Bayer HealthCare
Consumer Care

Rescheduling Application

for

Canesten® Plus
Topical Cream

Clotrimazole 10 mg/g, Hydrocortisone 10 mg/g

From Pharmacist Only Medicine
to Pharmacy Medicine

July 2012

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PART A

This submission to the New Zealand Medicines Classification Committee seeks rescheduling of Canesten Plus topical cream from the current classification of Pharmacist Only Medicine to Pharmacy Medicine.

Canesten Plus topical cream contains clotrimazole 10 mg/g and hydrocortisone 10 mg/g (as acetate). Clotrimazole topical cream at this strength is currently a Pharmacy Medicine – it is the hydrocortisone at a strength of 10 mg/g that is determining the current more restrictive classification.

A1. Name of the Medicine

The International Non-Proprietary Name of the active ingredient to be reclassified is hydrocortisone (as acetate).

The proprietary or brand name is Canesten® Plus.

Canesten is an umbrella brand name that covers a number of antifungal products, both for topical and vaginal use. The registered trade names of the other Canesten topical products are:-

Canesten - topical cream, clotrimazole 10 mg/g
Canesten - topical solution, clotrimazole 10 mg/mL
Canesten Once Daily Bifonazole Athlete's Foot – topical cream, bifonazole 10 mg/g
Canesten Once Daily Bifonazole Body – topical cream, bifonazole 10 mg/g

All of these medicines are Pharmacy Medicines. Canesten Plus topical cream is a new addition to this range of topical antifungal treatments, having been registered in September 2011.

A2. Name of the Company

This submission is made by:-

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A3. Dose Forms, Strengths and Pack Sizes

The following product is proposed for reclassification:-

Canesten Plus, clotrimazole 10 mg/g and hydrocortisone 10 mg/g (as acetate) topical cream, one tube of 30 g

While 15 g and 20 g tubes are also registered, only the 30 g tube of cream is planned to be commercialised, both in New Zealand and Australia.

A4. Indications

The currently approved data sheet for Canesten Plus, dated 10 October 2011(see Appendix 1), has the following indication:-

> "CANESTEN PLUS cream is indicated for dermatophyte and yeast infections of the skin when inflammation is prominent. This includes conditions such as fungal infected dermatitis, intertrigo and Candida nappy rash."

The currently approved labelling (see section A7) uses consumer-friendly language and consequently is more specific, with the uses being:-

> "For sensitive, itching, inflamed fungal skin infections that include tinea (athlete's foot, jock itch, ringworm), fungal skin rash, thrush infections of the skin, fungally infected nappy rash and eczema/dermatitis."

A5. Classification

The current classification of clotrimazole, taken from the Medsafe Web site on 2 July 2012, is:-

Clotrimazole, except in medicines for vaginal or external use	Prescription
Clotrimazole; for vaginal use	Restricted
Clotrimazole; for external use except in medicines for tinea pedis only or when sold in practice by a Podiatrist registered with the Podiatrists Board	Pharmacy Only
Clotrimazole; for dermal use in medicines for tinea pedis only or when sold in practice by a Podiatrist registered with the Podiatrists Board	General Sale

No change is sought to this classification schedule for clotrimazole.

The current classification of hydrocortisone, taken from the Medsafe Web site on 2 July 2012, is:-

Hydrocortisone, except when specified elsewhere in this schedule	Prescription
Hydrocortisone and hydrocortisone acetate but no other	Restricted

esters of hydrocortisone; for dermal use in medicines containing 1% or less but more than 0.5% by weight of hydrocortisone base with no other active ingredient except an antifungal and in a quantity of 30 g or less or 30 mL or less per container; in rectal medicines containing 1% or less but more than 0.5% by weight of hydrocortisone base and in combination with a local anaesthetic and in a quantity of 35 grams or less per container or up to 12 suppositories per pack

Hydrocortisone and hydrocortisone acetate but no other esters of hydrocortisone; for dermal use in medicines containing 0.5% or less by weight of hydrocortisone base with no other active ingredient except an antifungal and in a quantity of 30 grams or less or 30 millilitres or less per container; in rectal medicines containing 0.5% or less by weight of hydrocortisone base and in combination with a local anaesthetic and in a quantity of 35 grams or less per container or 12 suppositories or fewer per pack	Pharmacy Only

The classification sought for hydrocortisone is (changes are in blue):-

Hydrocortisone, except when specified elsewhere in this schedule	***Prescription***
Hydrocortisone and hydrocortisone acetate but no other esters of hydrocortisone; for dermal use in medicines containing 1% or less but more than 0.5% by weight of hydrocortisone base with no other active ingredient and in a quantity of 30 g or less or 30 mL or less per container; in rectal medicines containing 1% or less but more than 0.5% by weight of hydrocortisone base and in combination with a local anaesthetic and in a quantity of 35 grams or less per container or up to 12 suppositories per pack	***Restricted***
Hydrocortisone and hydrocortisone acetate but no other esters of hydrocortisone; for dermal use in medicines containing 0.5% or less by weight of hydrocortisone base with no other active ingredient and in a quantity of 30 grams or less or	***Pharmacy Only***

30 millilitres or less per container; for dermal use in medicines containing 1% or less by weight of hydrocortisone base in combination with an antifungal and in a quantity of 30 grams or less or 30 millilitres or less per container;
in rectal medicines containing 0.5% or less by weight of hydrocortisone base and in combination with a local anaesthetic and in a quantity of 35 grams or less per container or 12 suppositories or fewer per pack

In essence, the proposed change applies only to use of the medicine in combination with an antifungal, and allows for a greater strength of hydrocortisone (from 0.5% to 1%) when it is used in combination with an antifungal for dermal use.

The same proposal will be submitted in Australia.

A5.1 Classification Status in Other Countries

Antifungal preparations in combination with hydrocortisone are available globally, mostly as OTC medicines. The range of OTC classifications ranges from being restricted to a pharmacist selling the products right through to the equivalent of a New Zealand General Sales classification. The following table presents the legal classification of hydrocortisone topical preparations in selected countries – the classification in combination with an antifungal is also mentioned where this information is available.

Status of Hydrocortisone in Topical Preparations in Selected Countries

Country	Current Classification	Year of Switch from Prescription
Australia	Schedule 2 (Pharmacy Medicine) HYDROCORTISONE and HYDROCORTISONE ACETATE, but excluding other salts and derivatives, in preparations for human therapeutic use containing 0.5 per cent or less of hydrocortisone: (a) for dermal use, in packs containing 30 g or less of such preparations, containing no other therapeutically active constituent other than an antifungal substance; or	1999

	(b) for rectal use when combined with a local anaesthetic substance but no other therapeutically active constituent **except** unscheduled astringents: (i) in undivided preparations in packs of 35 g or less; or (ii) in packs containing 12 or less suppositories. Schedule 3 (Pharmacist Only Medicine) HYDROCORTISONE and HYDROCORTISONE ACETATE, but excluding other salts and derivatives, in preparations for human therapeutic use containing 1 per cent or less of hydrocortisone: (a) for dermal use, in packs containing 30 g or less of such preparations, containing no other therapeutically active constituent other than an antifungal substance; or (b) for rectal use when combined with a local anaesthetic substance but no other therapeutically active constituent **except** unscheduled astringents: (i) in undivided preparations, in packs of 35 g or less; or (ii) in packs containing 12 or less suppositories, **except** when included in Schedule 2.	
New Zealand	See A5 – Pharmacist Only Medicine	Unknown, probably pre-1992
USA	OTC – 0.5% strength OTC – 1% strength	1979 1990
Canada	Prescription – in combination with an antifungal	
Austria	OTC – in combination with an antifungal	Unknown
Belgium	OTC – in combination with an antifungal	Unknown
Denmark	OTC – maximum strength 1% Prescription – in combination with an antifungal	1989
Finland	OTC – in combination with an antifungal	1992
France	OTC – maximum strength 0.5%, maximum pack size 75 g	1996
Germany	OTC – for all indications. Maximum strength 0.25%, for adults and children over 8 years, maximum pack size 50 g.	1998
Ireland	OTC – in adults and children not under 10 years, maximum strength 1%, maximum pack size 15 g OTC – in combination with an antifungal	Unknown

Norway	OTC – up to 1% hydrocortisone and 25 g pack size OTC - in combination with an antifungal up to 15 g pack size	Unknown
Portugal	OTC	1995
Sweden	OTC OTC – in combination with an antifungal	1983 1992
UK	OTC – P (equates to a Pharmacy Medicine in New Zealand). For use in combination with miconazole nitrate or clotrimazole for adults and children not less than 10 years, maximum strength 1%, maximum pack size 15 g	1998

Table adapted from AESGP/WSMI publications http://www.aesgp.be status 2 July 2012 and data on file.

These figures demonstrate that during the 1990's there was a world-wide trend towards less restriction of hydrocortisone treatments, and in many instances this trend embraced classifications where the customer can self-select and purchase the product without the intervention of a healthcare professional. However, there has been little change in the last 12 – 15 years. With the additional safety information and experience gained during this time, Bayer believes it is now appropriate to consider further down-scheduling of the products.

A6. Extent of Usage

A6.1 Usage in New Zealand

A6.1.1 Usage of Canesten Plus in New Zealand

Canesten Plus was registered in New Zealand in October 2011. The product is not yet marketed here, with launch planned for September 2012 (the delay in launch caused by registration delays in Australia). Canesten Plus was the first clotrimazole/hydrocortisone combination to be registered in New Zealand since

Bayer discontinued Canesten HC cream in February 1999. Canesten HC cream was approved in New Zealand in October 1995 – however, it is understood the product was never marketed here.

A6.1.2 Usage of Antifungal/Hydrocortisone Topical Preparations in New Zealand

There are currently four antifungal/hydrocortisone topical preparations available in New Zealand. All are topical creams, as listed below:-

Brand Name	Active Ingredients	Classification	Pack Size	Sponsor
Daktacort	Hydrocortisone 10 mg/g, miconazole nitrate 20 mg/g	Pharmacist Only Medicine	15 g	Johnson & Johnson (NZ) Ltd
Micreme H	Hydrocortisone 10 mg/g, miconazole nitrate 20 mg/g	Pharmacist Only Medicine	15 g	Mylan New Zealand Ltd
Resolve Plus 0.5	Hydrocortisone 5 mg/g, miconazole nitrate 20 mg/g	Pharmacy Medicine	15 g, 30 g	Douglas Pharmaceuticals Ltd
Resolve Plus 1.0	Hydrocortisone 10 mg/g, miconazole nitrate 20 mg/g	Pharmacist Only Medicine	10 g (sample), 15 g, 30 g	Douglas Pharmaceuticals Ltd

Annual sales volumes of these products are presented on the next page:-

Brand Name	First Registration	Classification	Pack Size	Sales Volume (units - MAT to 20/5/12)
Daktacort	1984	Pharmacist Only Medicine	15 g	2
Micreme H	1988	Pharmacist Only Medicine	15 g	318,816
Resolve Plus 0.5	2001	Pharmacy Medicine	30 g	7,000
Resolve Plus 1.0	1999	Pharmacist Only Medicine	30 g	1,898

Micreme H is the only one of these products funded by PHARMAC. The sales volumes above may be a reflection of this funding situation. A large majority of Micreme H sales are made through dispensing rather than over-the-counter – this further suggests that many consumers visit a doctor for advice when fungal infections become inflamed, and subsequently receive a prescription to treat their problem.

A6.2 Usage World-Wide

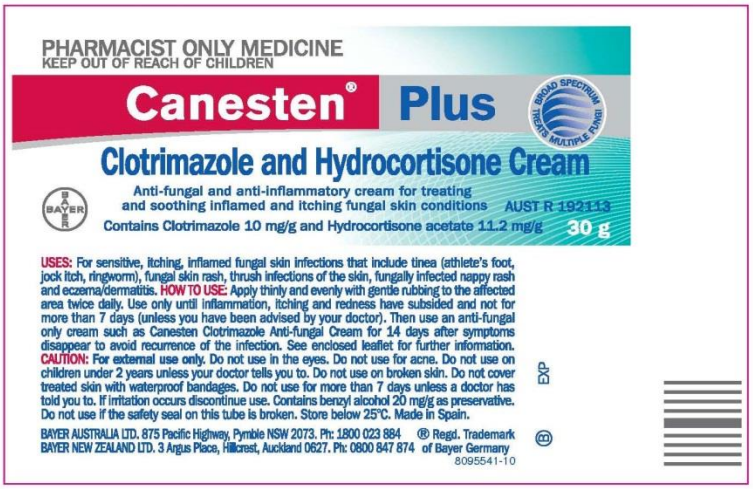
Bayer has clotrimazole plus hydrocortisone topical cream registered and marketed in a number of countries – it is understood that virtually all of these products are at a strength of 10 mg/g clotrimazole and 10 mg/g hydrocortisone. Total sales (number of grams sold) were approximately 96 million in 2009 – 2010 and 93 million in 2010 – 2011. These volumes equate to a world-wide, estimated patient exposure to a Canesten clotrimazole/hydrocortisone product for the period September 2009 – August 2010 of just over 6.4 million patients and for the period September 2010 – August 2011 of almost 6.2 million patients. (See latest PSUR – Appendix 2. The appendices to this report are provided electronically, hard copy is available on request.) Clearly, Canesten clotrimazole with hydrocortisone topical cream is a widely used product internationally.

A7. Labelling

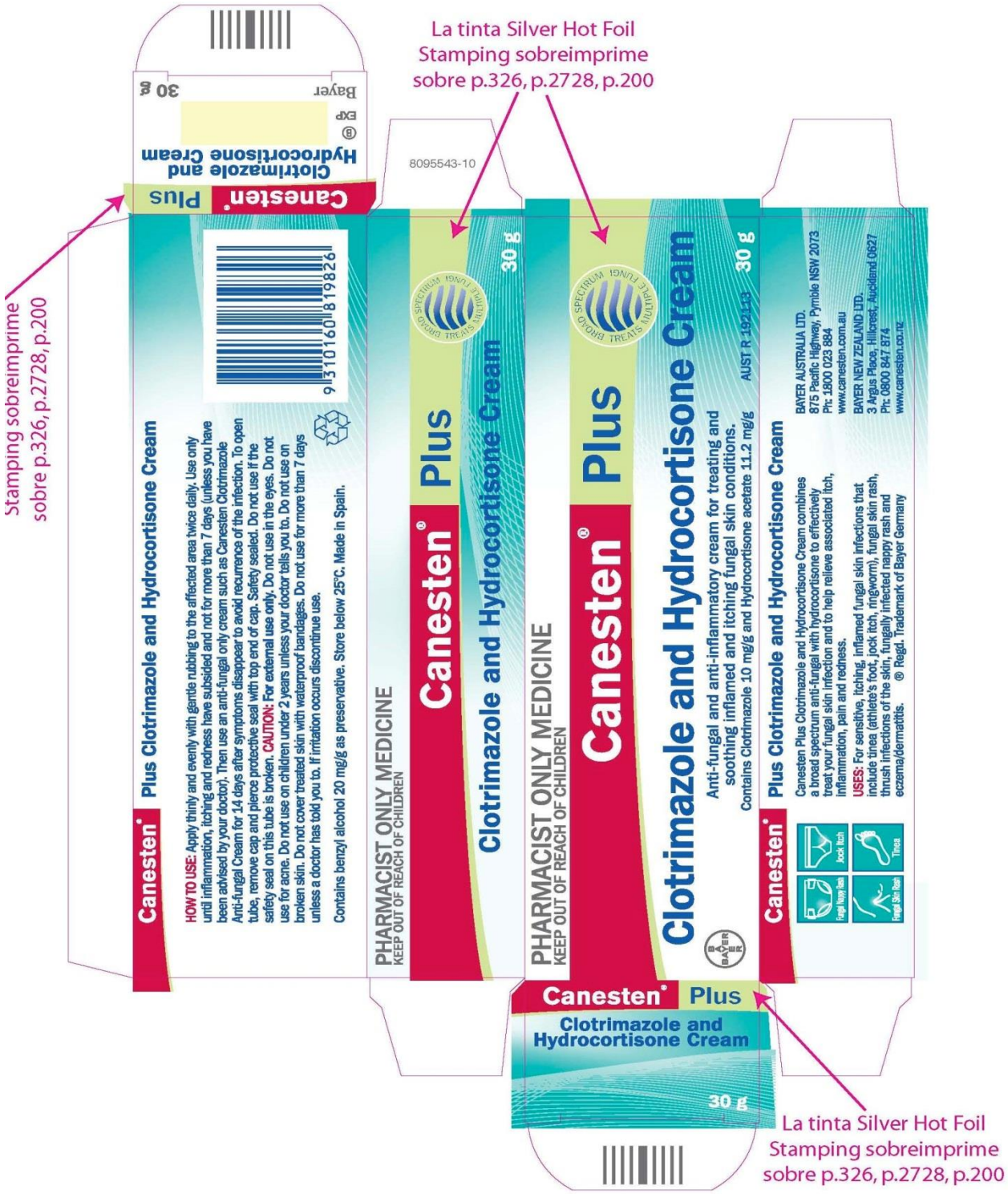
The currently approved product labels (tube and carton for the proposed 30 g pack size), which are approved for both New Zealand and Australia, follow on the next pages. Clearly, the classification statement on each label would need to be changed to PHARMACY MEDICINE should the proposed rescheduling be accepted, but no other changes to the labelling are envisaged. Bayer is of course open to suggestions from the Medicines Classification Committee, if the Committee feels that these labels could be further improved.

Bayer has used this basic format of labelling on their topical antifungal treatments for some time. While the tube labelling is challenging to fit all of the required information within the space allowed, the carton labelling is considered well designed to be highly legible and understandable to consumers.

Canesten Plus 30 g Tube Label



Canesten Plus 30 g Carton Label



Canesten Plus will be supplied with a pack insert which is a copy of the current Consumer Medicine Information for the product (see Appendix 3).

A8. Proposed Warnings

The currently required warnings for the product in **New Zealand** are (downloaded from the labelling statements database on 16 July 2012):-

Clotrimazole

- No required warnings

Hydrocortisone
For dermal use

- Do not use in children under 2 years old except on doctor's advice.
- Do not use for acne.
- Keep out of eyes.
- Do not use under bandages or dressings except on doctor's advice.
- Do not use for more than 7 days at a time, except on doctor's advice.

The currently required warnings for the product in **Australia (RASML 4)** are (downloaded from the Therapeutic Goods Administration web site on 16 July 2012):-

Clotrimazole
For dermal use

- No required warnings

Hydrocortisone
For dermal use

- CAUTION - Do not use for children under 2 years old unless a doctor has told you to.
- Do not use for more than 7 days unless a doctor has told you to.
- Do not use in the eyes.
- Do not use for acne.
- Do not use under waterproof bandages unless a doctor has told you to.

Additionally, there is a warning required by ARGOM for topical antifungal agents (but not required by RASML) – namely
"Continue treatment for 2 weeks after symptoms disappear to avoid recurrence."

The draft RASML 6 does not require any changes to these warnings for Australia.

The current labels for Canesten Plus incorporate all of the warnings above, which are essentially the same for Australia and New Zealand.

These warnings are considered appropriate for Canesten Plus. Additional warnings for use of the product as a Pharmacy Medicine are not considered necessary, as the warnings above cover the instances where caution is required. Adhering to these warnings, a consumer should be able to use Canesten Plus safely and effectively.

A9. Other Products

In addition to Canesten Plus (the subject of this submission), a number of other antifungal plus hydrocortisone products for topical administration currently sold in the New Zealand market, would be affected by the proposed reclassification. These are:-

Brand Name	Active Ingredients	Classification	Pack Size
Daktacort	Hydrocortisone 10 mg/g, miconazole nitrate 20 mg/g	Pharmacist Only Medicine	15 g
Micreme H	Hydrocortisone 10 mg/g, miconazole nitrate 20 mg/g	Pharmacist Only Medicine	15 g
Resolve Plus 0.5	Hydrocortisone 5 mg/g, miconazole nitrate 20 mg/g	Pharmacy Medicine	15 g, 30 g
Resolve Plus 1.0	Hydrocortisone 10 mg/g, miconazole nitrate 20 mg/g	Pharmacist Only Medicine	10 g (sample), 15 g, 30 g

PART B

Please note that throughout the following discussion, the term “hydrocortisone” is used to encompass hydrocortisone and hydrocortisone acetate, and no other salts of hydrocortisone. If there is a difference between hydrocortisone and hydrocortisone acetate, this is explicitly referenced.

Upon review of the current classifications of clotrimazole and hydrocortisone in New Zealand it is apparent that:-

(1) Clotrimazole is established as appropriate medication for consumer self-selection as a topical treatment of a range of fungal infections, classified Pharmacy Only Medicine
(2) Hydrocortisone at a strength of 0.5% is established as appropriate medication for consumer self-selection for the topical treatment of inflammatory conditions, classified Pharmacy Only Medicine
(3) Hydrocortisone at a strength of 1.0% is established as appropriate medication for the topical treatment of inflammatory conditions when selected with the assistance of a pharmacist, classified as Pharmacist Only Medicine

Given that these classifications are already established, and have been so for many years without cause for review, the following discussion does not cover them in further detail. The conditions they treat, their safety and efficacy, potential for abuse and all other factors taken into consideration in the assessment of suitability for over-the-counter sales are considered resolved. Therefore, this submission is limited to discussion of the following topics:-

- topical hydrocortisone 0.5% is relatively ineffective in comparison with the medication at 1.0% strength, whereas the safety profiles of the two strengths are relatively similar. Consumers deserve to have the most efficacious medicine available to them if safety is not compromised.
- consumers can make a differential diagnosis of dermal fungal infections with or without inflammation, without the mandatory input of a pharmacist.
- the current required labelling for Canesten Plus is appropriate for consumers to avoid the known risks of topical hydrocortisone treatment, including side effects and masking of disease.
- there is sufficient international precedence and experience to be confident that topical hydrocortisone at a strength of 1.0% is

appropriate for consumer self-selection and use when in combination with an antifungal medication.

If the statements above can be satisfactorily demonstrated, the proposed classification for topical antifungal medications in combination with hydrocortisone at a strength of 1% is appropriate and desirable.

1. Relative Efficacy and Safety of Various Strengths of Topical Hydrocortisone

1.1 Efficacy of Topical Hydrocortisone

Investigation into the relative efficacy of different strengths of topical hydrocortisone was carried out many years ago. Robinson and Robinson (1) found any concentration of less than 1.0% hydrocortisone to be relatively ineffective in 1954, and reviews of the medication since then have supported this view. In 1990 the FDA conducted an extensive review of the efficacy of hydrocortisone (2), part of which examined the relative effectiveness of 0.5% and 1% strengths. After evaluating 37 studies it was concluded that 1% hydrocortisone is more effective than 0.5% for a number of dermatologic conditions. David Frankel in his book Field Guide to Clinical Dermatology (2nd edition, 2005) goes further and states "Hydrocortisone 1% is the weakest topical corticosteroid that seems to be clinically effective; hydrocortisone 0.5% is of little benefit." Thus, it appears well-accepted today that topical hydrocortisone at a strength of 1% offers superior efficacy to a strength of 0.5% (5).

Conversely, strengths above 1% appear to offer little further advantage – Frankel again "Although hydrocortisone 2.5% would seem to be much stronger than hydrocortisone 1%, it is only marginally so". Similarly, the FDA review (2) found the 2.5% strength only slightly more effective than 1%. Thus, particularly for OTC indications such as inflamed fungal infections, the optimal strength of topical hydrocortisone is 1%.

Topical hydrocortisone has been available without prescription in Scandinavian countries since the 1950's (7) – the main criticism of the medicine during this time has been one of lack of efficacy. While safety is paramount, consumers are

entitled to have available the most efficacious medicines that risk-benefit analysis supports. Lack of efficacy in itself can be problematic, leading to overuse or change to inappropriate treatments. Good efficacy is particularly with a medicine such as topical hydrocortisone, where treatment is intended to be for a short period and lead to fast resolution of symptoms.

The bioavailability of topical hydrocortisone is affected by the choice of delivery method (2). Ointment formulations are considered more potent that other topical vehicles since ointments form a depot in the stratum corneum (3). Ointments also produce some degree of occlusion (3) and so are not considered suitable for many areas of the body. This is not currently of concern in New Zealand as there are no registered hydrocortisone ointments – however, MCC may wish to consider restricting any further reclassification of topical hydrocortisone to cream formulations only, or exclude ointment formulations.

1.1.1 Efficacy of Combination Treatments – Antifungal + Hydrocortisone

Fungal Infections

Fungi are the main etiologic agents responsible for the onset of diseases such athlete's foot and sweat rash in humans. Dermatophytes are responsible for athlete's foot and other dermatological fungal infections with *Candida albicans* often involved in sweat rash. Early symptoms of these diseases are a mild itch and slight inflammation that often do not worry the person infected and consequently treatment is not instigated.

However, left untreated these symptoms can quickly progress to intense itch and severe inflammation, pain increases and the skin barrier becomes more and more damaged (4). Bacterial co-infection can occur. The patient is motivated to treat their infection, and wants the itch and inflammation to be quickly resolved.

Similarly, skin diseases such as eczema and dermatitis can show secondary infections – there is increasing evidence that *Malassezia furfur* is an important etiological factor in seborrhoeic dermatitis (3).

Inflammation is an important process in fighting infection and initiating skin healing – it causes increased movement of immune system cells to the affected areas that help to counteract the infection and promote skin repair. However, inflammation often also causes erythema, burning and itching sensations that are unpleasant for the sufferer and increase the urge to scratch. If not resolved

quickly inflammation can spread and become chronic, causing delays in healing and skin barrier repair – thus, inflammation should be "switched off" to support healing, bringing relief to the patient and reducing the urge to scratch which leads to further inflammation and possible super-infection. Canesten Plus is superior to plain antifungals at reducing symptoms, and the presence of hydrocortisone may enhance the activity of the antifungal agent as superior cure rates are achieved (3). It has been found that compliance is improved amongst patients using such combination treatments as the rapid symptomatic improvement means patients are less inclined to stop the treatment prematurely (3).

The superior cure rates, improved compliance and fast resolution of irritating symptoms are sound clinical reasons for initially treating inflamed fungal infections with a combination antifungal and hydrocortisone, and then switching to an antifungal alone. While they can already purchase 0.5% hydrocortisone in combination with an antifungal, the proposed reclassification would offer consumers the convenience of self-selecting a highly efficacious medicine for this purpose.

Nappy Rash

The treatment of nappy rash is recognised as a skin disease in need of particular discussion due to both the age of the sufferer (generally children under 2 years of age) and the potential for partial occlusion of the treated area caused by disposable nappies.

While the use of topical hydrocortisone or antifungals, either alone or in combination, should not be the first line treatment for nappy rash, it is recognised that these medications have a role to play in the treatment of what can be an intractable problem (9). Topical hydrocortisone and antifungal medications are appropriate for more severe cases which have proven refractory to first line treatment approaches such as barrier creams (9). The maximum strength of hydrocortisone recommended is 1%.

Candida albicans is rarely found in infants without nappy rash, but is found in 41% - 77% of those with this problem – thus, topical clotrimazole, which is effective against this organism, is an appropriate treatment (10). Topical hydrocortisone is recognised a generally safe for use in children, and is commonly recommended for treatment of moderate to severe nappy rash (10). However, concerns remain as to its use, with some physicians recommending that it be used with extreme caution (8). These concerns are reflected in the conditions imposed by some countries on the availability of topical hydrocortisone without prescription – for example, in the United Kingdom the medication is only available for use in children aged 10 years or more, while in the USA it is not to

be used on children under 2 years or for the treatment of nappy rash unless under the supervision of a doctor. A general picture emerges that these two medications, either alone but possibly better in combination, have a role to play in the treatment of nappy rash, but caution must be exercised and this is best facilitated by the supervision of a physician.

The currently required labelling warnings for Canesten Plus are considered appropriate to guide the consumer to the correct use of this product for the treatment of nappy rash. While the product is indicated for nappy rash, the warnings clearly state that it should not be used in children under 2 years of age unless told to do so by a doctor, and that it should not be used under waterproof bandages. These warnings are unequivocal and easily understood, and it is expected that consumers will not use the product to treat nappy rash without first discussing the matter with their doctor on the basis of the currently labelling of the product. Ellis et al. (6) demonstrated that consumers do largely adhere to label instructions for topical hydrocortisone, and found that there is a high degree of physician involvement when consumers treat their children with this medicine. Given that access to doctors is probably more readily available in New Zealand than in the United States where this study was conducted, it is reasonable to think that the same is likely to be true in this country.

1.1.2 Differential Diagnosis

Dermatology encompasses over 3000 possible diagnoses (personal communication), many of which will have similar symptoms such as inflammation and pruritus. It can be extremely difficult for the patient to make an accurate diagnosis – even if the symptoms are similar to something they have had before, there is considerable potential for those symptoms to be generated by a different disease. The situation is only slightly improved with the input of a pharmacist, as clear diagnosis can often only be established through diagnostic tools such as microscopy and culture - either by a general practitioner or specialist.

However, the patient can readily recognise inflammation of the skin, with characteristic symptoms such as redness, heat and itching. Similarly, it is obvious when inflammation has resolved and topical hydrocortisone should no longer be applied. Consumers are not expected to experience difficulty in following the instructions on the label of Canesten Plus as to when combination treatment should be used and for how long.

There remains the question of whether or not the consumer can accurately identify an inflamed fungal infection. Many will have had the same complaint

previously, recognise the disease accurately and treat appropriately. For many inflammatory skin diseases that are not fungal infections, an appropriate treatment would be the application of topical hydrocortisone, and the use of Canesten Plus would resolve the problem. Although in these instances the antifungal component of the medicine is not required, the risk of harm is small. Unlike antibiotics, the risk of resistance to clotrimazole is minimal – no cases of resistance to this medicine are known of (Bayer communication).

Additionally, as previously discussed, dermatitis skin conditions can become fungally infected and in these instances the use of Canesten Plus instead of a plain hydrocortisone cream would resolve the problem completely, even though the consumer might be unaware of the fungal infection. Conversely, if the consumer unknowingly treats a fungal infection, or fungally infected dermatitis, with plain hydrocortisone cream, there is a very small risk of *tinea incognito* developing (see Section 1.2.2) and a larger risk of non-resolution or reoccurrence of symptoms and further, maybe prolonged, application of corticosteroid. On balance, the risk of applying an unneeded antifungal medicine does not appear greater than the risk of using a plain hydrocortisone cream when an antifungal is required.

1.2 Safety of Topical Hydrocortisone

1.2.1 Adverse Effects

Today it is well-accepted that there is virtually no systemic absorption from the topical application of hydrocortisone, and the risk of systemic corticosteroid side-effects is extremely low (2, 8). As such, these side-effects will not be further discussed.

A number of known side-effects from the topical application of corticosteroids exist – namely (http://dermnetnz.org/treatment/topical-steroids.html):-

- skin thinning (atrophy) and stretch marks (striae)
- purpura (leaking from or joining together of small blood vessels, leaving purple marks on the skin)
- periorificial dermatitis
- enlarged blood vessels (telangiectasia)

- susceptibility to skin infections
- disguising infection (see section 1.2.2)
- worsening of rosacea

The risk of these side effects depends on the strength of the steroid, the length of application, the site treated and the nature of the skin problem. It is generally agreed that hydrocortisone is the least potent and therefore safest of the corticosteroids available. Furthermore, there appears to be no distinction between different strengths of topical hydrocortisone – Medsafe, in the Prescriber Update Article "Topical Corticosteroids: Face Facts" make no differentiation between hydrocortisone 0.5% and hydrocortisone 1%, classing both strengths as mildly potent, while The New Zealand Dermatological Society classes all strengths of hydrocortisone from 0.5% to 2.5% as "mild". On this subject, New Zealand appears to be consistent with opinion from other countries as this view was consistently found in all references consulted.

The FDA reviewed safety data from thousands of subjects (2) and concluded that "the reactions reported for drug products containing 0.5% and 1% hydrocortisone are similar and that use of the higher 1% concentration does not appear to result in more severe reactions". Additionally, the level of reactions is itself very low. A search of the Medsafe SMARS database on 27 June 2012 for reports on hydrocortisone (which includes prescription products) revealed that there had been 18 reports of adverse reactions in New Zealand between 1 January 2000 and 31 December 2011, and only 9 of these were for topical preparations. Within the reporting period for the current PSUR (Appendix 2), a total of 2 medically confirmed ADR's and 22 unconfirmed ADR reports were received from over 6 million patient exposures. From this total of 24 reports, 2 were serious – both of which were medically unconfirmed. The information is in accordance with the established overall safety profile of clotrimazole with hydrocortisone, and it can be concluded that the benefit-risk balance for this combination product remains favourable.

Topical hydrocortisone has been available without prescription in Scandinavian countries since the 1950's without generating concerns as to its use by consumers (7).

While more potent steroids can generate serious adverse effects if used incorrectly, it is recognised that "guilt-by-association" is not a valid proposition and topical hydrocortisone is a relatively benign medication (7). In both the USA and the UK concerns have been raised in the past as to various potential side-effects that might be caused by hydrocortisone becoming available as an OTC medicine. However, these concerns have now largely been mitigated, both at the time through robust discussion amongst dermatologists and by the subsequent experience gained with consumers using topical hydrocortisone

(7,8). Thus, it appears topical hydrocortisone is a safe medication even if used incorrectly, and with appropriate labelling presents minimal risk to the public (7).

In summary, the evidence suggests that the overall risk of adverse events from topical hydrocortisone is very small, and that the relative risk between 0.5% topical hydrocortisone and 1.0% is virtually indistinguishable. On this basis, the current classification differences in New Zealand between these two strengths of topical hydrocortisone do not appear justified.

1.2.2 Ability to Mask Other Diseases

When a patient presents with skin disease, the doctor or pharmacist faces a considerable challenge as dermatology encompasses over 3000 possible diagnoses (personal communication), many of which will have similar symptoms such as inflammation and pruritus. Additionally, many dual possibilities exist, such as fungally infected atopic eczema. Best clinical practice if infection is suspected is to take scrapings for microscopy and culture – however, often a more pragmatic approach of "treat and see" can be taken, especially with the patient looking for immediate relief. In practice, 60% of patients with skin problems treat themselves without first seeking medical advice (8).

Occasionally such a "treat and see" approach can cause problems. One of the most common is a form of disease masking called *tinea incognito*, where the clinical appearance of a tinea infection has been altered by inappropriate treatment, usually with prolonged use of a topical steroid cream (5). Often an incorrect diagnosis of dermatitis has been made, hence the use of steroid cream. The condition symptomatically improves as the steroid resolves inflammation, but the infection spreads and when steroid cream treatment is ceased, symptoms reappear with renewed strength and different symptoms. Compared to an untreated *tinea corporis*, *tinea incognito* has a less raised margin, is less scaly, and is more pustular, extensive and irritable (http://dermnet.org/fungal/tinea-incognito.html). Treatment is to introduce a plain antifungal cream, or if the infection is very inflamed and itchy an antifungal plus a milder steroid can be used.

As the mildest steroid available, topical hydrocortisone is rarely the cause of *tinea incognito*. However, in order to minimise the already rare possibility that topical hydrocortisone cream at a strength of 1% might cause *tinea incognito*, the proposed reclassification is restricted to combination products with an antifungal rather than hydrocortisone alone. The proposed warning statement restricting

use to not more than 7 days will further protect the consumer from the possibility of *tinea incognito*.

1.2.3 Ability to Mask Diagnosis

While the "treat and see" approach is often successful, it can make subsequent diagnosis difficult if not successful. Treatment with a topical antifungal and/or hydrocortisone can interfere with the ability to take scrapings and the results obtained from those scrapings. If treatment has been used, it should be discontinued for a few days before such diagnosis is attempted. However, this possibility already exists with the treatments available in New Zealand as Pharmacy Medicines, and the proposed increase in strength of topical hydrocortisone is unlikely to materially affect instances where disease diagnosis is hampered. Thus, in terms of ability to mask diagnosis the proposed change is not considered to represent an increase in risk to the public.

2. Labelling

The current warnings on the approved Canesten Plus labels, which are proposed to stay the same, are a combination of the warnings required for topical clotrimazole and topical hydrocortisone in New Zealand and Australia. The warnings on the pack are:-

- For external use only
- Do not use in the eyes
- Do not use for acne
- Do not use in children under 2 years unless your doctor tells you to
- Do not use on broken skin
- Do not cover treated skin with waterproof bandages
- Do not for more than 7 days unless a doctor has told you to
- If irritation occurs discontinue use

In 1990 when the FDA reviewed topical hydrocortisone and subsequently made the 1.0% strength available over the counter, the following warnings were proposed for the USA (2):-

- For external use only
- Avoid contact with eyes
- If the condition being treated worsens or if symptoms persist for more than 7 days, discontinue use of this product and consult a physician
- Do not use for the treatment of diaper rash or on children under 2 years of age except under the advice and supervision of a physician
- Keep this and all drugs out of the reach of children
- In the case of accidental ingestion, seek professional assistance or contact a poison centre immediately

Essentially, the warnings required in the United States for hydrocortisone and those on the current labels of Canesten Plus (which are largely driven by the required warnings for topical hydrocortisone) are very similar. In 2005 Ellis et al. (6) reported on American consumer's compliance with these labelling requirements, noting that safe and effective use of the medication depended on consumer's ability to understand and follow the directions on the label. Although the study had some design weaknesses, being a telephone interview with a large degree of self-selection and relying on consumer recall, it also had some strengths as the interviewees were not aware they were being assessed for label compliance. Overall, non-compliance with the label instructions were infrequent, with 73% of use by adults and 72% of use by children judged to be fully compliant with the label. The most frequent non-compliant use was treatment of broken skin, which is outside the approved indications but not specifically warned against. Duration of use was generally short, suggesting that alternative treatment would be sought if a condition persisted. Even amongst non-compliant users, there was little evidence of systemic risk. The authors concluded "typically users of OTC HC products applied OTC HC treatments in accordance with the OTC label ……. OTC HC generally is used in a manner appropriate and likely to be safe".

This study (6) was conducted approximately 15 years after 1% topical hydrocortisone became available as an OTC product in the USA. It suggests that the required USA warnings are adequate to guide the consumer to safe use of the product, supported by the fact that there has been little impetus in the USA to review the 1990 reclassification decision. Although there was considerable opposition to making hydrocortisone an over-the-counter medicine at the time, it is now recognised that this opposition was unfounded (7), and the availability of

this medicine without prescription offered the consumer considerable convenience and cost-saving (7).

There is little reason to think New Zealand consumers would behave in a substantially different way to American consumers, and it appears logical that New Zealand consumers could also use topical hydrocortisone 1% safely and effectively.

In the United Kingdom, topical hydrocortisone is POM up to a strength of 1%. For athlete's foot and candidal intertrigo hydrocortisone can be supplied in combination with miconazole nitrate or clotrimazole, whereas hydrocortisone acetate can only be supplied in combination with miconazole nitrate – however, the reason for this difference when in combination with an antifungal medicine is not clear. Use is limited to adults and children not less than 10 years and pack size is limited to 15g for a cream or ointment (MHRA Web site). The label warnings listed below are required:-

- Contraindications – use on the eyes/face, ano-genital regions, broken or infected skin including cold sores, acne and athlete's foot (presumably this last condition does not apply when in combination with an antifungal)
- Not recommended for use on children under 10 years of age without medical supervision
- Do not use in pregnancy without medical advice
- Use sparingly over a small area once/twice a day for a maximum period of one week
- If the condition is not improved, consult your doctor

Again, these labelling requirements are essentially similar to those currently required in New Zealand for 0.5% hydrocortisone and proposed for the higher strength as an OTC medicine. Thus, the proposed labelling is consistent with current requirements in New Zealand and with international requirements. Analysis of the last 20 years' experience with over-the-counter hydrocortisone and clotrimazole does not suggest further warnings are needed on the label in order for consumers to use this medicine safely.

In summary, the discussion above has demonstrated that in comparison to topical hydrocortisone 0.5%, the stronger 1% presentation will provide the consumer with superior efficacy and comparable safety. Because of the very similar safety profiles between the two strengths, no new labelling requirements are considered warranted. The risk-benefit analysis for the proposed classification change is favourable. Consumers are entitled to access to the

most efficacious medicine, available with the fewest restrictions, when safety is not compromised. The proposed reclassification will deliver this entitlement, at the same time releasing pharmacists from unnecessarily having to be involved in all sales of the higher strength medicine.

APPENDICES

Appendix 1
Currently Approved Canesten Plus Data Sheet dated 10 October 2011

Appendix 2
Bayer Clotrimazole Periodic Safety Update Report No. 16 for the period 2-September-2010 to 1-September-2011

Appendix 3
Current Canesten Plus Consumer Medicine Information dated 17 May 2012

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