PUBLIC SUMMARY DOCUMENT
Product: TERBINAFINE, tablet, 250 mg and cream, 10 mg per g (1%), 15 g, Lamisil®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd (tablet), Novartis Consumer Health Australasia Pty Ltd (cream)
Date of PBAC Consideration: November 2007

1. Purpose of Application

These submissions sought to list terbinafine cream and to extend the current listing of terbinafine tablets on the PBS under the 2004-05 Budget measure to improve the access to appropriate medicines for an Aboriginal and/or Torres Strait Islander person for treatment of extensive fungal or yeast infection.

2. Background

The poorer health status of Indigenous Australians is well documented and on almost all social, economic and health indicators Indigenous people are more disadvantaged than the general Australian population. Chronic conditions such as diabetes, hypertension, hyperlipidemia, coronary heart disease and chronic renal impairment are highly prevalent in Aboriginal and Torres Strait Islander communities.

Access to appropriate medicines is a major factor in the provision of effective healthcare services and one of the measures announced in the 2004-05 Budget sought to facilitate this process. The objective of the Budget measure, *Primary Health Care Access Program for Aboriginal and Torres Strait Islander People – additional funding*, was to support activities which facilitate the inclusion of medicines in the *Schedule of Pharmaceutical Benefits* to treat conditions particular to Indigenous health needs.

An expert Advisory Panel was established with specific experience and knowledge of the role of medicines in Indigenous health settings. This Panel has noted the substantial need for antifungal medicines in this setting.

3. Registration Status

Terbinafine tablets are registered for the treatment in adults of ringworm (tinea corporis, tinea cruris and tinea pedis) due to infection caused by dermatophytes such as trichophyton (e.g. T. rubrum, T. mentagrophytes, T. verrucosum, T. violaceum), microsporum canis and epidermophyton floccosum, where oral therapy is considered appropriate owing to the site, severity or extent of the infection, and the infection is not responsive to topical therapy. Onychomycosis in adults (fungal infection of the nail) caused by dermatophyte fungi.

Terbinafine cream is registered for the treatment of cutaneous candidiasis and ringworm (tinea corporis, tinea cruris and tinea pedis) caused by dermatophytes such as Trichophyton (e.g. T. rubrum, T. mentagrophytes, T. verrucosum, T. violaceum), Microsporum canis and Epidermophyton floccosum.

4. Listing Requested and PBAC's View

Tablet

Authority Required

Treatment of a fungal or a yeast infection in an Aboriginal or a Torres Strait Islander adult involving susceptible organisms where oral therapy is considered appropriate owing

to the site, severity or extent of infection and the infection is not responsive to topical therapy.

Cream

Authority required

Treatment of a fungal or a yeast infection in an Aboriginal or a Torres Strait Islander person.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

The proposed therapy would provide an additional subsidised treatment for dermatophyte and Candida infections in an Aboriginal or Torres Strait Islander person.

6. Comparator

The tablet submission nominated griseofulvin as the comparator. The cream submission nominated miconazole as the comparator. These were considered appropriate by PBAC.

7. Clinical Trials

The tablet submission presented the results of 14 direct randomised trials comparing oral terbinafine 250mg daily to griseofulvin in adult patients with *tinea corporis*, *tinea cruris* or *tinea pedis*.

The trials published at the time of submission and presented in the terbinafine tablets submission are as follows:

Trial/First author	Protocol title	Publication citation
SF00411/Savin 1989 and 1990	A double-blind, clinical therapeutic trial of the efficacy and safety of oral SF86-327 (125 mg bid) compared to griseofulvin (250 mg bid) in patients with chronic tinea pedis of the moccasin type.	*Clinical and Experimental Dermatology* 1989; 14:116-119 *Journal of the American Academy of Dermatology* 1990; 23:807-809 *Journal of Dermatological Treatment* 1990; 1:43-46
SF0044/ Del Palacio Hernanz et al	A double blind, clinical therapeutic trial of the efficacy and safety of oral terbinafine compared to oral griseofulvin in patients with tinea corporis	*Clinical and Experimental Dermatology* 1990; 15:210-216 J*ournal of Dermatological Treatment* 1990; 1 Suppl. 2:39-40
Fattah et al	Two weeks treatment of tinea cruris/corporis with oral terbinafine (Lamisil)	*Journal of Pan-Arab League of Dermatologists* 1995; 6:79-85
Kazmi et al	Multicenter, randomized, double-blind comparative study on terbinafine versus griseofulvin in tinea pedis	Selected Papers from the Regional Congress of Dermatology. Special focus: '*Terbinafine in the treatment of dermatophytosis. Cyclosporin A in the treatment of severe psoriasis*'. Hong Kong: Medimedia Asia 1995:15-19

Leenutaphong et al	A randomized double blind comparative study of terbinafine vs. griseofulvin in tinea corporis and tinea cruris	In Evans EGV, Jafary MH (eds). *Dermatological Treatments: Preliminary Investigations in the Asia-Pacific Region. Proceedings, Asia Pacific Dermatology Symposium, New York (NY, USA), 15 June 1992*. London: Royal Society of Medicine Services Ltd 1992:11-15
Nada 1993 and 1994	One week treatment of oral Lamisil (terbinafine) vs. three weeks griseofulvin in the treatment of tinea cruris/corporis Open randomised controlled therapeutic trial of oral terbinafine (Lamisil) vs. griseofulvin, in the treatment of tinea cruris/corporis	*Journal of Pan-Arab League of Dermatologists* 1993; 4:87-92 In Hay RJ (ed). *International Perspective on Lamisil* (Series: CCT Healthcare Congress and Symposium; No. 101). London: CCT Healthcare Communications Ltd 1994:p125
Olumide et al 1994	Open trial comparing Lamisil and griseofulvin in the treatment of tinea pedis	In Hay RJ (ed). *International Perspective on Lamisil* (Series: CCT Healthcare Congress and Symposium; No. 101). London: CCT Healthcare Communications Ltd 1994:132-136
Voravutinon 1992 and 1993	Oral treatment of tinea corporis and tinea cruris with terbinafine and griseofulvin: a randomized double-blind comparative study in Southern Thailand	In Evans EGV, Jafary MH (eds). *Dermatological Treatments: Preliminary Investigations in the Asia-Pacific Region. Proceedings, Asia Pacific Dermatology Symposium, New York (NY, USA), 15 June 1992.* London: Royal Society of Medicine Services Ltd 1992:17-21 *Journal of Medical Association of Thailand* 1993; 76:388-393.
Widyanto et al 1993 and 1994	A randomised, double blind comparative study of terbinafine vs. griseofulvin in tinea pedis	In Shuster S, Jafary MH (eds). *Terbinafine in the treatment of superficial fungal infections. Proceedings of the Asia-Pacific symposium on Lamisil (Series: International Congress and Symposium; No. 205).* London: Royal Society of Medicine Services Ltd 1993:21-24 In Hay RJ (ed). *International Perspective on Lamisil* (Series: CCT Healthcare Congress and Symposium; No. 101). London: CCT Healthcare Communications Ltd 1994:193-195
Wingfield et al 2004	Treatment of tinea imbricata: a randomized clinical trial using griseofulvin, terbinafine, itraconazole and fluconazole	*British Journal of Dermatology* 2004; 150:119-126
Zeid et al 1994	Short term oral Lamisil (terbinafine) in the treatment of moccasin tinea pedis	*Journal of Pan-Arab League of Dermatologists* 1994; 5:113-119.
Koh et al 2003[#]	Use of terbinafine for tinea in Australian Aboriginal communities in the Top End.	*Australasian Journal of Dermatology* 2003; 44:243-249

[#]Two non-randomised studies conducted in Aboriginal communities in the Northern Territory

The cream submission presented two direct randomised trials, comparing terbinafine 1% cream (once daily in the key trial, Leenutaphong et al and twice daily in the supportive

trial, Vermeer et al) administered for one week and miconazole 2% cream (twice daily) administered for 4 weeks, in patients with tinea pedis. Follow-up ranged from 10 weeks in Leenutaphong et al (1999) to 6 weeks in Vermeer et al (1996).

These studies are published as follows:

Trial/First author	Protocol title	Publication citation
Leenutaphong et al, 1999	Double- blind study of the efficacy of one week terbinafine cream compared to four weeks miconazole cream in patients with *tinea pedis*.	*Journal of the Medical Association of Thailand* 1999; 82: pp1006-10.
Vermeer et al, 1996	One week treatment of terbinafine cream (Lamisil) has the same clinical efficacy as four weeks treatment with local miconazole cream (Daktarin).	*Journal of the European Academy of Dermatology and Venereology* 1996; 5(Suppl.1):S80.

8. Results of Trials

The results for overall treatment effectiveness for terbinafine tablets are summarised in the table below. The table shows the proportion of patients with each condition who received effective therapy.

Results for overall treatment effectiveness[a] for terbinafine tablets

Trial ID	Terbinafine 250mg	Griseofulvin 500mg	Relative risk (95% CI)	Risk difference (95% CI)
SF00411	14/16 (88%)	5/11 (45%)	1.93 (0.98 – 3.77)	0.42 (0.08 – 0.76)
SF0042	9/14 (64%)	7/16 (44%)	1.47 (0.75 – 2.90)	0.21 (-0.14 – 0.55)
SF0043A / SF0043B	119/126 (94%)	108/126 (86%)	1.10 (1.01 – 1.20)	0.09 (0.01 – 0.16)
Voravutinon 1992 / 1993	27/31 (87.1%)	17/31 (54.8%)	1.59 (1.12 – 2.25)	0.32 (0.11 – 0.53)
Widyanto et al 1993	19/22 (84.6%)	7/21 (33.3%)	2.59 (1.38 – 4.85)	0.53 (0.28 – 0.78)
SF0025	36/39 (92%)	29/36 (81%)	1.15 (0.95 – 1.38)	0.12 (-0.04 – 0.27)
Leenutaphong et al 1992	14/22 (63.6%)	15/30 (50%)	1.27 (0.79 – 2.05)	0.14 (-0.13 – 0.41)
Kazmi et al 1995	75/92 (81.5%)	60/91 (65.9%)	1.24 (1.04 – 1.48)	0.16 (0.03 – 0.28)
Pooled result from random effects model			1.31 (1.11 – 1.54)	0.21 (0.11 – 0.32)
Chi-square (Q) for heterogeneity			19.0, P=0.008	18.1, P=0.01
I^2 statistic			63.2%	61.3%

[a]Overall treatment effectiveness is based on mycological cure / complete cure. At each visit, the following clinical signs and symptoms were scored on a scale of 0-3 (0=absent, 1= mild, 2=moderate and 3=severe): erythema; pustules; desquamation; incrustation; vesiculation and pruritus. Skin scrapings were taken for microscopy for microscopy and culture. Complete cure was defined as microscopy and culture negative with no residual clinical signs and symptoms. Mycological cure was defined as microscopy and culture negative, mild residual erythema and/or desquamation and/or pruritus (total score less than or equal to 2), but no other clinical signs. Not all trials were included in this analysis due to differences in the outcomes measured.

Terbinafine was associated with higher overall effectiveness compared to griseofulvin in terms of both the pooled relative risk and the pooled risk difference. All trials reported

point estimates that were in favour of oral terbinafine 250 mg over griseofulvin 500 mg daily. However, there was substantial heterogeneity amongst the study results.

Overall, the safety profile of terbinafine appeared comparable to that of griseofulvin. However, unlike griseofulvin, terbinafine was associated with rare cases of liver failure, some leading to liver transplant or death. On the other hand, the PBAC noted that griseolfulvin's product information lists alcohol as an interaction.

The results of the key and supportive trials with terbinafine cream are summarised in the table below:

Results of effectiveness outcomes (per protocol patients)

Key trial: Leenutaphong et al (1999)	**Terbinafine cream 1% once daily**	**Miconazole cream 2% twice daily**	**Relative risk (95% CI)**	**Risk difference (95% CI)**
End of follow-up (10 weeks)				
Mycological cure	10/19 (53%)	11/20 (55%)	0.96 (0.53,1.71)	-0.02 (-0.34,0.29)
Clinical efficacy[b]	9/19 (47%)	9/20 (45%)	1.05 (0.53, 2.07)	0.02 (-0.29,0.34)
Supportive trial: Vermeer et al (1996)	**Terbinafine cream 1% twice daily**	**Miconazole cream 2% twice daily**	**Relative risk (95% CI)**	**Risk difference (95% CI)**
End of follow-up (6 weeks)				
Mycological cure	116/124 (94%)	116/120 (97%)	0.97 (0.91,1.02)	-0.03 (-0.09,0.02)
Clinical effectiveness[c]	108/124 (87%)	105/120 (88%)	1.00 (0.90,1.10)	0.00(-0.09,0.08)

[b]clinical efficacy was determined on the basis of mycological cure with a total signs and symptoms score of 2 - signs and symptoms of infection included erythema, scaling, vesiculation, pustules, crusting and pruritus and were rated by the physician on a scale of 0=absent, 1=mild, 2=moderate, 3=severe, to give a clinical score (maximum score=18); [c]clinical effectiveness or clinical cure defined as mycological cure and the presence of a maximum of two symptoms – scale was not defined in the published report.

There were no statistically significant differences between treatment with terbinafine cream (1%) and treatment with miconazole cream (2%) on any outcome at the end of the follow-up periods. Although the point estimate in the Leenutaphong et al (1999) trial indicates little difference between the two treatments, the confidence intervals (CI) for mycological cure (relative risk (RR) = 0.96; 95% CI [0.53, 1.71]) and clinical efficacy (RR = 1.05; 95% CI [0.53, 2.07]) are wide and do not exclude a relative treatment effect favouring miconazole over terbinafine.

Overall, the safety profile of terbinafine cream appears comparable to that of miconazole cream. Redness, itching or stinging occasionally occur at the site of application but rarely requires discontinuation of therapy. These symptoms must be distinguished from allergic reactions which are rare but require discontinuation of therapy.

For PBAC's view of these results, see Recommendation and Reasons.

9. Clinical Claim

The tablet submission claimed that meta analyses showed that terbinafine 250 mg per day is associated with a significantly higher overall effectiveness rate compared to griseofulvin 500 mg per day with comparable tolerability.

The cream submission claimed that terbinafine cream 1% has equivalent efficacy and safety compared to miconazole 2% cream in the treatment of fungal or yeast infection.

The submissions also claimed that terbinafine has the additional advantage of shorter duration of treatment leading to better compliance.

For PBAC's view of these claims, see Recommendation and Reasons.

10. Economic Analysis

A trial-based economic evaluation was presented for the tablets. The choice of a cost-effectiveness approach was considered valid. The resources included were drug costs only. The submission estimated the incremental cost/extra patient who has been successfully treated during the trial period to be <$500. A modelled economic evaluation was not presented due to the lack of data in the Aboriginal and Torres Strait Islander population.

A trial-based cost-minimisation approach was presented for the cream. The choice of a cost-minimisation approach was considered to be valid. The resources included were drug costs only. A modelled economic evaluation was not presented. The PBAC considered this a deficiency of the submission (see *Recommendation and Reasons*).

11. Estimated PBS Usage and Financial Implications

The submissions estimated the likely number of patients/year on terbinafine to be less than 10,000 at a financial cost/year to the PBS of less than $1 million per year of listing by year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of terbinafine tablets on the PBS for the treatment of a dermatophyte infection in an Aboriginal or Torres Strait Islander person (ATSI), on the basis of acceptable cost-effectiveness compared with griseofulvin, under the 2004-05 Budget measure to facilitate the access to appropriate medicines for an Aboriginal and/or Torres Strait Islander person.

The PBAC noted advice from the Expert Advisory Group on Antimicrobial Resistance (EAGAR), and agreed that terbinafine tablets be restricted to use in the treatment of dermatophyte infections rather than yeast or fungal infections as requested, as terbinafine does not have a major role in the treatment of serious or invasive fungal infections other than the treatment of dermatophytosis.

The PBAC noted that whilst there were no high quality studies in ATSI populations, pooled published trial results for Asian and African settings showed similar efficacy.

The PBAC considered that a maximum quantity of 42 tablets and 0 repeats would be appropriate in terms of waste minimisation and maximising cost-efficiency of treatment if tinea pedis was one of the major uses for the drug. The PBAC noted that terbinafine was

already PBS listed with a maximum quantity of 42 tablets and 1 repeat for the treatment of onychomycosis due dermatophyte infection where topical treatment has failed.

The PBAC recommended the listing of terbinafine cream on the PBS for the treatment of a fungal or yeast infection in an Aboriginal or Torres Strait Islander person, on a cost-minimisation basis compared with miconazole cream, under the 2004-05 Budget measure to facilitate the access to appropriate medicines for an Aboriginal and/or Torres Strait Islander Person.

The PBAC considered that the randomised control trial (RCT) - based evidence for comparative effectiveness was sparse. Evidence on effectiveness in Australian Indigenous patients was not available, so RCT data did not reflect target population. In addition, incidence estimates probably under-estimate the extent of cutaneous fungal infection in Indigenous populations, especially when the risk of re-infection is considered. The PBAC considered that the applicability of findings from the trial populations to Australian Indigenous populations may not be clear, as many Indigenous communities live in conditions that favour re-infection, and prevalence is high.

The PBAC considered that the trial-based cost-minimisation data should be regarded as indicative only and that the additional cost of listing terbinafine would be magnified if the incidence were higher than estimated, or if treatment were prolonged. The PBAC noted that the terbinafine cost advantage disappears if there is a need for once daily dosing for more than about 2 weeks.

The PBAC considered that the once daily for 1 week for terbinafine is likely to favour compliance, in comparison with twice daily for 4 weeks for miconazole. However, Australian Indigenous conditions may call for a longer duration of terbinafine use and a modelled economic approach could have estimated the cost, given the characteristics of the PBS target population.

The PBAC considered that the wording of the restriction for terbinafine cream should include fungal or yeast infection as terbinafine cream is active against both dermatophytes and Candida.

Recommendation

TERBINAFINE, tablet, 250 mg:
Add the following to the restriction:

Restriction:	Authority required Treatment of a dermatophyte infection in an Aboriginal or a Torres Strait Islander person where topical treatment has failed.
Maximum quantity:	42
Repeats:	0

TERBINAFINE, cream, 10 mg per g (1%), 15 g,
List with the following restriction:

Restriction:	Authority required (STREAMLINED) Treatment of a fungal or a yeast infection in an Aboriginal or a Torres Strait Islander person.
Maximum quantity:	2
Repeats:	3

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Novartis welcomes the decision by the PBAC to recommend the listing of terbinafine tablets and cream for use by Aboriginal and Torres Strait Islander persons and the opportunity to contribute to the improvement of Indigenous health.