

**Rescheduling Application
for**

**Canesten[®] Plus
Topical Cream**

Clotrimazole 10 mg/g, Hydrocortisone 10 mg/g

**From Pharmacist Only Medicine
to Pharmacy Medicine**

January 2018

INDEX

	<u>Page</u>
PART A	2
Name of the Medicine	2
Name of the Company	3
Dose Forms, Strengths and Pack Sizes	3
Indications	4
Classification	4
Extent of Usage	12
Labelling	15
Proposed Warnings	17
Other Products	19
PART B	20
Efficacy and Safety of Fixed Dose Combination Treatment of an Antifungal with Hydrocortisone	21
Nappy Rash Indication	24
Increased Risk of Masking Symptoms	26
Prolonged Use	28
Pharmacy Medicine Classification Not Offering Better Accessibility	28
Conclusion	30
REFERENCES	32

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. An alternative brand name for this medicine is also approved for distribution – Canesten Extra. Canesten Extra is currently available in the New Zealand marketplace, whereas Canesten Plus is no longer available. Should this application be successful, Bayer plans to relaunch Canesten Plus as a Pharmacy Only Medicine – the product would encompass the restrictions proposed within this application for Pharmacy Only classification

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. Thus, this is a submission proposing the reclassification of hydrocortisone and hydrocortisone acetate 1% for dermal use when combined with an antifungal substance.

A1. Name of the Medicine

The International Non-Proprietary Name of the active ingredient to be reclassified is hydrocortisone (as acetate), when in combination with an antifungal medicine (in this case, clotrimazole).

The proprietary or brand name is Canesten® Plus. An alternative brand name, Canesten Extra, is also approved for distribution in New Zealand but would be retained as a Pharmacist Only option for this combination of medicines and so is not the subject of this application.

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
- Canesten Fungal Nail Treatment Set - topical cream, bifonazole 10 mg/g plus topical ointment urea 400 mg/g, plus a scraper and plasters

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

A2. Name of the Company

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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 15 g

Currently 15 g, 20 g and 30 g tubes are registered, but only the 30 g tube of cream has been commercialised. However, the 30 g tube is considered too large to be appropriate for the proposed Pharmacy Medicine classification, and a 15 g tube would be commercialised should this proposal be accepted.

A4. Indications

The last approved data sheet for Canesten Plus, dated 20 November 2012¹, 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^{2,3} (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.”

However, this broad range of indications is not considered appropriate for a Pharmacy Only Medicine. Consequently, and in response to previous MCC considerations when considering reclassification of this medicine (see section A5), the proposed indications for Canesten Plus as a Pharmacy Medicine are^{4,5}:-

“For sensitive, itching, inflamed fungal skin infections that include tinea (athlete’s foot, jock itch, ringworm) and fungal skin rash.”

In particular, fungally infected nappy rash is not considered appropriate as it is not consistent with the other label warnings required for the product (see section A8), and eczema/dermatitis is not considered appropriate as due to the complexity of diagnosis of this range of conditions the input of a health care professional is considered essential.

A5. Classification

The current classification of clotrimazole, taken from the Medsafe Web site on 8 January 2018, is:-

Clotrimazole, except in medicines for vaginal or external use	Prescription
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Clotrimazole; for vaginal use	Restricted
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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 8 January 2018, is:-

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 **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 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 **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):-

<i>Hydrocortisone, except when specified elsewhere in this schedule</i>	<i>Prescription</i>
<i>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 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</i>	<i>Restricted</i>
<i>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 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 15 grams or less or 15 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</i>	<i>Pharmacy Only</i>

Essentially, the proposed change applies only to use of the medicine in combination with an antifungal, and allows a greater strength of hydrocortisone (from 0.5% to 1%) when it is used in combination with an antifungal for dermal use to be classified as a Pharmacy Only Medicine.

A5.1 Recent Classifications of Hydrocortisone in Combination with an Antifungal in New Zealand and Australia

The current classification of hydrocortisone has not been changed in New Zealand since 1992, apart from a pack size increase from 15 g or 15 mL to 30 g or 30 mL during 2000 to harmonise with Australia. However, MCC has considered a number of proposals to change the classification in recent years.

Bayer New Zealand Limited submitted a proposal to change the classification in July 2012. The proposed classification at that time, with proposed changes in blue, was:-

<i>Hydrocortisone, except when specified elsewhere in this schedule</i>	<i>Prescription</i>
<i>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</i>	<i>Restricted</i>
<i>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 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;</i> 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	<i>Pharmacy Only</i>

The proposal included that the indications and warnings in place for the Restricted Medicine were equally appropriate for the proposed Pharmacy Only Medicine.

MCC considered this proposal at their 48th meeting in October 2012, and recommended that the proposal not be accepted⁶. The reasons for the recommendation were concerns with:-

- a. the nappy rash indication. The Committee considered that parents or caregivers would not be able to make a diagnosis of fungally infected nappy rash, and that there were potentially severe consequences with misdiagnosis.
- b. prolonged use. The Committee noted that patients may not use the medicine for the 7 days as directed on the packaging, and if used for too short or too long a period the medicine may be ineffective or there may be adverse effects.
- c. safety and efficacy of hydrocortisone when presented as a fixed dose combination with an antifungal. The Committee noted that no evidence had been provided that combining hydrocortisone with an antifungal decreases the amount of absorption or improves its safety profile.

The same proposal was submitted by Bayer in Australia in October 2012. In its decision of March 2013, the Advisory Committee on Medicines Scheduling (ACMS) recommended to retain the current scheduling for hydrocortisone⁷, with which the delegate concurred. The reason for this recommendation was the increased concentration of hydrocortisone, which posed increased risks of masking symptoms, particularly in children, exacerbation of bacterial infections through inappropriate application, and inappropriate use of a higher concentration with no demonstrated increase in benefit from the proposed down-scheduling.

Bayer Australia Ltd. submitted a proposal to down-schedule again in February 2015. The proposal was modified from that of 2012, in that indications were reduced to the treatment of tinea and other fungal skin infections, warnings strengthened to exclude children under 12 years old and the pack size reduced to 15 g or less. In its interim decision of October 2015⁸, the ACMS recommended the proposal be accepted. The reasons for the recommendation were:-

- a. Hydrocortisone 1% is more effective than 0.5% and the relative risk of adverse effects between these two strengths is hardly distinguishable.
- b. The safety profile for short term dermal use is good.
- c. Tinea and fungal infections are common, and itching and inflammation may occur with these infections.
- d. The 15 g pack size minimises duration of use
- e. The proposed warnings reduce the risk of inappropriate use.
- f. Easier access to a more effective product may be beneficial to consumers

This recommendation has now been enacted in Australia – following is an extract from the Australian Poisons Standard October 2017, taken from www.legislation.gov.au on 10 January 2018:-

Schedule 2

HYDROCORTISONE and HYDROCORTISONE ACETATE, but excluding other salts and derivatives, in preparations for human therapeutic use:

- a) for dermal use in preparations containing 0.5 per cent or less of hydrocortisone, in packs containing 30 g or less of such preparations, containing no other therapeutically active constituent other than an antifungal substance; or
- b) for dermal use in preparations containing 1 per cent or less of hydrocortisone, in packs containing 15 g or less of such preparations, containing an antifungal substance and no other therapeutically active constituent:
 - i) for the treatment of tinea (tinea pedis, tinea cruris, tinea corporis) and other fungal skin infections; and
 - ii) not labelled for the treatment of children under 12 years of age; or
- c) for rectal use in preparations containing 0.5 per cent or less of hydrocortisone, 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

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 dermal use, in packs containing 2 g or less of such preparations, containing no other therapeutically active constituent other than aciclovir (5% w/w or less) in adults and adolescents (12 years of age and older); or
- c) 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.

Canesten Plus as a Pharmacy Only Medicine was launched in Australia during January, 2017. The proposed labelling for New Zealand provided with this submission^{4,5,9} is that currently available in Australia.

Consistent with the process for harmonisation of the New Zealand and Australian schedules, the MCC considered the Australian decision made above at its 55th meeting of May 2016. The resulting recommendation was to maintain the current

classification i.e. to not harmonise with the decision made in Australia. The Committee's reasons for maintaining the status quo were¹⁰:-

- a. concern regarding lack of consultation with a pharmacist
- b. record keeping and monitoring provided by a pharmacist was valued
- c. change of classification to pharmacy only medicine would not significantly improve accessibility
- d. the side effect profile of hydrocortisone 1%

This third submission proposing change to the classification of hydrocortisone in combination with an antifungal will address the concerns of the MCC expressed at both the 48th and the 55th meeting.

A5.2 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, apart from Australia which has been fully discussed in section A5.1 – 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
Canada	OTC – 0.5% strength OTC – 1% strength	1986 2014
Belgium	OTC, including in combination with an antifungal	Unknown
Denmark	OTC – maximum strength 1% Prescription – in combination with an antifungal	1989
Finland	OTC – hydrocortisone up to 2.5% OTC – in combination with an antifungal	Pre 1965 1992
France	OTC – maximum strength 0.5%, maximum pack size 75 mg	1997

Germany	OTC – for all indications. Maximum strength 0.25%, for adults and children over 6 years, maximum pack size 50 g. Prescription - in combination with an antifungal	1996
Ireland	OTC, pharmacy only – in adults and children not under 10 years, maximum strength 1%, maximum pack size 15 g Prescription – in combination with an antifungal	Unknown
Netherlands	Prescription	
Norway	OTC, general sale – up to 1% hydrocortisone and 25 g pack size OTC, pharmacy only – 1% hydrocortisone in combination with an antifungal, max. pack size 20 g	Unknown
Portugal	OTC in combination with an antifungal	1995
Sweden	OTC, general sale – max. pack size 50 g OTC, general sale – 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 treatment of athlete's foot and candida intertrigo, maximum strength 1%, maximum pack size 15 g. May be supplied on General Sale: A cream for the treatment of insect bite and sting reactions, only for use in adults and children aged 10 years and over, max. strength 1%, max. pack size 15 g.	1987
USA	OTC – 0.5% strength OTC – 1% strength	1979 1991

Table adapted from AESGP/WSMI publications <http://www.aesgp.eu> status 10 January 2018 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. There has been

a small resurgence towards less restriction lately with both Australia and Canada further reclassifying the substance to a less restrictive specification. Bayer believes this is a reflection of the additional safety information and experience gained during this time. Many of the countries that New Zealand would generally regard as having reliable regulatory systems (Australia, Canada, UK, USA) now have a less restrictive classification for hydrocortisone in combination with an antifungal than New Zealand currently maintains. Bayer believes it is now appropriate to consider further down-scheduling to allow Canesten Plus to be marketed as a Pharmacy Only Medicine providing labelling requirements and pack size restrictions are met.

A6. Extent of Usage

A6.1 Usage in New Zealand

A6.1.1 Usage of Canesten Plus as a Pharmacist Only Medicine in New Zealand

Canesten Plus was approved for distribution in New Zealand in October 2011. 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.

Only the 30 g pack size of Canesten Plus was commercialised. Sales volumes for the past 3 years have been:-

	New Zealand Pharmacy Unit Sales MAT to 12/07/15*	New Zealand Pharmacy Unit Sales MAT to 10/07/16*	New Zealand Pharmacy Unit Sales MAT to 09/07/17*
Canesten Plus 30 g	4019.2	3169.3	2470.1

*Aztec Scan Data New Zealand Pharmacy Units

Unit sales information further into 2017 is not provided, as soon after July 2017 Canesten Plus was discontinued and replaced with Canesten Extra, an event likely to skew sales information temporarily. Furthermore, out-of-stock situations caused primarily by lack of harmonisation with Australia have been impacting on sales since the beginning of 2016.

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

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

Brand Name	Active Ingredients	Classification	Pack Size	Sponsor
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

Source: Medsafe Web site accessed 11 January 2018

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

Brand Name	First Registration	Classification	Pack Size	Sales Volume (units - MAT to 9/7/17)*
Micreme H	1988	Pharmacist Only Medicine	15 g	31,955.2
Resolve Plus 0.5	2001	Pharmacy Medicine	30 g	5218.5
Resolve Plus 1.0	1999	Pharmacist Only Medicine	30 g	1573.8

*Aztec Scan Data New Zealand Pharmacy Units

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 suggests that many consumers visit a doctor for advice when fungal infections become inflamed, and subsequently receive a prescription to treat their problem.

Although sales are relatively small in comparison for Resolve Plus, it is apparent that the Pharmacy Medicine classified product is more widely distributed. While there are a number of possible reasons for this, it appears that ease of access by way of less restrictive scheduling could be influencing how consumers buy this product.

A6.2 Usage of Canesten Plus as a Pharmacy Only Medicine in Australia

Canesten Plus 15 g has been available in Australia for almost 12 months. In that time Bayer Australia has received 1 report of mis-use, and none of adverse effect occurrence (data on file).

A6.3 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 the period September 2015 – September 2016 and 86 million in the period September 2016 – September 2017¹¹. These volumes equate to a world-wide, estimated patient exposure to a Canesten clotrimazole/hydrocortisone product of 6.4 million and 5.7 million respectively¹¹. Clearly, Canesten clotrimazole with hydrocortisone topical cream is a widely used product internationally.

A7. Labelling

The proposed labelling, which is the currently available product labels (tube and carton for the proposed 15 g pack size) in Australia, follow on the next pages.

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 15 g Tube Label



A copy of this label is provided as a reference⁴ for ease of manipulation and enlargement if necessary.

Canesten Plus 15 g Carton Label



A copy of this label is provided as a reference⁵ for ease of manipulation and enlargement if necessary.

As discussed in section A4, the indications on the labelling have been reduced so that only tinea and fungal skin rash are included. Eczema/dermatitis and fungal nappy rash have been excluded, addressing the concerns expressed by MCC at the 48th meeting regarding the potential for misdiagnosis of fungally infected nappy rash and the possible serious consequences should a misdiagnosis occur.

Supplementary to the additional warnings, as discussed below, the following changes have been made in comparison to the currently approved Pharmacist Only Medicine labelling:

- the logo for nappy rash is removed
- all reference to nappy rash treatment and use in children under 12 years of age is removed.
- all reference to thrush, eczema and dermatitis is excluded.

Canesten Plus as a Pharmacy Medicine would be supplied with a pack insert⁹, which is essentially a copy of the Consumer Medicine Information for the product. Providing a pack insert will give the consumer more information than is possible with a simple carton label, and reinforces the indications and warnings stated on the carton label. This is one way Bayer seeks to maximise consumer understanding of the product, leading to better compliance with usage instructions and warnings.

A8. Proposed Warnings

The currently required warnings for the proposed Canesten Plus product in New Zealand are (downloaded from the Labelling Statements Database on 11 January 2018):-

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 (Medicines Advisory Statements Specification July 2017¹²) are:-

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 ARGOM¹³ for topical antifungal agents (but not required by RASML) – namely
“Continue treatment for 2 weeks after symptoms disappear to avoid recurrence.”

The proposed 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 hydrocortisone as a Pharmacist Only Medicine, and as such they should of course also be included for Canesten Plus as a Pharmacy Medicine.

A8.1 Proposed Conditions of a Pharmacy Medicine

However, for a Pharmacy Medicine Bayer considers additional restrictions in terms of indications, patient population and label warnings are necessary in order to maximise the risk profile of the medicine for consumers.

The proposed details below apply only to the use of Hydrocortisone 1% in combination with an antifungal for dermal use that allows for efficacious treatment for adults and children 12 years and over in a smaller pack size (15 g or less).

Proposed Indications:

For sensitive, itching, inflamed fungal skin conditions that include

- Tinea conditions - athlete's foot (*tinea pedis*), jock itch (*tinea cruris*), ringworm (*tinea corporis*)
- Fungal skin rash

Instructions:

- Apply thinly and evenly to the affected area twice daily.
- Use only until inflammation, itching and redness have subsided.
- Do not use for more than 7 days.
- Use an antifungal only cream for 14 days after symptoms disappear.

Proposed Warnings:

- Do not use in children under 12 years.
- Do not 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 on broken skin.
- Do not cover treated skin with waterproof bandages.
- If irritation occurs discontinue use.

In comparison with the currently approved Pharmacist Only Canesten Plus product, Bayer proposes the following additional warning for use of the product as a Pharmacy Medicine as above:

“Do not use in children under 12 years of age”

The currently approved indications for nappy rash, thrush, eczema and dermatitis are removed from Canesten Plus products in pack sizes of 15 g or less and contraindicated in children less than 12 years of age.

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, could be affected by the proposed reclassification depending on the strategy the sponsor adopts for each product. These are:-

Brand Name	Active Ingredients	Classification	Pack Size	Possible Effect of Reclassification
Micreme H	Hydrocortisone 10 mg/g, miconazole nitrate 20 mg/g	Pharmacist Only Medicine	15g	Not affected with current labelling. Could be changed to a Pharmacy Medicine if labelling changed.
Resolve Plus 0.5	Hydrocortisone 5 mg/g, miconazole nitrate 20 mg/g	Pharmacy Medicine	15g, 30g	May be unaffected or labelling change may be required, depending on outcome.
Resolve Plus 1.0	Hydrocortisone 10 mg/g, miconazole nitrate 20 mg/g	Pharmacist Only Medicine	10 g (sample), 15g, 30g	Not affected with current labelling. Could be changed to a Pharmacy Medicine if labelling changed.

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 (and General Sales Medicine for *tinea pedis*)
- (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 in consultation with 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. Furthermore, having already been considered twice by the MCC and twice by ACMS, the areas of concern regarding reclassifying 1% hydrocortisone in combination with an antifungal have been clearly stated^{6,7,10}. Thus, this submission addresses those areas of concern, assuming that all other areas have been satisfactorily addressed by earlier submissions. Thus, this submission focusses on the following:-

- the safety and efficacy of hydrocortisone in a fixed dose combination with an antifungal, including the side effect profile of 1% hydrocortisone
- the nappy rash indication
- increased risk of masking symptoms
- exacerbation of bacterial infections
- inappropriate use of a higher concentration
- the potential for prolonged use
- concern regarding lack of consultation, record-keeping and monitoring with a pharmacist
- change of classification not significantly improving accessibility

B.1 Efficacy and Safety of Fixed Dose Combination Treatment of an Antifungal with Hydrocortisone

Efficacy

Fungi are the main etiologic agents responsible for the onset of diseases such as 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 damaged¹⁴. 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 etiologic factor in seborrheic dermatitis¹⁵.

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 symptoms¹¹, and the presence of hydrocortisone may enhance the activity of the antifungal agent as superior cure rates are achieved¹⁵. 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 prematurely¹⁵.

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.

The purpose of the proposed reclassification is to provide adults and children over 12 years old with a readily available, efficacious product to treat inflammation associated with Dermatophytes that are responsible for Tinea and fungal skin rash.

Safety

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^{18,20}.

A number of known side-effects from the topical application of corticosteroids exist and may include²⁷:

- skin thinning (atrophy) and stretch marks (striae)
- purpura (leaking from or joining together of small blood vessels, leaving purple marks on the skin) and haemorrhage
- periorificial dermatitis
- enlarged blood vessels (telangiectasia)
- susceptibility to skin infections
- masking and aggravation of infections
- worsening of rosacea
- dermatitis (contact and facial)

The risk of these side effects is dependent on the strength of the steroid, the length of application, the site treated and the nature of the skin problem²⁷. 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. Lee classes hydrocortisone 0.5% to 1% as Class I and “mild”²¹. Medsafe, in the Prescriber Update Article “Topical Corticosteroids: Face Facts” December 2005, makes no differentiation between hydrocortisone 0.5% and hydrocortisone 1%, classing both strengths as mildly potent (<http://www.medsafe.govt.nz/profs/PUarticles/steroidface.htm>). The New Zealand Dermatological Society classes all strengths of hydrocortisone from 0.5% to 2.5% as “mild” (<http://www.dermnetnz.org/treatments/topical-steroids.html>). The FDA reviewed safety data from thousands of subjects²⁰ 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 TGA Database of Adverse Event Notifications (DAEN) on 18 February 2015 for reports on hydrocortisone shows there were 140 reports of adverse reactions in Australia between the period of 1 January 2000-18 October 2014. Over the 14 years only eight cases were suspected resulting from combination hydrocortisone and antifungal and the reactions were classified as mild²²:-

- Application site reaction (x 3)
- Skin discolouration
- Blister (x 2)
- Dermatitis
- Erythema (x 2)
- Skin atrophy

The reactions above are flagged in the proposed pack insert for Canesten Plus as a Pharmacy Medicine⁹ as potential adverse events that may be a result of overuse or inappropriate use. Thus, the potential consumer is alerted to these possible side effects and informed to seek the advice of a doctor or pharmacist should they occur. Moreover, consumers are advised strongly through labelling not to use the medication for more than 7 days, thereby protecting them against side-effects that are the result of overuse

Recent PBRER's for clotrimazole no longer separate out adverse events for the clotrimazole/hydrocortisone product. However, Bayer also markets plain hydrocortisone and hydrocortisone/dexpanthenol combination topical products in other countries and useful information regarding adverse event incidence for topical hydrocortisone can be derived from the relevant PBRER for these products²³. Within the reporting period for the current Bayer Periodic Safety Update Report for topical hydrocortisone, a total of 20 medically confirmed adverse drug reactions and 18 unconfirmed adverse drug reaction reports were received from over 21 million subject exposures²³. From this total of 38 reports, 15 were serious. The majority of reported events were in the general disorders and administration site conditions category, following by the skin and subcutaneous tissue disorders category. The report notes that this pattern of adverse events is expected for topical products of this type.

The most recent PBRER's for both clotrimazole¹¹ and hydrocortisone²³ concluded that the benefit-risk balance for the products remain favourable. An increase in adverse events due to combining the two active ingredients has not been observed¹⁵, and so it is appropriate to conclude that the benefit-risk profile of the combination product is also favourable.

Topical hydrocortisone has been available without prescription in Scandinavian countries since the 1950's without generating concerns as to its use by consumers²⁴. While more potent steroids can generate serious adverse effects if used incorrectly, "guilt-by-association" should not be applied - topical hydrocortisone is a relatively benign medication²⁴. 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 medicine²⁰. 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^{18,23}.

In conclusion, topical hydrocortisone is a safe medication and with appropriate labelling presents minimal risk to the consumer²³. 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% topical hydrocortisone is virtually indistinguishable. On this basis, the current classification differences in New Zealand between these two strengths of topical hydrocortisone does not appear justified. Furthermore, there is no data available to the writer's knowledge that suggests combination with an antifungal changes the safety profile of hydrocortisone.

B2. Nappy Rash Indication

The background information provided below is for the current Pharmacist Only Hydrocortisone 1% plus antifungal medicines (pack size of 30 g). The nappy rash indication clearly states it should not be used in children under 2 years of age unless advised by your doctor. It is proposed that the Pharmacist Only medicine (Canesten Extra) retain the current indications and warnings.

In this reclassification submission Bayer proposes to remove the indication for nappy rash and exclude use in children under 12 years of age for the Pharmacy Medicine (Canesten Plus).

The treatment of nappy rash is recognised as a skin condition 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 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 problem¹⁶. Topical hydrocortisone and antifungal medications are appropriate for more severe cases which have proven refractory to first line treatment approaches such as barrier creams¹⁶. 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 treatment¹⁷. Topical hydrocortisone is recognised as generally safe for use in children, and is commonly recommended for treatment of moderate to severe nappy rash¹⁷. However, concerns remain as to its use, with some physicians recommending that it be used with extreme caution¹⁸. 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 current combination products are considered appropriate to guide the consumer to the correct use of this product for the treatment of nappy rash. While products may be 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 these products to treat nappy rash without first discussing the matter with their doctor. Ellis et al.¹⁹ 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.

In summary, Bayer accepts MCC concerns regarding the treatment of nappy rash and that the involvement of a pharmacist is essential for this vulnerable patient group. Consequently, the Pharmacy Medicine product proposed does not have a nappy rash indication as part of its label, and is only recommended for adults and children 12 years of age and over. It has been demonstrated that consumers do comprehend and follow label instructions for products of this type¹⁹, and so the proposed labelling is considered an effective protective mechanism against the use of the Pharmacy Medicine product for the treatment of nappy rash.

B3. Increased Risk of Masking Symptoms

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, 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.

Occasionally a “treat and see” approach can cause problems. One of the most common is a form of disease masking called *tinea incognita*, where the clinical appearance of a tinea infection has been altered by inappropriate treatment, usually with prolonged use of a topical steroid cream²⁵. 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/or different symptoms. Compared to an untreated *tinea corporis*, *tinea incognita* has a less raised margin, is less scaly, and is more pustular, extensive and irritable (<http://dermnetnz.org/fungal/tinea-incognita.html>). Treatment is to introduce a single antifungal cream, or if the infection is very inflamed and itchy an antifungal plus a milder steroid can be used. The incidence of *tinea incognita* (TI) appears to have increased over recent years, although no large series of cases has been reported in children. In a large case study of children with *tinea incognita*, no cases were seen in children younger than 1 year of age²⁶.

As the mildest steroid available, topical hydrocortisone is rarely the cause of *tinea incognita*. However, in order to minimise the already rare possibility that topical hydrocortisone cream at the strength of 1% might cause *tinea incognita*, the proposed reclassification is restricted to combination products with an antifungal rather than hydrocortisone alone. The warning statement restricting use to not more than 7 days and the reduced pack size to 15 g or less will further protect the consumer from the possibility of *tinea incognita*.

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 current treatments available as Pharmacy Only

medicines, and the proposed increase in strength of topical hydrocortisone is unlikely to materially affect instances where condition diagnosis is hampered.

Thus, in terms of ability to mask diagnosis the proposed changes are not considered to represent an increase in risk to the public.

Treatment with topical hydrocortisone or an antifungal/hydrocortisone combination also has the potential to mask misdiagnosis of bacterial infections and other non-fungal infections such as scabies, herpes simplex and viral conditions such as molluscum contagiosum²⁷. At first the infection appears to resolve, or partially resolve, but over time it persists.

In practice, 60% of consumers with skin problems treat themselves without first seeking medical advice¹⁸. The complexities of dermatological diagnosis mean that healthcare professionals are also susceptible to misdiagnosis in this area. Given these two facts, it is inevitable that some misdiagnosis will occur. The current classification of 0.5% hydrocortisone with/without combination with an antifungal as a Pharmacy Medicine indicates the risk of such misdiagnosis has been assessed as suitably low. Reclassification of 1% hydrocortisone in combination with an antifungal to Pharmacy Only Medicine will not change this risk profile – in fact, since many infectious complications of topical steroid treatment are of fungal origin²⁷, the risk profile is potentially improved.

Concerns regarding masking of other diseases or misdiagnosis have been addressed with the suggested changes to the proposed Pharmacy Medicine Canesten Plus product, ensuring proper use and limiting over-usage. The advice to consumers to limit treatment to 7 days and the proposed limited pack size of 15 g effectively protects them from persisting with the treatment of such a misdiagnosis and to seek the assistance of a healthcare professional.

The changes proposed align New Zealand with Australia, the UK and Ireland. The instructions “use sparingly twice daily” is equivalent to 7 days treatment supply for a 15 g pack. This pack size reduction will effectively prevent overuse, which can lead to difficulties in diagnosis, in the absence of the mandatory intervention of a pharmacist that the Pharmacist Only Medicine classification brings.

Furthermore, in order to address the concerns of the Australian delegate regarding “masking symptoms particularly in children” the Pharmacy Medicine in Australia is contraindicated in children under 12 years of age. Bayer proposes that this contraindication also be applied in New Zealand for the proposed reclassification. This proposal is more restrictive than that currently in place in the UK and Ireland where hydrocortisone topical products are restricted to children 10 years of age and older.

B4. Prolonged Use

Prolonged use is recognised as a key concern for topical hydrocortisone, as such use increases the likelihood of side effects occurring.

This concern has been addressed within this proposal for rescheduling in the following ways:-

- with the reduced pack size of 15 g or less. For most applications, 15 g of cream represents about 7 days of treatment, and at most less than 2 weeks treatment. Thus, prolonged treatment would require re-purchase of the product, which requires a deliberate behaviour on the part of the consumer that seems less likely, and such re-purchase would require further interaction at the pharmacy and so offer another opportunity for healthcare professional intervention.
- the instructions for usage remain suitable. The limitation of usage only until inflammation, itching and redness have subsided and not more than seven day usage is emphasised, with follow-up treatment of a plain antifungal treatment.
- The product is contra-indicated in children under 12 years of age – thus, prolonged treatment of younger children, who are more vulnerable to side-effects, is avoided.

Thus, though labelling and pack size limitation the risk of possible increased effects as a result of prolonged usage, which was already small (as the risk of side-effects from 1% hydrocortisone are similar to those of 0.5% hydrocortisone), has been minimised.

B5. Pharmacy Medicine Classification Not Offering Better Accessibility

New Zealand and Australian legislated levels of access to medicines both have four levels of access, ranging from total decision making by a doctor (prescription) to total decision making without any possible assistance from a healthcare professional (general sales). Between these two are Pharmacist Only Medicines, where interaction with a pharmacist is mandatory and sale details are recorded, and Pharmacy Medicines, where interaction with a pharmacist is available should it be required.

These four levels are specifically designed to provide different levels of access to medicines for the consumer, depending on the medicine's suitability. The New Zealand and Australian systems differ from those in other parts of the world where the Pharmacist Only category tends not to exist.

In pharmacy, Pharmacist Only Medicines are kept behind the counter and are not available for self-selection by the consumer, whereas Pharmacy Medicines are placed on shelving where consumers can view the product range and self-select. Clearly then consumers have enhanced access to Pharmacy Medicines since they are able to review the range of medicines available in the category and make their own decisions regarding which they would prefer based on their personal knowledge, the label information available and possible pharmacist assistant input. Screening of the consumer choice occurs at the time of purchase, but the consumer's freedom to determine their own medicine is greatly enhanced.

Bayer endorses the current system of four levels of access for consumers to medicines, and views each category as an important step in the continuum of healthcare professional to consumer decision-making. The Pharmacy Medicine category is viewed as an important category in which consumers can expand their medicinal literacy and exercise greater control over which medicines they use. We believe the Pharmacy Medicine category greatly improves consumer's accessibility to medicines and offer's pharmacists the opportunity to be involved in consumer's decision processes without the necessity of supervising every sale if such intensive input is not required.

B6. Conclusion

This is effectively the third submission for MCC consideration proposing a change of classification of Canesten Plus from Pharmacist Only Medicine to Pharmacy Medicine. Based on previous evaluation findings, changes to the product are proposed designed to address outstanding concerns.

- The current required labelling for these preparations will be revised for consumers to avoid risks of topical hydrocortisone treatment and including side effects and masking of other diseases.
- The concern of overusage has been addressed with the proposal to **reduce the pack size to 15g** of 1% hydrocortisone with an antifungal as a Pharmacy Medicine.
- The concern of inappropriate use in young children has been addressed with the proposed contraindication **“not to be used in children under 12 years of age”**.
- The concern of general inappropriate use has been addressed with the proposal to restrict the use of the proposed Pharmacy Medicine product to **tinea and fungal skin infections**.
- The concern regarding bacterial infections through inappropriate application has been addressed with the proposal of a reduced pack size (15g) and additional information in the pack.
- Any concerns regarding exacerbation of bacterial infections due to inappropriate application are addressed with the proposed conditions.

Topical hydrocortisone 1% is more effective in comparison with the medication at 0.5% strength, whereas the safety profiles of the two strengths are similar. Consumers have the right to the most efficacious medicine available if safety is not compromised.

Consumers are able to make a differential diagnosis of dermal fungal infections with or without inflammation, without the mandatory input of a pharmacist if appropriate measures are taken with the labelling.

There is sufficient international precedence and experience to be confident that topical hydrocortisone at a strength of 1% is appropriate for consumer self-selection and use when in combination with an antifungal medication.

As a Pharmacy Medicine, access to professional advice from a pharmacist will always be available if required.

The proposed reclassification of topical antifungal medications in combination with hydrocortisone at the strength of 1% to treat inflammation associated with tinea is appropriate and desirable.

Bayer intends to work with and assist stakeholders to educate pharmacy staff including pharmacists about combination hydrocortisone/antifungal medicines.

Bayer proposes rescheduling of 1% hydrocortisone/antifungal combinations for dermal use in packs containing 15 g or less from Pharmacist Only Medicine to Pharmacy Medicine. The proposed medicine will provide adults and children 12 years and over, with a readily-available and efficacious treatment for relief of itching and inflammation associated with athlete's foot (*tinea pedis*), jock itch (*tinea cruris*), ringworm (*tinea corporis*) and fungal skin rashes. Fungal infections with inflammation often do not respond to antifungal treatment until the inflammation is resolved – thus, there is a defined need for the proposed treatment over and above plain antifungal treatments.

The risk-benefit analysis for the proposed classification change is highly favourable. In comparison to topical hydrocortisone 0.5% the 1% presentation will provide the consumer with superior efficacy and comparable safety. Whilst the two strengths have very similar safety profiles, Bayer proposes several measures, including changes to pack size and labelling, to ensure continued safety. The restrictions and addition of warnings proposed in this rescheduling application optimises the risk-benefit profile and has addressed concerns previously expressed by the reclassification Committee.

Consumers are entitled to access the most efficacious medicine available with the fewest restrictions when safety is not compromised. The proposed rescheduling of Hydrocortisone and Hydrocortisone acetate 1% when combined with antifungal substances for dermal use to Pharmacy Medicine will deliver access to the most efficacious medicine.

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