Proposal for Reclassification of

Canesten® Bifonazole Cream

Bifonazole 10 mg/g

Addition of Supply by a Podiatrist registered with the Podiatry Board

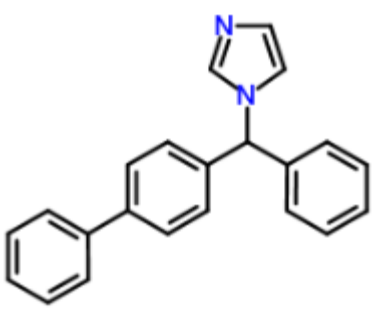
July 2016

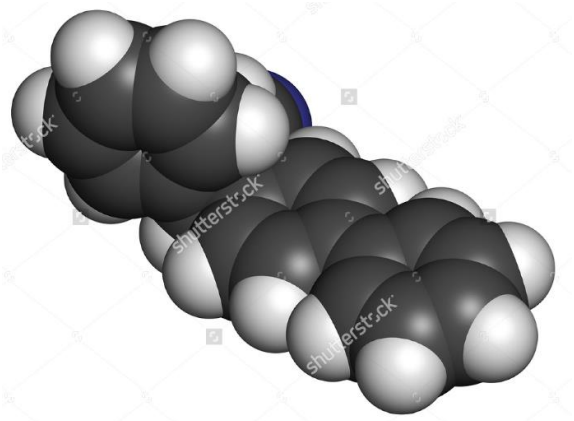
INDEX

PART A

A1. Name of the Medicine

The International Non-Proprietary Name of the medicine is bifonazole, which has the chemical formula $C_{22}H_{18}N_2$.





The proprietary or brand name of the product in New Zealand is Canesten® Once Daily Bifonazole. There are two medicinal presentations available – Canesten Once Daily Bifonazole Body cream (30 g) and Canesten Once Daily Bifonazole Athlete's Foot cream (20 g).

A third presentation, Canesten Bifonazole Anti-Fungal cream (20 g), is also available as a component of the medical device procedure kit Canesten Fungal Nail Treatment Set for the treatment of onychomycosis. This procedure kit contains a 10 g tube of 40% urea ointment, plasters and a scraper for nail debridement, and bifonazole cream for follow up treatment of the fungal infection once debridement is complete.

All three presentations contain bifonazole 10 mg/g.

A2. Name of the Company

This submission is made by:-

Bayer New Zealand Limited
P. O. Box 2825
Shortland Street
Auckland

Ph: (09) 443-3093

[redacted]

A3. Dose Forms, Strengths and Pack Sizes

The current classification of bifonazole is:-

General Sale
For dermal use in medicines for tinea pedis only or in shampoos containing 1% or less.

Pharmacy Only
For dermal use **except** in medicines for tinea pedis only or in shampoos containing 1% or less.

Prescription
Except for dermal use.

There are no further restrictions on the use of bifonazole as specified through the label statements database[1].

Bayer New Zealand Limited currently markets the three presentations of bifonazole cream 10 mg/g as discussed in section A1. All presentations are sold in packs of one.

A4. Indications

The current approved indications for Canesten Once Daily Bifonazole cream, as per the current labels[2,3,4,5], are:-

> Effective treatment for fungal skin conditions such as tinea, athlete's foot, ringworm, jock itch and yeast infections of the skin, with one single daily application.

The indications are the same for both products, with the athlete's foot presentation being smaller as less product is generally required for treatment of athlete's foot.

The indication for the cream component of the Fungal Nail Treatment set is the same, with emphasis on the dermal treatment of the nail bed for residual infection after nail debridement.

This proposal includes retaining these indications.

A4.1 Dosage Recommendation

The current directions for use on the carton label for all Canesten bifonazole presentations, approved by Medsafe[2,3,4,5], are:-

> Clean and dry the affected area thoroughly. Rub sparingly into the affected area once daily. Continue treatment for two weeks after symptoms disappear to avoid recurrence.

This proposal includes retaining these dosage instructions.

A5. Classification

The current classification of bifonazole, taken from the Medsafe Web site on 26 July 2016[6], is:-

Bifonazole, except for dermal use	Prescription
Bifonazole for dermal use **except** in medicines for tinea pedis only or in shampoos containing 1% or less	Pharmacy Only
Bifonazole for dermal use in medicines for tinea pedis only or in shampoos containing 1% or less	General Sales

Compare this bifonazole classification with the classification of similar topical antifungal medicines such as clotrimazole and miconazole.

The current classification of clotrimazole, taken from the Medsafe Web site on 26 July 2016[6], 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 external use in medicines for tinea pedis only or when sold in practice by a podiatrist registered with the Podiatrists Board	General Sales

The current classification of miconazole, taken from the Medsafe Web site on 26 July 2016[6], is:-

Miconazole, except when specified elsewhere in this schedule; except in medicines for tinea pedis only or when sold in practice by a podiatrist registered with the Podiatrists Board	Prescription
Miconazole, for vaginal use; for the treatment of oral candidiasis	Restricted
Miconazole 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
Miconazole for external use in medicines for tinea pedis only or when sold in practice by a podiatrist registered with the Podiatrists Board	General Sales

The principal difference between the classification of bifonazole and the classification of similar topical antifungals is that many other topical antifungals are classified as General Sales when sold in practice by a podiatrist registered with the Podiatrists Board. This difference arose as a result of a Medicines Classification Committee recommendation from the 46th meeting[3] (November 2011), that the pharmacy-only classification for medicines used by podiatrists should include the wording “except when supplied by a podiatrist registered with

the Podiatry Board", or words of similar meaning. This resulted from a submission from Podiatry New Zealand and the recommendation encompassed the medicines amorolfine, ciclopirox, clotrimazole, econazole, isoconazole, ketoconazole, miconazole, nystatin, terbinafine and tioconazole.

The MCC minutes of this meeting[7] noted "Podiatrists provide diagnostic, preventative and rehabilitive treatment of conditions affecting the feet and the lower limbs. Overall the Committee felt that the request was sensible, specifically from a consumer convenience point of view. The Committee noted that acceptance of the proposal would still ensure that access to the medicine would occur through a health professional who could provide advice on the safe and appropriate use of the medicine." In light of this recommendation by MCC, and the fact that topical bifonazole is already a Pharmacy Medicine, it is assumed that questions around benefits to the consumer and the public of this proposed change, potential risk of harm, ease of self-diagnosis, interactions, contra-indications, precautions, possible resistance, adverse events and potential for abuse or misuse have previously been addressed and resolved – they are not further discussed in this proposal. Likewise, it appears accepted that podiatry practice is an appropriate place for consumers to seek information and source product for fungal foot infections and this is also not further discussed or justified in this proposal.

Unlike company submissions at the time, the request and supporting information from Podiatry New Zealand was not made public. As a result it is not clear if bifonazole was merely overlooked or deliberately omitted from the list of medicines to be considered, and if deliberately omitted it is unclear if specific reasons for this omission existed. Bayer considers it likely that bifonazole's omission was an oversight.

In July 2012 Bayer sought to rectify this assumed omission with a request to include bifonazole in the range of topical antifungals that could be sold in practice by a podiatrist registered with the Podiatry Board. Bayer acknowledges that at the time the request was made by letter only, and that it became confused with a parallel reclassification proposal for a clotrimazole with hydrocortisone product, and offer our apologies for this situation. The committee concluded they had insufficient information to make a recommendation[8].

The classification sought for bifonazole is:-

Bifonazole, except for dermal use	*Prescription*
Bifonazole for dermal use except in medicines for tinea pedis only, in shampoos containing 1% or less, or when sold in practice by a podiatrist registered with the Podiatrists Board	*Pharmacy Only*
Bifonazole for dermal use in medicines for tinea pedis only, in shampoos containing 1% or less or when sold in practice by a podiatrist registered with the Podiatrists Board	*General Sales*

Essentially, this submission supports the MCC recommendation to permit selected topical antifungals to be sold in podiatry practices, and now seeks to have bifonazole added to the range of topical antifungals already available in this way. A development since this topic was last discussed by MCC is that Canesten Fungal Nail Treatment set is now available in New Zealand, and should this proposal ultimately be accepted then this product for the treatment of onychomycosis would also become available to be sold by podiatrists. This will be further discussed in Part B.

A5.1 Classification Status in Other Countries

Given the specificity of this proposal, and the fact that in some countries such as Australia such a classification may not be able to be implemented due to limitations imposed by regulation, the classification status in other countries does not appear to be of particular relevance. Nonetheless, some information on classification in other major relevant countries is given below.

Bifonazole OTC classification in other markets

Country	OTC Classification Year	Classification details
Australia	1997	General sale for treatment of the scalp (2002) and treatment of tinea pedis (2006).
Canada		Not registered or marketed in this country.
Germany	1988	
UK		Pharmacy only status unless a cream for the treatment of athlete's foot which is General Sale (GSL). Maximum strength 1%, maximum pack size 30g of product for GSL products.
USA		Prescription

Table adapted from AESGP/WSMI publications http://www.aesgp.eu status 25 July 2016.

A6. Extent of Usage

A6.1 New Zealand

Canesten Bifonazole is a widely used product in New Zealand. Scan data (source: Aztec IRI Worldwide) from pharmacies gives the following moving average total sales volumes:-

		New Zealand Pharmacy		
		Canesten Once Daily Bifonazole Athlete's Foot Cream 20 g	Canesten Once Daily Bifonazole Body Cream 30 g	Canesten Fungal Nail Treatment Set (20 g cream)
Units	MAT To 22/06/14	[redacted]	[redacted]	[redacted]
	MAT To 21/06/15			
	MAT To 19/06/16			

There were no sales of the Canesten Fungal Nail Treatment Set to June 2014 as the product was launched in October 2014.

A6.2 World-Wide

Worldwide patient exposure to bifonazole is estimated as 260.6 million patients[9]. For bifonazole formulations for the PSUR reporting period 02 Dec 2014 through 01 Dec 2015, exposure per dosage form was as follows[9].

Estimated Worldwide Patient Exposure to Bifonazole from 2 Dec 2014 to 1 Dec 2015

Topical Dose Form	Units*
Cream Nail Set	[redacted]

* Based on assumption that patients were treated with one package of the formulation.

Clearly, bifonazole is extensively used world-wide making the efficacy, adverse event profile and safety of this product very well understood.

A7. Labelling

Because this proposal is to allow podiatrists to sell bifonazole cream, and so therefore does not remove the sale of bifonazole from the supervision of a healthcare professional, Bayer considers that the currently approved labels for the products in question would not require changing.

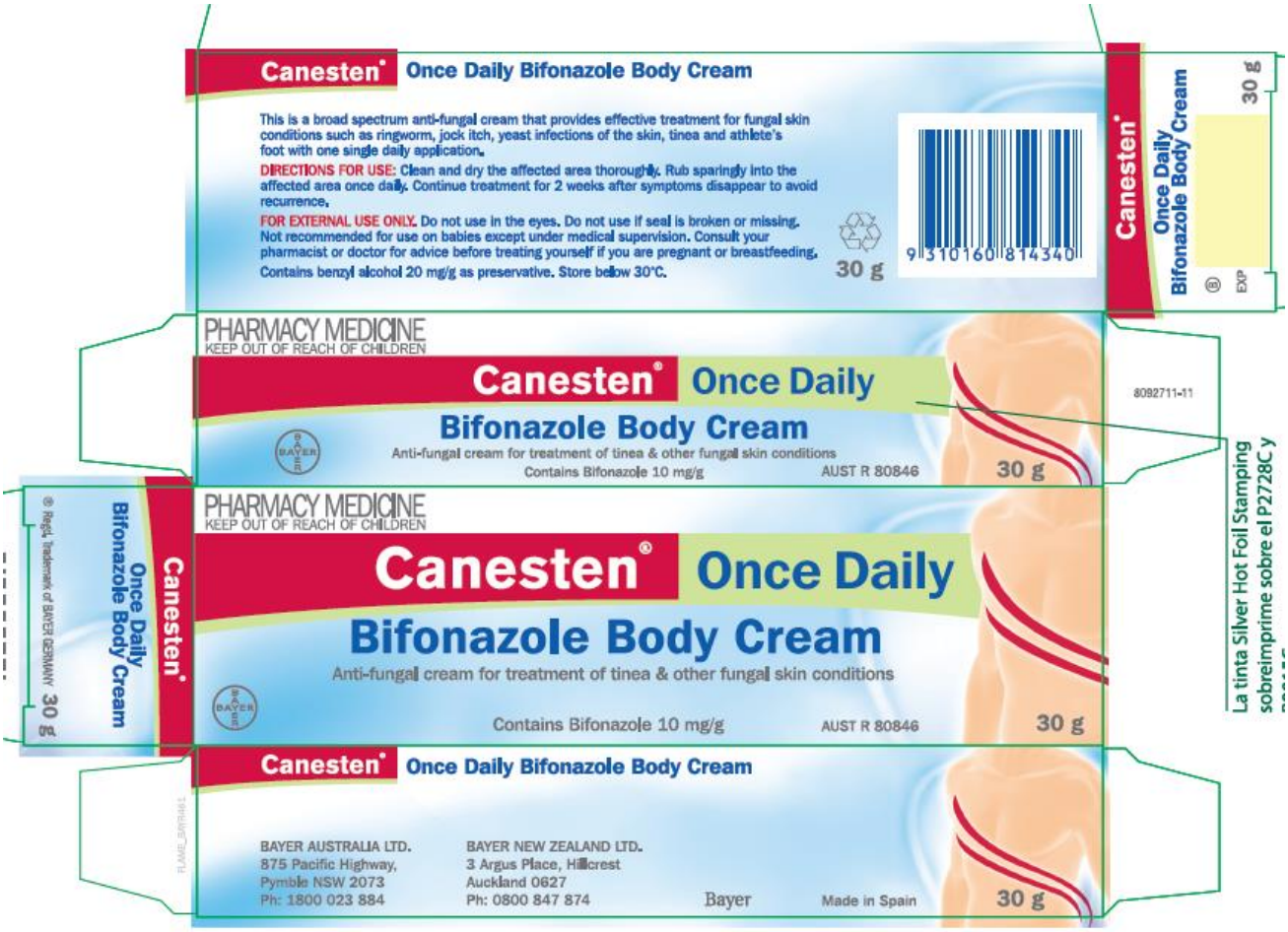
The currently approved labels, both tube label and carton, for Canesten Once Daily Bifonazole Athlete's Foot cream and Canesten Once Daily Bifonazole Body cream are provided on the next pages. Complete .pdf's are provided as references[2,3,4,5] to allow for close-up viewing of the labelling.

Canesten Once Daily Bifonazole Athlete's Foot cream – Tube Label (actual size)

Canesten Once Daily Bifonazole Athlete's Foot cream – Carton (reduced)

Canesten Once Daily Bifonazole Body cream – Tube Label (actual size)

Canesten Once Daily Bifonazole Body cream – Carton (reduced)



A8. Proposed Warnings

As mentioned previously, Medsafe does not require any warnings to be applied to bifonazole cream sold as an over-the-counter medicine (Label Statements Database as of 26 July 2016[1]).

However, Bayer voluntarily applies the following warnings to bifonazole cream labelling:-

- Do not use in the eyes
- Not recommended for babies except under medical supervision
- Consult your pharmacist or doctor for advice before treating yourself if you are pregnant or breastfeeding

These warnings are derived from the Bayer company core data sheet for topical bifonazole[10], and are consistent with the Consumer Medicine Information available for Canesten Once Daily Bifonazole Cream products[11].

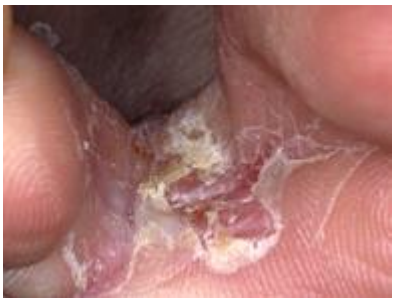
A9. Other Products

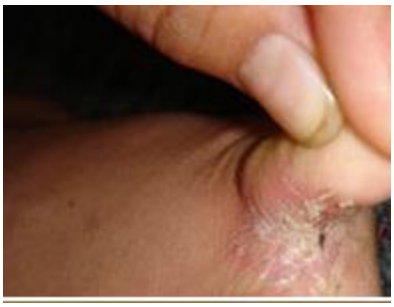
There are no other bifonazole cream products registered or marketed in New Zealand apart from the Bayer products mentioned in this submission (Medsafe Web site Product Application Search 26 July 2016).

PART B

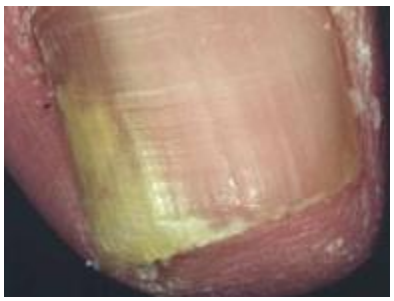
B1. FUNGAL INFECTIONS IN PODIATRY

By its recommendation to permit sale of topical antifungal product by podiatrists[7], MCC has already recognised that podiatrists can diagnose and treat fungal infections of the feet and lower legs. Infections seen by podiatrists include athlete's foot (tinea pedis), and less commonly mycetoma.





Onychomychosis, an infection of the nails by dermatophytes that does not spontaneously resolve[18], is also seen frequently. It can result from paronychia (inflammation of the skin around a finger or toenail) or untreated tinea pedis.



Mean prevalence is around 4.3% of the population, and toenails are seven times more likely to be affected than fingernails[18]. [redacted]

[redacted]

People at risk of developing onychomycosis are those[18]:-

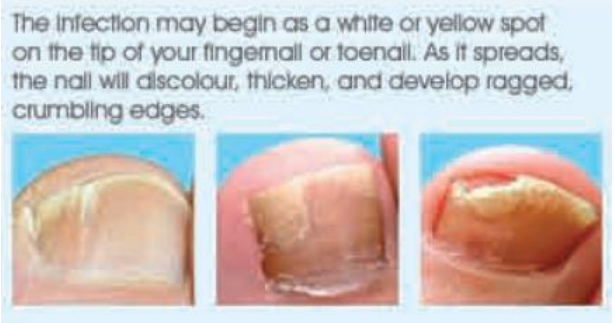
- with damaged nails
- who are elderly
- with diabetes (twice as likely to those without diabetes to have onychomycosis)
- with psoriasis
- who are exposed to wet work, ill-fitting shoes, swimming pools and nail biting
- who do more physical activity
- who smoke 2 or more packets of cigarettes a day

Since the elderly and those with diabetes often utilise podiatrists for foot care, it is not surprising that podiatrists are identifying patients with onychomycosis relatively frequently.

Amorolfine nail lacquer (Loceryl) is currently classified as a Pharmacy Medicine, the result of a recommendation from the 46th meeting of the MCC. The minutes of this meeting noted:-

> "The Committee agreed that most decisions to treat using amorolfine were empirical and the risk of misdiagnosis was equal for doctors and pharmacists. The alternative to topical was use of an oral treatment associated with a number of serious adverse reactions. Treatment of fungal nail infections was usually for the purpose of appearance. Topical treatment has no obvious safety issues, a good therapeutic margin, it is hard to overdose using it and patients cannot abuse it. Reclassifying topical preparations to pharmacy-only would improve consumer convenience.
>
> The question arose as to whether self-diagnosis and continued use of topical amorolfine would deny patients access to better treatments. The Committee considered this to be unlikely and the product information advises consumers to seek medical advice if their nail does not appear to be responding to the course of topical treatment."

Thus, the appropriateness of self-diagnosis and self-treatment of onychomycosis is accepted in New Zealand and is not further discussed in this proposal. Involvement from a trained podiatrist in the consumer's treatment decision is most likely to result in improved outcomes.



B2. CANESTEN ONCE DAILY BIFONAZOLE CREAMS

In response to Bayer's July 2012 letter requesting that bifonazole cream be added to the list of products that could be sold in practice by a podiatrist registered with the Podiatry Board, the minutes of the 48th meeting of the MCC[8] stated:-

"The Committee agreed there was not enough data included with the submission to make a recommendation on the reclassification of bifonazole……...however, a submission with supporting data which answered the queries discussed would be considered at a future meeting if submitted."

There appears to be two issues with the submission made at the time. Firstly, the issue was clouded by the subsequent mention of clotrimazole + hydrocortisone. Bayer has now resolved this issue by making this stand-alone submission.

The second issue is that very little is known about the proposal made by Podiatry New Zealand for other topical antifungal products and its subsequent acceptance. It is not known if bifonazole was excluded from the proposal deliberately or by simple omission (all though the second seems more likely), and it is not known what supporting information was provided with this proposal making it difficult to replicate the supporting information for bifonazole.

There is little doubt that bifonazole has a very similar efficacy and safety profile to other azole antifungals[12,13]. The risk-benefit profile of bifonazole for the treatment of dermatomycoses is favourable[9], and latest analysis suggests no further risk minimization is required. Furthermore, bifonazole offers the patient some advantages over other topical azoles:-

Broad Antimycotic Spectrum and High Intensity Antimycotic Activity

Bifonazole has a very broad antimycotic action spectrum, typical of the azoles, extending to nearly all fungi pathogenic in man[14]. It has increased fungicidal activity on filamentous fungal elements, in particular of dermatophytes, owing to a twofold inhibition of ergosterol biosynthesis in fungal cells[14]. Bifonazole acts more strongly against filamentous fungi and fungal elements – this is important in Candida species infection as the parasitic, invasive mycelia are most sensitive to bifonazole.

Once Daily Application

Bifonazole is characterized by a long retention time on the skin (around 48 hours[10]) – it remains longer on the skin that either clotrimazole or miconazole, and does so at higher concentrations than clotrimazole[14]. Further, the uptake of bifonazole into fungal cells reaches a maximum after only 20 – 30 mins and remains there for approximately 120 hours, continuously inhibiting ergosterol biosynthesis[14]. These characteristics allow for once daily treatment[2,3], in contrast to other azoles such as clotrimazole which require application two or three times per day[15]. Once daily application facilitates compliance with the treatment regime – this is of particular importance as the patient is recommended to continue treatment for two weeks after symptoms have resolved in order to prevent recurrence. It is a known challenge for patients to adhere to usage recommendations without symptomatic reminders that treatment is required - the potential to develop a usage habit, such as application at bedtime, is assisted by once daily treatment.

Very Low Systemic Load

Pharmacokinetic studies demonstrate that topical application of bifonazole results in extremely low plasma concentrations[10], and systemic effects from this medicine are highly unlikely.

Cleary, the athlete's foot presentation of Canesten Once Daily Bifonazole cream is likely to be the one with more application in podiatry – however, medicinal classification in New Zealand does not allow for such level of detail. The minutes of the 48th meeting of the MCC queried as to why a product intended for use on various parts of the body was included when the reclassification would allow the product only to be sold by a podiatrist – for products with broad indications such as bifonazole this is practically unavoidable. As with any healthcare professional practice, podiatrists will stock and sell those presentations best suited to their patient's needs.

B3. CANESTEN FUNGAL NAIL TREATMENT SET

Canesten Fungal Nail Treatment Set is a medical device procedure kit that contains urea ointment, a scraper and plasters for nail debridement (partial

removal)/avulsion(full removal), and bifonazole cream 10 mg/g for subsequent treatment of the exposed nail bed. It was launched onto the New Zealand market in October 2014, after proving very popular in Australia when launched there, and has been equally popular with consumers in New Zealand (see A6.1).

Canesten Fungal Nail Treatment set is one of a number of medical device treatments for onychomycosis that have been recently launched in this country – another is Nailclin (a paint on formulation containing white thyme oil, eucalyptus, citriodora, ethanol and lactic acid that penetrates the nailplate and changes the environment of the nail resulting in the fungi being unable to grow), Excilor (a debridement product containing acetic acid, ethyl lactate, pentylene glycol, dimethyl isorbide, ammonio methacrylate copolymer and water) and Restoranail (containing 16% polyureaurethane in organic solvents). They join the more traditional medicinal nail lacquers such as Loceryl (amorolfine) and Apo-Ciclopirox Nail Lacquer as options for the treatment of fungal nail infections.

B3.1 Efficacy of Canesten Fungal Nail Treatment Set

Nail avulsion or debridement is a useful adjunct to both topical and systemic pharmaceutical treatment of onychomycosis[18], as it helps to reduce fungal mass and increases the penetration of the fungal treatment. A randomized controlled trial demonstrated a 77% better mycological cure for 8% ciclopirox lacquer plus debridement than for debridement alone.

Canesten Fungal Nail Treatment set has been studied in a double-blind, randomized, multi-centre, placebo-controlled phase 3 trial to prove the superiority of bifonazole vs. placebo after 4 weeks of onychomycosis treatment. Reference 16 is the Bayer internal study report and reference 17 is the resultant published paper. All patients were treated with 40% urea paste to achieve non-surgical ablation (2 – 4 weeks) and then treated for 4 weeks with bifonazole cream 10 mg/g or placebo. At the primary endpoint, 2 weeks after the end of treatment, the overall cure rate was superior in the bifonazole-treated group (54.8% vs. 42.2%, $P = 0.0024$) and the proportion with mycological cure was higher with bifonazole treatment (64.5% vs. 49.0%, $P = 0.0001$). These results mirror those for ciclopirox discussed above, and support the use of combination treatment.

While the cure rates discussed above for Canesten Fungal Nail Treatment set may not seem impressive, they must be viewed within the overall treatment of such infections. Onychomycosis can be resistant to any treatment and 16% - 25% of patients do not achieve a cure by current treatments[18]. Thus, an absolute improvement in cure rate of up to 16% is clinically significant.

Furthermore, Canesten Fungal Nail Treatment set offers consumers the following advantages over other topical treatments for onychomycosis:-

- the combination treatment of 40% urea and 1% bifonazole can improve treatment outcomes compared to other topical treatments
- Canesten Fungal Nail Treatment Set shortens the treatment duration to 2 months or less whereas other topical treatments can take up to 12 months to complete the treatment regimen
- reduced treatment time has the potential to improve adherence to the regimen, with likely improved treatment outcomes

Bayer believes the labelling of Canesten Fungal Nail Treatment set[19] has been optimised to refer the consumer to a pharmacist or doctor when appropriate.

B3.2 Safety of Canesten Fungal Nail Treatment Set

The secondary objective of the study specific to Canesten Fungal Nail Treatment set[16,17] was to compare the safety and tolerability of bifonazole vs. placebo. During both the urea treatment phase and the bifonazole/placebo treatment phase, adverse event incidence was slightly higher in the placebo group. The incidence of adverse events considered to be treatment related was low, and the authors concluded that this treatment was well-tolerated.

The adverse events were mostly of mild intensity. Side effects are fully discussed and the patient advised on what to do if they are experienced in the pack insert[19].

The authors concluded:-

> "Treatment of onychomycosis with urea for non-surgical nail removal followed by antifungal treatment with bifonazole is well tolerated and highly efficient. Removal of infected nails with urea alone is a procedure with a good therapeutic response. The addition of 4 weeks of bifonazole treatment after urea nail ablation produced significant benefit in terms of mycological cure (and therefore overall cure) 2 weeks after treatment is stopped and this is sustained for around 3 months."[17]

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