistically significantly elevated. There was histopathological evidence of dose related cell enlargement in the liver and adrenal cortex. In view of the effects on the liver and the repeated gastrointestinal intolerance, no dose used in this study was considered a no effect level.

Beyond 3 Months

In the rat chronic toxicity study, in which the compound was administered in the diet, clotrimazole doses equivalent to 10, 25, 50 or 150 mg/kg b.w./day were given for up to 78 weeks (five groups of n = 50 male and n = 50 female Carworth CFE rats). The high-dose group was not treated between weeks 27 and 53 to determine if observed liver changes were reversible. Body weight gains in high dose rats and 50 mg/kg/day females were retarded. Haemocrit and haemoglobin values of 50 and 150 mg/kg/day females were slightly decreased, as were haemoglobin levels of high dose males. Alkaline phosphate activity of high-dose males was elevated at week 78. SGPT levels of the high-dose males were elevated at weeks 26 and 78, but not at week 52 following the period of withdrawal. At necropsy, livers were dose-dependently enlarged and discoloured. Histopathologically, hepatic changes were directly related to dose and duration of treatment. There was evidence of reversal of drug-induced liver changes in 150 mg/kg/day animals at week 52. Results of determinations of clotrimazole plasma levels suggest significant induction of liver microsomal enzymes. There was no evidence of carcinogenic potential.

In the dog chronic study, twice daily doses 12.5, 25 or 75 mg/kg were administered orally in capsules 5 days per week for 6 or 12 months. Some animals dosed for 12 months were observed for an additional 3 or 6 months without treatment. Persistent dose dependent emesis was seen in study animals. High dose dogs had a small weight loss. Blood activities of alkaline phosphatase and SGPT were elevated during the treatment period, but returned to normal in the 6 month post treatment period. Necropsy revealed enlarged

adrenals at the end of treatment and after 6 months observation period. Histopathologically, a dose related thickening of the adrenal cortices was considered the result of exaggerated pharmacodynamics since no damage to the renal parenchyma was seen and reversal began after clotrimazole treatment ceased.

B2.5.3 Genotoxicity

In vitro Findings

Clotrimazole gave a negative response in the Salmonella/microsome test for point mutations at doses up to and including 500 ug/plate using 4 histidine auxotrophic Salmonella typhimurium strains.

Clotrimazole was also evaluated for genotoxicity in the *in vitro* rat primary hepatocyte Unscheduled DNA Synthesis (UDS) assay. None of the criteria used to indicate UDS were approached by treatment with the test compound, and no dose related response was observed. So clotrimazole was evaluated as inactive in the UDS assay.

Clotrimazole was evaluated for mutagenic effects in the forward mutation assay in V79 cell cultures. There was no significant dose related or reproducible increase in mutant frequency above that of the negative controls and it was concluded that clotrimazole was non-mutagenic in the V79 - HPRT forward mutation assay.

In vivo Findings

Clotrimazole was shown to be non-mutagenic in the dominant lethal test in male mice which is designed to detect clastogenic effects of mutagens resulting from induction of chromosomal aberrations in the germ cells.

A micronucleus test with clotrimazole was conducted in male and female mice to assess the potential for a clastogenic effect in an *in vivo* system. No relevant indications of a clastogenic effect of clotrimazole were found after a single oral treatment with doses up to and including 750 mg/kg b.w.

The mutagenic effect of clotrimazole was tested on the spermatogonia of Chinese hamsters *in vivo*. In this cytological test the spermatogonial metaphases of treated animals were examined for structural changes in the chromosomes. The frequency of metaphases with aberrations, with and without gaps, and/or

metaphases with translocations was determined. The evaluation of structural chromosomes did not reveal any marked difference between control animals and those treated with clotrimazole doses 100 mg/kg/day for 5 consecutive days. Thus clotrimazole was not mutagenic in the hamster spermatogonium chromosome test.

B2.5.4 Carcinogenicity

The carcinogenic potential of clotrimazole has been investigated in the rat 78 week study. There was no evidence of carcinogenic potential at doses up to and including dietary concentrations equivalent to 150 mg/kg/day.

B2.5.5 Reproductive and Developmental Toxicity

Reproduction and/or developmental toxicity studies were conducted using the oral route of clotrimazole administration in mice, rats and rabbits.

In the rat fertility study, groups of FB30 males and females received dietary doses equivalent to 5, 10, 25 or 50 mg/kg b.w. Males were dosed for 10 weeks prior to mating and throughout a 3 week mating period. Females were treated from 10 weeks prior to mating until sacrificed on either day 13 of gestation or 4 weeks postpartum. Neonatal survival was reduced at 50 mg/kg. Clotrimazole dietary doses up to and including 25 mg/kg b.w. did not impair the development of the pups. Doses up to and including 50 mg/kg/day did not impact fertility. The potential for clotrimazole to be embryotoxic and/or teratogenic was studied in mice, rats and rabbits. In the first study in mice there was no evidence of maternal toxicity, embryotoxicity, foetotoxicity or teratogenicity at oral doses up to and including 200 mg/kg/day.

In the initial Segment II study in rats, oral doses of 25, 50, 100 or 200 mg/kg b.w. were administered to pregnant FB30 females. The high dose was discontinued because of lethality. The 100 mg/kg/day dose was maternally toxic, resulting in adverse clinical signs and significantly reduced body weight gains during treatment and over the entire gestation period. Possibly as a result of maternal toxicity, there was a significant increase in the number of resorptions and foetal weights were distinctly, but not statistically significantly, reduced. Clotrimazole at oral dose levels up to and including 50 mg/kg/day produced no maternal toxicity or evidence of developmental toxicity. There was no evidence of teratogenicity at any dose level.

In rabbits, clotrimazole administered orally at doses of 60, 120 or 180 mg/kg b.w. per day was not maternally toxic, embryotoxic, foetotoxic or teratogenic.

B2.5.6 Other Toxicity Studies

The local and systemic tolerance of clotrimazole in different dosage forms was assessed in subacute intravaginal studies in dogs and monkeys.

Three groups of 5 female dogs were treated with vehicle only, and 1% clotrimazole cream, respectively. The third group served as mechanical control. Each dog was treated once daily, for 30 days. A thirty day post dosing observation period followed. The mechanical control group was sham-dosed with the applicator. There were no differences in behaviour, physical condition, food consumption, body weights and clinical chemistry. Vaginal cytology indicated no drug-induced cellular changes.

Ten female beagles were administered 100 mg clotrimazole tablets once intravaginally. Animals were observed 1 and 4 hours post-administration. All animals tolerated the application with adverse effects. Four female beagles received 100 mg clotrimazole tablets daily for 14 days. Animals were weighed pre-treatment and during weeks 1 and 2. The condition of the vaginal mucosa was examined 4 and 24 hours post administration on the first and second days and 24 hours post administration on succeeding days. Haematology was performed 4 and 24 hours after the first and fourteenth administration. All animals tolerated intravaginal administration of 100 mg clotrimazole for 14 days. Three groups of 4 adult female monkeys, *Macaca mulatta* were treated with vehicle only or 1% clotrimazole cream; the third group served as mechanical control. Cream and vehicle was inserted into the vaginal vault using a vaginal applicator for 93 days at a rate of 2.5 g per monkey. A thirty day post-dosing observation period followed. The mechanical control group was sham-dosed with the applicator. There were no differences in behaviour, vaginal cytology, or clinical parameters between groups or individual monkeys.

B2.6 Clinical Data

B2.6.1 Pathogenesis and Epidemiology

Candida spp. are part of the lower genital tract flora in 20 to 50% of healthy asymptomatic women. Symptoms of candidal vaginitis occur due to excessive growth, usually due to cases when the natural balance is disrupted.

Candidal infection occurs rarely before puberty, during lactation and in healthy post-menopausal women unless oestrogen is replaced. It is estimated that 75% of women of child bearing age will experience at least one episode of candidal vulvovaginitis, and approximately 40 to 50% of these will have a second attack. A smaller proportion of women, probably less than 5% of the adult female population, have chronic recurrent candidal vulvovaginitis (≥ 4 episodes a year) (4).

B2.6.2 Clinical Trials – Efficacy and Safety of Clotrimazole

Please see Appendix 4 for a comprehensive overview and summary analysis of the efficacy and safety (including comparative) of clotrimazole in the treatment of gynaecological indications. A synopsis for each individual study is provided. This overview and summary includes reference to the clinical studies that were submitted to Medsafe as part of the original marketing authorisation application. The purpose of providing this updated document to the Medicines Classification Committee is to provide a comprehensive overview of all the available efficacy and safety data including literature.

However, due to its long and successful history as an antifungal treatment, there is little doubt as to the clinical efficacy of clotrimazole in treating gynaecological thrush infections. Similarly, clotrimazole has been available without prescription in New Zealand for approximately 13 years, virtually without incidence (see Appendix 5 – New Zealand CARM data, and Appendix 6 for Australian adverse event data) for both gynaecological and other topical fungal treatments. Clotrimazole is now available as a Pharmacy Medicine for the treatment of other topical fungal infections, and recently has been reclassified in Australia to General Sales for the treatment of athlete's foot (following a similar reclassification in New Zealand). Thus, the safety of clotrimazole has been reviewed relatively recently in both countries, and has been found by both the

MCC and the NDPSC to be sufficiently safe to warrant a General Sales classification. As the levels of systemic absorption are negligible for intravaginal administration (as they are for other topical applications) (8), the suitability of the safety profile for clotrimazole for the proposed classification of Pharmacy Medicine for vaginal use would not seem to be in question.

B2.6.3 Use in Pregnancy

Clotrimazole is categorised as Category A according to the Australian Prescribing Medicines in Pregnancy (4th edition). Category A medicines are those which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed. Similarly, the approved New Zealand data sheet (which is based on the approved Australian Product Information) for Canesten states:-

“In the first trimester of pregnancy, intravaginal Canesten Clotrimazole should be used only when the medical practitioner considers it essential for the welfare of the patient. Administration of Canesten Clotrimazole vaginal pessaries to a small number of women in the 2nd and 3rd trimesters of pregnancy has produced no obvious untoward effect on the course of the pregnancy or on the foetus. This limited experience is insufficient to detect with reasonable certainty events occurring with an incidence of less than 3%. If treatment is carried out during pregnancy, Canesten Clotrimazole vaginal pessaries are the preferable choice as they can be inserted without the use of an applicator.”

In contrast, systemic therapy with fluconazole is to be avoided in pregnancy except in patients with severe or potentially life threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the foetus. There are no adequate and well controlled studies of the use of fluconazole in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for three or more months with high dose fluconazole therapy (400 to 800 mg/day) for coccidiomycosis. The relationship between fluconazole use and these events is unclear.

There are clear benefits to the mother and foetus in treating vaginal thrush when it occurs during pregnancy, and the importance of treating vulvovaginal candidiasis during pregnancy is now well-established. In addition to relieving the considerable discomfort the mother may be experiencing, evidence has

demonstrated that infection can be passed on to the baby (in the form of oral thrush or other fungal infections) during passage through the birth canal. Ninety percent of new-born babies colonised with *Candida albicans* within the first week of life develop an infection after 1 – 3 weeks.

A retrospective analysis compared medically recorded birth weight/gestational age, the prevalence of preterm birth and low birth weight infants of newborn infants without birth defects born to mothers with or without clotrimazole treatment during pregnancy in the data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities (6). The 17-year data set included 38,151 newborn infants and 8.1% were born to mothers who received clotrimazole treatment during pregnancy. There was an increase in mean gestational age among the exposed infants, relative to the unexposed, resulting in a significant (34 - 64%) reduction in the prevalence of preterm births. The authors speculate that the protective effect of topical clotrimazole during pregnancy may be attributable to the beneficial effect of clotrimazole in the restoration of the abnormal colonization of the female genital organs and its known antibacterial and/or antiprotozoal effect.

As pregnancy is a time of increased occurrence of thrush (5), an increased incidence of vaginal thrush treatment is also likely to occur. In these cases, use of the safest products available is clearly desirable, and clotrimazole falls into this category.

B2.6.4 Risk of Resistance

Only limited resistance to clotrimazole has been observed *in vitro*, despite attempts to induce the emergence of resistant strains of *A. fumigatus*, *C. albicans*, *Cryptococcus neoformans*, and *T. mentagrophytes* by passage through successive concentration gradients. Development of resistant *C. albicans* did occur when prolonged incubation periods were used rather than the usual method of rapid passage through increasing clotrimazole concentrations. This observed resistance reverted to previous sensitivity when the fungus was exposed to drug-free media.

Overall, resistance to azole anti-fungals is not a clinically significant problem. Mechanisms used by prokaryotic bacteria to develop resistance, and to pass that resistance from one bacterial cell/species to another, are not found in eukaryotic fungi. Since the early 1990's, there have been reports of resistance to azoles, but these have been almost exclusively confined to systemic use of fluconazole, in specific clinical settings, mainly in AIDS patients with chronic oropharyngeal/oesophageal candidosis or cryptococcosis treated long-term or intermittently with

fluconazole. These patients typically had end-stage disease and low CD4 counts. The advent of triple therapy for HIV infection has led to a marked reduction in the incidence of these fungal infections and thus clinically relevant yeast resistance. Importantly, the development of resistance to these systemic therapies has not been reported for treatments lasting less than several weeks.

Topical antifungal agents, such as clotrimazole and miconazole, are available as OTC medicines in many countries, and have been used for many years. As yet there have been no documented resistance problems in yeasts and dermatophytes. Treatment failure and relapse do occur, for example in vaginal candidosis, but these are always associated with host defects rather than failure of the antifungal. There is very little robust evidence for the emergence of resistance as a consequence of the use of topical antifungal agents; the results of studies to investigate the potential for development of resistance of candidal infections to clotrimazole did not demonstrate resistance. It is not surprising that these topical agents do not induce resistance, given that the predisposing factors for fluconazole resistance, i.e. long-term therapy of chronic yeast infections in severely immunocompromised hosts, do not apply.

A recent article published in the United Kingdom (7) addressed the question of correlation between antifungal resistance and the over-the-counter availability of antifungals in general and azoles in particular. The article concluded that there is the potential for development of resistance as a result of increased general sale availability of topical clotrimazole for short-term application. However, there is no robust evidence to support this, as current resistance data are compiled from a very small number of intensive care and oncology patients treated with systemic antifungal agents for long periods, and cannot be extrapolated to the community at large. In addition, experience of extensive usage of topical clotrimazole over many years for the treatment of a number of different superficial mycoses without emergence of significant resistance does not support this author's hypothesis. There is no evidence to suggest that the availability of topical clotrimazole products for short term application have been associated with the emergence of azole resistance in New Zealand or Australia. Additionally, there is no reason to think that the proposed change in classification to Pharmacy Medicine would change this situation.

B2.6.5 Post-Marketing Safety Data

In the last decades excellent efficacy and tolerability of clotrimazole in the treatment of vaginal and dermal fungal infections has been documented worldwide in hundreds of clinical studies involving many thousands of patients.

Clotrimazole is well established first line therapy for local anti-fungal infections. Clotrimazole has a very low incidence of adverse reactions or significant side effects, as well as a low potential for harm, and therefore, today clotrimazole is available in many countries as a self medication or over the counter treatment for both vaginal and dermal fungal infections. The most common reported adverse reactions for clotrimazole vaginal preparations are rash with or without pruritus and rarely allergic reactions. It is difficult to determine whether such reactions are due to the underlying condition or a true reaction to the medicine or formulation vehicle.

Spontaneous adverse event reports to the company or regulatory authority are small when compared to the estimated global patient exposure. During the last safety reporting period (01 September 2004 to 31 August 2005) the estimated patient exposure calculated from sales volume was 49,994,503 compared with 57,704,655 during the previous interval for all topical formulations. These estimates were based on the assumption that a patient was treated with an individual product. The worldwide patient exposure for the vaginal preparations during the last safety reporting period (01 September 2004 to 31 August 2005) was 19,658,947 (compared to 22,983,512 in the previous period) and a total of 125 spontaneous reports were received. Seven serious events were reported although a confirmed causal relationship was not established. The latest Periodic Safety Update Report (PSUR) excluding line listings dated 28 October 2005 is provided in Appendix 7.

The experience of clotrimazole in New Zealand and Australia is consistent with the global post marketing reports. In New Zealand, only six adverse reactions have been reported to CARM for clotrimazole since data began to be collected and collated (prior to 1982). Of these, only one did not involve multiple drug treatment, and only one was classified as severe (but not serious) – see Appendix 5.

No deaths have been reported to the Australian Adverse Drug Reaction Advisory Committee (ADRAC) in association with clotrimazole. The adverse reactions reported to ADRAC for clotrimazole (all presentations) are usually related to effects on the skin (rash, itching, dermatitis), paraesthesia (numbness or tingling sensation) or application site reactions. For the reports where the therapeutic use of the clotrimazole product is reported to ADRAC (code term: moniliasis) the safety profile is consistent to the wider profile observed for all preparations, the most common report being application site reaction (see Appendix 6).

The safety profile of clotrimazole compares favourably with that of other azoles. The majority of reports to ADRAC in relation to miconazole, which is an alternative topical azole treatment, are application site reactions and paraesthesia. This is consistent in the subset of reports where vaginal candidiasis (code term: moniliasis) is offered as the indication (See Appendix 6).

Because of the very low number of reports of adverse events for clotrimazole in New Zealand, comparison of this data against other alternative treatments does not provide useful or meaningful information. However, comparison of reports to ADRAC in the last three years (01 September 2002 to 31 August 2005) is also provided (see Appendix 6), and give some insight as it is likely that the New Zealand experience would be similar.

In the case of clotrimazole a total of 11 reports were received by ADRAC and the total number of clotrimazole packs sold in Australia by Bayer during this time was 5.9 million (3.2 million being vaginal preparations), giving an incidence rate of 0.0002%. A total of 49 reports in relation to miconazole and miconazole nitrate were received by ADRAC during the same period. Using Australian sales data from IMS, the total number of miconazole/miconazole nitrate units sold in Australia was estimated to be 2.7 million units, giving an incidence rate of 0.002%. This estimation is based on a sum of total unit sales from Daktarin™ (topical and oral gel), Monistat™ (vaginal formulations), and Resolve™ (topical and vaginal range). Of the total unit sales for miconazole/miconazole nitrate the estimation of vaginal preparations was 0.46 million (being based on unit sales for Monistat™ products and Resolve™ 2% vaginal cream). Thus, the incidence of reported adverse events for clotrimazole appears to be approximately one tenth that of miconazole/ miconazole nitrate – however, the reasons for this are not clear.

™ Daktarin and Monistat are registered trademarks of Johnson and Johnson group of companies

™ Resolve is a registered trademark of Ego Pharmaceuticals Pty Ltd

B3. Canesten for Vaginal Use as Pharmacy Medicines

B3.1 Rationale for Classification Change

Primarily Bayer seeks the proposed classification change for clotrimazole for vaginal use simply because the product is ready for it. Approximately 13 years of experience with the product as a Pharmacist Only Medicine in New Zealand, and a virtual absence of reported adverse events or other problems during that time, suggests that the product is eminently suitable to be considered for further relaxation of the restrictions on it. As with the principles that surround the harmonisation of classifications between Australia and New Zealand, Bayer believes a principle of scheduling should be that a product be classified at the lowest level of classification possible, given the current level of knowledge and experience with that product. Thus, Bayer's essential question for the Medicines Classification Committee is not "*Why should clotrimazole be classified as a Pharmacy Only Medicine?*" – the essential question is "*Why not?*"

Furthermore, the advantages of extending the access of clotrimazole to pharmacy shelves include easy accessibility for patients with less embarrassment. Discussing uro-genital symptoms can cause embarrassment for women, and on some occasions on the part of the pharmacist particularly if male. The lack of privacy at the pharmacy counter can make this situation worse. United Kingdom pharmacists report that often customer's don't give the "full story" or a "truthful account" when questioned (12). Thus, easier access to the medicine may result in earlier treatment.

The symptoms of vaginal thrush cause the sufferer considerable discomfort. Market research amongst women has indicated that the majority would welcome easier access to relief of their symptoms than they currently have through pharmacies. In order to achieve rapid relief from the symptoms, and ensure effective treatment of the infection, immediate access is desirable (12). Where there are no safety impediments, this convenience to the purchaser outweighs the benefit of availability of pharmacist advice at the point of sale.

Bayer has a full range of clotrimazole vaginal formulations marketed as Canesten, and for most uncomplicated cases of thrush the efficacy across the range is equivalent. Whilst many women will self-select the product they consider to be tried and tested from previous use, being able to view the range offers consumers additional choice they may have been unaware of. Also, it may prompt women to seek advice from the pharmacy personnel regarding which

product might be most appropriate - this can be less confronting than the need to describe symptoms up front and may lead to greater consumer satisfaction with the treatment selected.

Last, but by no means least, the best use of the pharmacist's time as a health-care professional resource must be considered. Like all professionals, pharmacist's time is limited, and the added value of a pharmacist's input into every purchase of a clotrimazole vaginal product must be weighed against other potential uses of this time. There is a current trend for medicines to be classified as Pharmacist Only Medicines for which there is a great deal less experience and knowledge that is available for clotrimazole – orlistat and the possibility of such medicines as domperidone and simvastatin becoming Pharmacist Only Medicines are examples. For these newer medicines, pharmacist involvement in the purchasing decision is essential, adding considerable value for the customer. However, the pharmacist's time is not unlimited and down-scheduling of clotrimazole to Pharmacy Medicine would free pharmacists from the obligation to participate in every sale, where their ability to add value is limited due to the already broad experience and excellent safety profile of the product.

Thus, the proposed rescheduling offers benefits to the consumer in terms of ease of access, removal of embarrassment and product range consideration, and benefits to the public in terms of freeing pharmacists to focus on higher needs customers.

B3.2 Justification for Pharmacy Medicine Classification

As previously mentioned, clotrimazole is already classified in New Zealand as either a Pharmacy Medicine or General Sales Medicine for dermal use. Thus, the appropriateness of this medicine as a Pharmacy Medicine appears not to be in question, and only the appropriateness of clotrimazole being rescheduled to a Pharmacy Medicine *for vaginal use* needs to be addressed.

New Zealand does not have a clear definition of the dividing lines between Pharmacist Only Medicines and Pharmacy Medicines. Thus, it is appropriate to consider the Australian definitions. The Interim Guidelines for the National Drugs and Poisons Schedule Committee (March 2003) detail the characteristics of Pharmacy Medicines as being substances or preparations for therapeutic use that fall within the following criteria:

Suitable for self treatment of a minor ailment or symptom capable of being monitored by the consumer

The symptoms of vulvovaginal candidiasis are itching, burning, soreness and redness of the vulva. Sufferers of candidal vulvovaginitis recognise it as 'thrush' and usually suffer the same symptoms on each occasion. Vaginal candidiasis normally presents as white, odourless vaginal discharge or possibly as frequent reoccurrence of attacks of candidal vulvitis. It is generally accepted that both conditions should be treated simultaneously to prevent reoccurrence of vulval candidiasis due to untreated candidal infection in the vagina.

Canesten vaginal thrush products are for use by women who have had a previous medical diagnosis of vaginal thrush - this is clearly stated on both the product carton and the package leaflet. They will, therefore, be well aware of the symptoms of vaginal thrush, and able to self-diagnose a subsequent attack before seeking treatment (14). A description of the symptoms and clear warnings and precautions are provided on the product carton. Additionally, the symptoms and warnings are expanded and elaborated on in the Canesten Consumer Medicine Information and the product leaflet, and symptoms that are not indicative of vaginal thrush are listed to provide further assurance of *correct* diagnosis without the advice of a pharmacist.

Symptoms of thrush tend to be quite noticeable, and so the condition can be easily monitored by the consumer. The carton label and leaflet stress the advice to consult a doctor if the condition does not improve within four days. The leaflet also stresses the importance of finishing the course of treatment for the longer treatment period presentations, to completely resolve the infection and not just the symptoms.

Extremely low abuse potential

These medicines are highly unlikely to be misused, abused, illicitly used or induce any kind of dependency. It is difficult to conceive how the product could be abused in any way.

Low potential of harm from inappropriate use

The quality use of the medicine can be achieved through the labelling on the packaging and leaflet (discussed in the next section).

It is acknowledged that the use of a pessary may not be straightforward for some patients. It is not usual practice, however, for a pharmacist to demonstrate the

insertion of a pessary. In the absence of a pharmacist, the patient information leaflet gives clear instructions, including pictorial information, on the insertion of the pessary, application of the cream and that the products are not to be taken by mouth. This is considered suitable for patients who have previously had thrush, as they most likely will have been treated with an intra-vaginal preparation consisting of a pessary and/or cream.

The labelling clearly states that the product should only be used if a previous confirmed diagnosis has been made by a doctor. However, as a Pharmacy Medicine, advice or counselling from a pharmacist is available if necessary. In the next section, a proposed Bayer training programme for pharmacy assistants is outlined to identify when such advice or counselling from the pharmacist may be required.

Should the consumer incorrectly self-diagnose, or Canesten be mistakenly purchased for another disease state, the consequences are unlikely to be harmful to the patient. In most cases, the symptoms of the disease will fail to resolve - the label clearly states that if no relief is gained within four days of commencing treatment the consumer should refer to a doctor. This means that any other disease the patient may be suffering will at worst have treatment delayed for four days. While possibly uncomfortable or unpleasant, this is unlikely to cause the consumer harm.

Of more concern in considering potential for harm is the possibility that recurrent vaginal thrush is a symptom of a more serious underlying disease (as opposed to a simple disease state in itself) such as diabetes or some form of immunosuppression. The proposed labelling clearly states that if the consumer has had three or more infections in the last 6 months, the advice of a doctor should be sought. Fully developed cases of diabetes or immunosuppression are likely to cause other symptoms that would motivate the patient to visit a doctor independent of vaginal thrush occurring.

Intervention by a pharmacist on every purchasing occasion has no appreciable effect on the potential for inappropriate use or mis-diagnosis by the patient, as the pharmacist is unable to truly verify a patient's self-diagnosis based on her description of symptoms. A diagnosis unsupported by laboratory findings can never be entirely reliable, and as a Pharmacy Medicine the pharmacist is available should the customer wish to seek counselling or advice, or should the pharmacy assistant believe that such advice would be of benefit. The current classification of clotrimazole for vaginal use as a Pharmacist Only Medicine does not obviate the need for a patient to seek medical examination and vaginal microbiological testing in the event of uncertain diagnosis. This situation is unchanged with a Pharmacy Medicine classification.

Additionally, the Consumer Medicine Information and pack insert not only lists risk factors and symptoms suggestive of thrush, but also symptoms that are not indicative of thrush and cases where immediate presentation to a doctor is warranted (see Part A). This limits the potential for inappropriate use.

Low or well characterised incidence of adverse effects or side effects, and contraindications for which advice or counselling is available

The use of the medicine is substantially safe and adverse events reported to Bayer and regulatory authorities globally are low when compared to the global use of vaginal preparations of clotrimazole. Clotrimazole has a well characterised safety profile as described in this application that has been established through hundreds of clinical studies and decades of post marketing use globally. The use of clotrimazole vaginal preparations are also well established as first line use for the treatment of vaginal candidiasis and vulvovaginal candidiasis in both Australia and New Zealand.

Furthermore the treatment of vulvovaginal candidiasis during pregnancy with topical clotrimazole is regarded as safe (see Section B2.6.3). Clotrimazole vaginal preparations are classified in Australia as Pregnancy Category A, and this classification provides further assurance that the product is relatively safe in terms of adverse events.

Product contraindications are limited to allergic reactions only. Those patients affected will be well aware of their allergies, and involvement of a doctor or a pharmacist in the usage decision is of limited assistance in identifying possible new cases.

Only minor or well characterised interactions with commonly used substances or food for which advice or counselling is available.

Clotrimazole administered topically or vaginally has no known interactions with any other medicine.

Due to the low systemic absorption of clotrimazole the opportunity for drug-drug interactions with clotrimazole with common medicines is negligible. In comparison, miconazole administered systemically is known to inhibit CYP3A4/2C9 and therefore in patients on oral anticoagulants, such as warfarin, caution should be exercised and anticoagulant effect should be monitored as these patients may be at risk of increased bleeding or bruising.

Fluconazole is an oral therapy marketed as a single 150 mg oral dose for the treatment of vaginal candidiasis. As a systemic therapy the opportunity for drug

interactions is increased. Fluconazole is an inhibitor of the cytochrome P450 system, particularly the CYP2C and to a lesser extent the CYP3A isoforms. Whilst it is acknowledged that a single dose of fluconazole is unlikely to have significant bearing on the plasma levels of concomitant medicines, the benefit:risk still needs to be evaluated for an individual patient.

Like other topical oil based formulations the clotrimazole creams and pessaries can potentially impact the effectiveness of barrier contraception methods made from latex such as condoms or diaphragms. Thus information in this regard is clearly indicated on the proposed package leaflet. This message is further reinforced to consumers by condom manufacturers in the supplied literature and leaflets i.e. that oil based topical products can decrease the effectiveness of the latex condoms and should be not be used concurrently. Pain on sexual intercourse is a known symptom of vaginal thrush, and women with thrush are thus less likely to be using such latex products, further minimising the associated risk.

A wide therapeutic index

The quantity of active substance that is absorbed via the vagina or skin is very small. Clotrimazole is metabolised rapidly and exhibits a short 1 - 2 hour half life.

No information is available on cases of overdosage with vaginally applied clotrimazole. To date no dose-dependent enhancement of the pharmacological effect of clotrimazole has been observed at normal doses.

Given these characteristics of the product, the therapeutic index appears to be very broad and certainly well in excess of normal doses required for therapeutic effect.

Low risk of masking a serious disease

The most obvious concern in down-scheduling clotrimazole vaginal preparations to Pharmacy Medicine is the inappropriate treatment of a different condition as a consequence of misdiagnosis, and, more importantly, whether or not this will have a deleterious impact on the outcome of the condition left untreated.

Vulval symptoms of itching and soreness may also be due to a range of conditions other than thrush, such as systemic disease, allergy, vulvodynia, epithelial disorders, neoplastic disorders or other infections (particularly bacterial vaginitis). The majority of these other conditions (at risk of being inappropriately treated) are rare, compared with the distressingly common condition of vaginal candidiasis.

Systemic diseases are usually chronic conditions and will not respond to topical antifungal therapy, necessitating follow up visits to the doctor. Allergies, epithelial disorders and neoplastic conditions will likewise not respond. Many of these diseases will not present in the same way as candidiasis in any event. In addition, these medical conditions do not present with classical candidal vaginal discharge.

If symptoms do not subside within 4 days (lack of response to antifungal therapy), the accuracy of the self-diagnosis should be checked by a doctor. The proposed carton label and package insert stresses the advice to consult a doctor if the condition does not improve within four days. A delay of up to 4 days is highly unlikely to increase the risk, or seriously compromise the clinical outcome, of any patients who might otherwise have visited their doctor earlier for consultation.

The diagnosis of candidal infections can only be confirmed by microbiological testing. Many physicians and pharmacists currently recommend treatment for candidal vaginitis and vulvitis on the basis of the description of the symptoms, with the advice to consult a doctor if the condition does not respond. As previously commented, it is inconceivable that the pharmacist can do more than provide advice based on a description of symptoms by the patient. The package leaflet and label provide a specific description of the symptoms of thrush as:

- vaginal itching
- vaginal soreness
- a white odourless discharge from the vagina (like cottage cheese)
- pain during intercourse.

The labelling also clearly states that the patient must have been treated for thrush previously. In the absence of a pharmacist, the carton label therefore asks specific questions of the patient concerning their symptoms and previous experience of thrush.

As an additional safeguard, the labelling also contains the warnings that patients should not use the product, but seek advice from a doctor should their symptoms be accompanied by:

- abnormal or irregular vaginal bleeding
- blood stained discharge
- vulva or vaginal sores, ulcers or blisters
- lower abdominal pain
- pain when passing urine
- fever or chills
- foul smelling or unusual colour vaginal discharge.

These symptoms are considered inconsistent with thrush and therefore in need of full evaluation by the patient's physician. This labelling further helps to direct patients suffering from other conditions or infections (e.g. bacterial vaginosis, Trichomonas or genital herpes) who may be experiencing symptoms that are similar but not fully indicative of thrush.

Low risk of compromising medical management of a disease

In terms of compromising the medical management of a disease, the primary concern is if the treatment of thrush could affect the medical management of another disease (incorrect diagnosis and inappropriate use having already been discussed).

It is difficult to conceive that treatment of vaginal thrush could interfere with the medical management of another disease in any way. Systemic absorption of vaginally administered clotrimazole is very low, and no interactions with other medications are known of. Thus, the potential for affecting any systemic treatment appears extremely low.

B3.3 Proposed Transition to Pharmacy Medicine

Assuming clotrimazole for vaginal use is rescheduled to Pharmacy Medicine, Bayer will undertake a four stage programme to facilitate the transition and promote safe and responsible use of the product. The four parts of the programme are:-

- improve the Canesten labelling
- improve the Canesten Consumer Medicine Information and consequentially the pack insert
- training for pharmacy assistants to identify possible unsuitable use of the product
- make information available to consumers to promote appropriate use of the product

B3.3.1 Canesten Labelling

As previously mentioned in Part A, Bayer proposes to change the product carton labels for use as a Pharmacy Medicine. The changes will be:-

Change to Performance Based Labelling

Performance based labelling has been demonstrated as a readily understandable form of labelling that improves consumer understanding of the information provided, and allows for greater comprehension of all of the information on the label.

Provide Information on the Label

In particular, Bayer proposes that the symptoms of vaginal thrush be more clearly stated on the labels, by including them in the purpose statement, so that the consumer can assess the appropriateness of the product *prior to purchase* without having to refer to an alternative information source. Currently the pharmacist fulfils this role to some extent, but with the pharmacist absent from the purchasing decision the labelling must reliably assure appropriate use of the product.

Proposed wording for the symptoms of vaginal thrush is:-

Vaginal thrush (vaginal candidiasis is a common infection caused by yeast-like fungi. Symptoms include itching, burning, discharge.

Thus, the labels identify the predominant symptoms of vaginal thrush. Also, the Consumer Medicine Information and pack insert allow for differential diagnosis as they alert the consumer to symptoms that are not associated with vaginal thrush such as malodorous discharge, abdominal pain and vulval blistering.

Furthermore, the labels promote correct selection of the product by alerting the consumer that medical advice should be sought if:-

- she is unsure about using the product
- it is her first attack of thrush
- she has had 3 or more infections in the last 6 months
- she is pregnant or thinks she might be
- she suffers from diabetes
- she is under 18 years of age

The labels advise the consumer to consult a doctor if:-

- she has not had thrush before
- the symptoms do not start to clear within 4 days after commencement of treatment

While all of this information is on the current labels, the improved format is designed to improve consumer uptake of the information provided.

B3.3.2 Canesten Consumer Medicine Information and Pack Insert

Bayer proposes to rewrite the current Consumer Medicine Information to improve consumer ability to correctly identify vaginal thrush, and their own suitability for self-treatment or if medical advice is required. As the pack insert is the CMI, this also means that pack inserts will be updated in a similar manner.

See Appendix 3 for draft pack inserts. However, Bayer plans to further modify these drafts to include information allowing the consumer to identify symptoms of diabetes or immunosuppression, thereby allowing the consumer to possibly identify causes if she is suffering repeated attacks of vaginal thrush.

B3.3.3 Pharmacy Assistant Training Programme

While, as a Pharmacy Medicine, the pharmacist is not obligated to be involved in the purchasing decision for Canesten, all purchasers will still have face-to-face contact with Pharmacy Assistants. Pharmacy Assistants are able to undertake useful screening for appropriate use of the product, and easily identify situations where the pharmacist should be called in for further advice. Bayer intends to provide training and product support materials for these Pharmacy Assistants to facilitate this process.

Because Pharmacy Assistants are not medical professionals, any screening they undertake should be able to be limited to a few simple questions. Canesten for vaginal use can fulfil this requirement. The likely proposed questions a Pharmacy Assistant should ask are:-

	Answer Yes	Answer No
Have you used this type of product before?	Continue	Refer to pharmacist as possible first diagnosis and should be referred to a doctor
Have you used this type of product more than 3 times in the last 6 months?	Refer to Pharmacist for possible underlying disease	Continue
Last time you used this type of product, did it work well for you?	Continue	Refer to pharmacist for possible misdiagnosis
Are you, or do you think you might be, pregnant?	Refer to pharmacist for further advice	Sell product to customer

All of the questions above are covered on the label, and the product is able to stand alone and allows the consumer to make appropriate decisions about the issues covered above. However, the support of Pharmacy Assistants will serve to further emphasize the importance of these issues and ensure that consumers make the best possible decision regarding the use of Canesten.

Bayer already provides a comprehensive training programme for pharmacy personnel that allow Pharmacists and Pharmacy Assistants to better understand the disease and the suitability of the Canesten product range for treatment. This will practise will continue and be expanded should clotrimazole vaginal preparations be down-scheduled.

B3.3.4 Provision of Consumer Information

Educational literature can be made available not only to health professionals but also to women to help dispel the misunderstandings and save the embarrassment which is attached to this sensitive condition. By providing brochures and leaflets explaining the signs and symptoms of the condition, the causes and predisposition to the disease, preventative measures to lower the risk of an attack and appropriate treatment to be used, women will be able to responsibly take a more active role in their healthcare.

Bayer already undertake a full consumer promotional programme for the Canesten gynaecological products, including TV advertising. Should the product be reclassified, some change of emphasis in this programme is envisaged, so that the importance of correct diagnosis and contacting a doctor if symptoms do not start to resolve in 4 days is emphasized.

APPENDICES

Appendix 1

NDPSC Evaluation Report and Bayer company response

Appendix 2

United Kingdom reclassification to General Sale documentation

Appendix 3

Draft Proposed Pack Inserts

Appendix 4

Canesten Clotrimazole for Gynaecological Indications Clinical Overview

Appendix 5

New Zealand Adverse Event data (CARM)

Appendix 6

Australian Adverse Event data (TGA)

Appendix 7

Clotrimazole Periodic Safety Update Report 28 October 2005

REFERENCES

All references are available on request.

1. Owen MK, Clenney TL. Management of vaginitis. *Am Fam Phys*; 2004;**70**: 2125-32
2. Plempl M On the action kinetics of clotrimazole *Chemotherapy* 1982; **28**:S22-31
3. Ringdahl, EN. Treatment of recurrent vulvovaginal candidiasis. *Am Fam Phys* 2000; **61**:3306-12
4. Fong, IW Clinical and Cost Considerations in the Pharmacotherapy of Vulvovaginal Candidiasis. *PharmacoEconomics* 1996 **9(6)** 497-505
5. Young GI, Jewell D. Topical treatments for vaginal candidiasis (thrush) in pregnancy. The Cochrane Database of Systematic Reviews 2005.
6. Czeizel AE et al. Preterm Birth reduction after clotrimazole treatment during pregnancy. *Eur J Obstet and Gynecol and Reproductive Biol* 2004; **116**:157-63
7. Hudson MMT, Antifungal resistance and over the counter availability in the UK: a current perspective. *J Antimicrob Chemother* 2001 **48**:345-350
8. Ritter W, Mycoses of the Female Genitals. Current Diagnostics and Therapy Int. Workshop Luxembourg Oct. 1987. Ed.: H Ludwig, Schattauer Verlag, Stuttgart 35-38 (1988).
9. Abbott J, Clinical and Microscopic Diagnosis of Vaginal Yeast Infection: A Prospective Analysis. *Annals of Emergency Medicine* 1995 **25**:5 587-591
10. Lo M K, Vaginal Discharge: Four Minute Guide. *New Zealand Doctor* 1 June 2005 p31
11. Lo M K, Relieving the Age Old Irritations of Thrush. *New Zealand Doctor* 21 September 2005
12. Watson M C et al, Community Pharmacist's Views and Beliefs About the Treatment of Symptoms Suggestive of Vaginal Thrush in Community Pharmacies *Pharmacy World & Science* 2000 **22(4)** 130-135

13. Sobel J D, Limitations of Antifungal Agents in the Treatment of Candida Vaginitis : Future Challenges *Drug Resistance Updates* 1999 **2** 148-152
14. Pirotta M V, “Not Thrush Again!” Women’s experience of Post-Antibiotic Vulvovaginitis *MJA* 7 July 2003 **179** 43-46