HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

27 January 2010

ONYTEC 80 mg/g, medicated nail lacquer

B/1 glass vial of 3.3 ml (CIP: 395 010-4)

B/1 glass vial of 6.6 ml (CIP: 395 011-0)

Applicant: BAILLEUL-BIORGA

ciclopirox

ATC code: D01AE14

Date of Marketing Authorisation: 01/07/2009

Reason for request: inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

ciclopirox

1.2. Originality

ONYTEC is a water-soluble nail lacquer formulation based on ciclopirox. It rinses off in water.

1.3. Indication

"Mild to moderate onychomycosis caused by dermatophytes and/or other ciclopirox-sensitive fungi, without lunula involvement. »

1.4. Dosage

"Topical use on fingernails and toenails and immediately adjacent skin (perionychium, hyponychium).

Unless otherwise specified, ONYTEC nail lacquer should be applied to the clean, dry affected nail(s) in a thin layer once a day. The medicated nail lacquer must be applied to the entire nail plate, 5 mm of surrounding skin and, if possible, to the free edge of the nail. ONYTEC nail lacquer takes about thirty seconds to dry. Treated nails must not be washed for at least six hours, and patients are therefore advised to apply the product in the evening before retiring. After this time the normal hygiene routine can be resumed.

There is no need to use a solvent or abrasive (i.e. a nail file) to remove ONYTEC nail lacquer; washing the nails is sufficient. ONYTEC can be re-applied if it is accidentally washed off.

Patients are advised to regularly remove the free edge of the nail and any onycholytic matter using nail clippers.

Treatment must be continued until complete clinical and mycological healing has been achieved, and until a healthy nail has regrown. Fingernails normally take about six months to heal, while toenails take nine to 12 months.

A test should be performed to detect fungi four weeks after the end of treatment in order to prevent any active substance residue distorting the culture findings.

As this is a topical treatment, no dose adjustment is necessary for specific patient populations.

Complementary oral treatment must be considered if the condition does not respond to treatment with ONYTEC nail lacquer and/or if several fingernails or toenails are affected".

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

D : Dermatologicals
D01 : Antifungals for dermatological use
D01A : Antifungals for topical use
D01AE : Other antifungals for topical use
D01AE14 : Ciclopirox

2.2. Medicines in the same therapeutic category

Comparator medicines

Strictly comparable medicines are filmogenic solutions (MYCOSTER 8% and LOCERYL 5%)

INN	Product name	Galenic form	Indication
ciclopirox	MYCOSTER 8%, and its generics	(Filmogenic) solution for topical application, supplied in 3-ml vial with a brush	First-line treatment of cases of onychomycosis without lunula involvement
ciclopirox olamine	MYCOSTER 1%	Cream Solution for topical application in spray vial	Cases of dermatosis (with or without suprainfection) and onychomycosis caused by dermatophytes
amorolfine	LOCERYL 5%	(Filmogenic) solution for topical application, supplied in 2.5-ml vial, with 10 spatulas	First-line treatment of cases of onychomycosis without lunula involvement
Bifonazole + urea	AMYCOR ONYCOCHOSET	Ointment 10 g tube with a scraper and 20 adhesive dressings	Topical treatment of ungual mycoses of the hands and feet

2.3. Medicines with a similar therapeutic aim

All topical and general antifungals indicated for the treatment of onychomycosis.

➤ Antifungals for topical application

Polyenes

Amphotericin B: FUNGIZONE

Imidazoles

Bifonazole: AMYCOR

Econazole: DERMAZOL, PEVARYL

Fenticonazole: LOMEXIN

Isoconazole: FAZOL

Ketoconazole: KETODERM

Miconazole: DAKTARIN

Allylamines

Terbinafine: LAMISIL

➤ Antifungals for oral application

Griseofulvin: GRISEFULINE

Terbinafine: LAMISIL

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The application is based on one controlled trial (study CH-OPLC-001-CLPRX-02)¹, conducted on 467 patients suffering from distal onychomycosis.

Objective

The primary objective of this study was to assess the non-inferiority (delta threshold = 10%) of ONYTEC (*water-soluble 8% ciclopirox lacquer*) versus the reference product (MYCOSTER=PENLAC, *non-water soluble 8% ciclopirox lacquer*) in the treatment of onychomycosis. The study included a placebo group.

A protocol amendment specified that a superiority analysis versus MYCOSTER (secondary purpose) would be carried out if non-inferiority was demonstrated.

Inclusion and exclusion criteria

Inclusion criteria:

- men or women aged from ≥ 18 to ≤ 70 ,
- distal onychomycosis affecting at least one big toenail (target nail),
- of mild to moderate severity (affecting 25% to 60% of the distal surface adhering to the nail bed, with no lunula involvement),
- confirmed by a positive culture and microscopic examination using potassium hydroxide (KOH).

Main exclusion criteria:

- systemic antifungal used within the past 6 months,
- topical antifungal applied within the past 4 weeks,
- onychomycosis caused by a non-dermatophytic mould or fungus,
- superficial white onychomycosis,
- proximal sub-ungual onychomycosis,
- presence of yellow spots on the nail (fungal infection extending from the distal part to the proximal part of the nail),
- presence of psoriasis,
- uncontrolled diabetes,
- chemotherapy or immunosuppressant therapy within the past 12 weeks,
- systemic administration of glucocorticoids, antimetabolites or immunostimulants within the past 4 weeks.

Treatments:

The patients (N=467) were randomised into three groups (ratio 2:1:2) to receive:

- ONYTEC (n=182) or Placebo (n=97), in a double-blind design: 1 application of a fine layer by brush in the evening before retiring.
- MYCOSTER (n=188), in an open-label design: 1 application of a fine layer by brush in the evening before retiring, removed weekly using isopropyl alcohol and a nail file (according to the product SPC).

Treatments were applied for 48 weeks (with the free edge of the infected nail removed once a month), and this was followed by 12 weeks post-treatment monitoring.

Primary efficacy endpoint:

Complete healing, defined as negative mycological tests (microscopic examinations with KOH and culture), accompanied by complete replacement of the affected nail by a new, healthy nail at week 48 (end of treatment) and confirmed at week 52.

The international scientific coordinator (ISC) performed a blinded assessment of the response to treatment.

¹ Baran R, et al. An innovative water-soluble biopolymer improves efficacy of ciclopirox nail lacquer in the management of onychomycosis. J Eur Acad Dermatol Venereol. 2009, 23, 773-781

Main secondary efficacy endpoints:

- Clinical success: reduction in the area of nail infected to $\leq 10\%$ of the total area of nail (but $> 0\%$), assessed blind by the ISC, together with negative mycological tests (microscopic examinations with KOH and culture).
- Responders: subjects experiencing either complete healing or clinical success.
- Improvement: patients in whom the area of nail infected had reduced by at least 20% by the end of treatment, assessed by the ISC, together with negative mycological tests (microscopic examinations with KOH and culture).
- Reduction in the area of nail affected: area of nail affected reduced to $\leq 10\%$ of the total nail area (including 0%), assessed by the ISC.
- Negative culture.
- Negative microscopic examinations (KOH).

Assessment hypotheses

Fischer's exact test was used for the comparison versus placebo.

Non-inferiority versus MYCOSTER was established if the lower limit of the confidence interval of the difference in complete healing rates between ONYTEC and MYCOSTER was greater than - 10%. Superiority was established if the lower limit of the confidence interval was > 0 .

A post-hoc analysis was carried out at weeks 52 and 60 after amendment of the protocol.

Results

➤ **Analysis population**

A total of 466 patients (men: 63.3%, mean age: 49.84 years) were randomised and included in the intention-to-treat population (ITT population). The medical characteristics of the patients in the various treatment groups were similar (Table 1).

Table 1: Main clinical characteristics of randomised patients

Characteristics on inclusion	Placebo (n=97)	ONYTEC (n=181)	MYCOSTER* (n=188)
Total number of nails with onychomycosis (mean $\pm$ SD)	3.98 $\pm$ 2.44	4.36 $\pm$ 2.55	4.09 $\pm$ 2.54
Percentage of target nail affected (mean $\pm$ SD)	43.4 $\pm$ 18.8	44.5 $\pm$ 19.9	44.1 $\pm$ 18.8
Positive microscopic examination (KOH) (% patients)	100	100	100
Dermatophyte positive culture (%)
<i>Trichophyton mentagrophytes</i>	100	100	100
<i>T. rubrum</i>	39.2	36.8	37.8
<i>T. spp</i>	52.6	54.4	50.5
<i>Epidermophyton floccosum</i>	5.1	5.5	6.9
Other dermatophytes	1.0	1.6	2.7
2.1	1.7	2.1
Initial clinical presentation
Superficial white onychomycosis (mycotic leukonychia), n (%)	10 (10.3%)	22 (12.2%)	9 (4.8%)
Mild onychomycosis (< 25% of the nail affected, no involvement of proximal tissue), n (%)	9 (9.3%)	11 (6.1%)	17 (9%)
Moderate onychomycosis ($\geq 25\%$; $\leq 65\%$ of the nail affected, no involvement of proximal tissue), n (%)	67 (69.1%)	130 (71.8%)	132 (70.2%)
Severe onychomycosis (>65% of the nail affected, and/or involvement of proximal tissue and lunula, and presence of yellow spots), n (%)	20 (20.6%)	40 (22.1%)	38 (20.2%)

*reference product (MYCOSTER=PENLAC, non-water-soluble 8% ciclopirox lacquer)

➤ **Efficacy**

Primary efficacy endpoint: complete healing²

The results for the primary efficacy endpoint are shown in Table 2.

Table 2: Efficacy result for the primary criterion of "complete healing" at weeks 48, 52 and 60

Placebo (N=94)	ONYTEC (N=175)	MYCOSTER** 8% (N=185)	ONYTEC vs. placebo Value of p	ONYTEC vs. MYCOSTER difference
Primary efficacy endpoint: percentage of patients experiencing complete healing (n)
W 48, ITT pop	0 (0/94)	5.7 (10/175)	3.2 (6/185)	0.0165	2.5 (-1.8 ; +6.8)
W 48, PP pop	0 (0/89)	6 (10/167)	3.4 (6/177)	0.0166	2.6 (-1.9 ; +7.1)
Results for the follow-up period (weeks 52 and 60), post-hoc descriptive analysis
W 52, ITT pop	1.1 (1/94)	9.1 (16/175)	4.9 (9/185)	0.0078	4.3 (-1 ; +9.6)
W 60, ITT pop	1.1 (1/94)	11.4 (20/175)	5.4 (10/185)	0.0015	6 (0.3 ; +11.8)

* affected nail entirely replaced by a new, healthy nail, plus negative mycological tests (microscopic examinations with KOH and culture),

**reference product (MYCOSTER=PENLAC, *non-water-soluble 8% ciclopirox lacquer*)

In respect of the primary efficacy endpoint (complete healing at week 48, confirmed at week 52), the hypothesis that ONYTEC is superior to placebo was demonstrated by the ITT analysis. In the per-protocol analysis, the lower limit of the 95% CI of the difference between the two active treatment groups was above the predetermined non-inferiority threshold (-10%), which indicates that ONYTEC is no, inferior to MYCOSTER. In the ITT analysis, the lower limit of the confidence interval of the difference between the two active treatment groups was < 0, which does not indicate that ONYTEC is superior to MYCOSTER.

The post-hoc analysis carried out at the end of the post-treatment monitoring period (week 60) after amendment of the protocol showed a higher healing rate in the ONYTEC group compared to the MYCOSTER group. However, this result is of limited significance given the open-label nature of the study, the diversity of assessment periods and the size of the effect in quantitative terms.

Secondary efficacy endpoints:

The descriptive analysis of the results in terms of the secondary endpoints is presented in Table 3. Overall, these results are in line with those obtained for the primary efficacy endpoint.

² Affected nail entirely replaced by a new, healthy nail, plus negative mycological tests (microscopic examinations with KOH and culture)

Table 3: Results for the secondary efficacy endpoints at week 48 and post-hoc descriptive analysis at weeks 52 and 60

Placebo (N=94)	ONYTEC (N=175)	MYCOSTER (N=185)	ONYTEC vs. placebo p	ONYTEC vs., MYCOSTER difference
Clinical success (% , n)
W 48, ITT pop	6.4 (6/94)	18.3 (32/175)	14.1 (26/185)	0.0094	4.2 (-3.4 ;+11.8)
W 48, PP pop	6.7 (6/89)	19.0 (32/168)	14.5 (26/179)	0.0091	4.5 (-3.3 ;+12.4)
W 52, ITT pop	10.6 (10/94)	15.4 (27/175)	13.5 (25/185)	NS	1.9 (-5.4;+9.2)
W 60, ITT pop	12.8 (12/94)	14.9 (26/175)	10.3 (19/185)	NS	4.6 (-2.3;+11.4)
Responder rate (% , n)
W 48, ITT pop	6.4 (6/94)	24 (42/175)	17.3 (32/185)	0.0002	6.7 (-1.6 ;+15.1)
W 48, PP pop	6.7 (6/89)	25 (42/168)	17.9 (32/179)	0.0003	7.1 (-1.5 ;+15.7)
W 52, ITT pop	11.7 (11/94)	24.6 (43/175)	18.4 (34/185)	0.0160	6.2 (-2.3;+14.7)
W 60, ITT pop	13.8 (13/94)	26.3 (46/175)	15.7 (29/185)	0.0204	10.6 (2.2;+19)
Improvement
W 48, ITT pop	30.9 (29/94)	41.7 (73/175)	39.5 (73/185)	0.0878	2.3 (-7.9 ;+12.4)
W 48, PP pop	32.6 (29/89)	43.1 (72/167)	41.2 (73/177)	NS	1.9 (-8.6 ;+12.3)
W 52, ITT pop	30.9 (29/94)	40 (70/175)	38.4 (71/185)	NS	1.6 (-8.5;+11.7)
W 60, ITT pop	29.8 (28/94)	43.4 (76/175)	36.2 (67/185)	0.0355	7.2 (-2.9;+17.3)
Area of nail affected reduced to ≤ 10%
W 48, ITT pop	10.6 (10/94)	28 (49/175)	18.9 (35/185)	0.0011	9.1 (0.4+17.8)
W 48, PP pop	11.4 (10/88)	29.2 (49/168)	19.6 (35/179)	0.0010	9.6 (0.6+18.6)
W 52, ITT pop	16 (15/94)	28.6 (50/175)	21.6 (40/185)	0.0248	6.9 (-2;+15.9)
W 60, ITT pop	14.9 (14/94)	33.7 (59/175)	19.5 (36/185)	0.0009	14.3 (5.2;+23.3)
Negative culture
W 48, ITT pop	69.1 (65/94)	89.1 (156/175)	90.8 (168/185)	0.0001	-1.7 (-7.9 ; +4.5)
W 60, ITT pop	67 (63/94)	78.3 (137/175)	77.8 (144/185)	0.0566	0.4 (-8.1; +9)
Negative microscopic examination with KOH
W 48, ITT pop	60.6 (57/94)	67.4 (118/175)	74.6 (138/185)	NS	-7.2 (-16.5 ; +2.2)
W 60, ITT pop	57.4 (54/94)	61.1 (107/175)	67.6 (125/185)	NS	-6.4 (-16.3; +3.5)

An exploratory analysis of sub-groups according to clinical presentation (Table 4) showed a less favourable response in the sub-group of patients with onychomycosis regarded as severe (> 65% of the nail affected, and/or involvement of proximal tissue and the lunula, and presence of yellow spots). It should be noted that the product's indication does not include this population.

Table 4: Efficacy at week 48 according to location and severity (exploratory analysis).

Placebo (N=94)	ONYTEC (N=175)	MYCOSTER (N=185)	p vs. placebo	p vs. MYCOSTER
Superficial white onychomycosis (mycotic leukonychia)
Complete healing	0/10	0/22	1/9	NS	NS
Clinical success	0/10	3/22	0/9	NS	NS
Responders	0/10	3/22	1/9	NS	NS
Mild onychomycosis (< 25% of the nail affected, no involvement of proximal tissue)
Complete healing	0/8	1/10	1/17	NS	NS
Clinical success	2/8	4/10	8/17	NS	NS
Responders	2/8	5/10	9/17	NS	NS
Moderate onychomycosis (≥25%; ≤ 65% of the nail affected, no involvement of proximal tissue)
Complete healing	0/65 (0%)	8/126 (6.3%)	4/130 (3.1%)	0.0528	NS
Clinical success	4/65 (6.2%)	26/126 (20.6%)	17/130 (13.1%)	0.0108	NS
Responders	4/65 (6.2%)	34/126 (27%)	21/130 (16.2%)	0.0005	NS
Severe onychomycosis (>65% of the nail affected, and/or involvement of proximal tissue and lunula, and presence of yellow spots)
Complete healing	0/20	1/39 (2,6)	1/38 (2,6)	NS	NS
Clinical success	0/20	2/39 (5,1)	1/38 (2,6)	NS	NS
Responders	0/20	3/39 (7,7)	2/38 (5,3)	NS	NS

3.2. Adverse effects

The incidence of adverse events was 23% (107/466) and was similar in the various treatment groups. Only 1.1% of the adverse events were regarded as related to the study treatments (no patients in the ONYTEC group, 2 patients in the MYCOSTER group and 3 in the placebo group). The adverse events comprised two cases of infection/aggravation of fungal infection; one case of pruritus in the placebo group; one case of oedema of the legs; and one case of petechia in the MYCOSTER group. None of these events were regarded as severe and none of them led to treatment being discontinued. No systemic adverse effect was observed.

Some abnormalities were observed at the application site at various observation time points, with no particular increase over time (Table 5).

Table 5: Abnormalities at the application site

Placebo (N=97)	ONYTEC (N=181)	MYCOSTER (n=188)	Total (N=466)
Erythema	6.2% (6/97)	2.8% (5/181)	10.6% (20/188)	6.6% (31/466)
Burning	4.1% (4/97)	2.8% (5/180)	10.7% (20/187)	6.3% (29/464)
Itching	7.2% (7/97)	2.8% (5/180)	1.6% (3/187)	3.2% (15/464)
Pain	2.1% (2/97)	1.7% (3/180)	3.2% (6/187)	2.4% (11/464)
Oedema	1% (1/97)	0% (0/181)	0% (0/188)	0.2% (1/466)

3.3. Conclusion

ONYTEC was compared to a non-water-soluble 8% *ciclopirox lacquer* (MYCOSTER) (open-label) and to placebo (double-blind) in a controlled study conducted on 467 patients suffering from distal onychomycosis (100% dermatophytic) of moderate severity (70% of the cases). The primary objective was to assess the non-inferiority of ONYTEC to that of MYCOSTER (delta threshold = 10%), and if appropriate to assess its superiority (secondary objective).

The treatments were applied every day for 48 weeks, and the patients were monitored for a further 12 weeks after the end of treatment. The assessment was performed at weeks 48, 52 and 60 (the latter two analyses were post-hoc analyses).

In the ITT analysis carried out at W 48, the rate of complete healing (nail entirely replaced by a new, healthy nail, with mycological tests producing negative results), the primary efficacy endpoint, was 5.7% (10/175) in the ONYTEC group, 3.2% (6/185) in the MYCOSTER group and 0% (0/94) in the placebo group ($p < 0.05$ versus placebo). ONYTEC was therefore superior to placebo, but no conclusions can be drawn as to its superiority to MYCOSTER (lower limit of the 95% CI of the difference between ONYTEC and MYCOSTER $[-1.8; 6.8] < 0$). In the per-protocol analysis carried out at week 48, ONYTEC was shown to be non inferior to MYCOSTER 8% (the lower limit of the 95% CI of the difference between ONYTEC and MYCOSTER $[-1.9; +7.1]$ was above the predetermined non-inferiority threshold (-10)).

However, this result is of limited significance given the open-label nature of the study (possibility of monitoring bias), the diversity of assessment periods and the size of the effect in quantitative terms.

Safety was satisfactory. No systemic adverse effect was observed. The abnormalities observed at the application site (erythema, itching, burning and pain) were mild and transient.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Onychomycosis is a mild, frequent and recurrent disease.

This medicinal product is intended for use as part of curative treatment.

It is a first-line medicinal product.

The efficacy/adverse effects ratio of this product is moderate in this indication.

There are treatment alternatives.

Public health benefit

Though mild to moderate onychomycosis is a relatively common condition, the public health burden it's representing is small.

There is a therapeutic need to improve the management of these infections, especially among patients at increased risk of complications, but this is not a public health need.

As another ciclopirox-based medicinal product is available on the market, and in view of the results of the non-inferiority trial presented, this medicinal product is not expected to have any impact in terms of morbidity. Furthermore, in the absence of any data, it is not possible to assume that ONYTEC will have any impact on the quality of life of patients treated.

Furthermore, it is not certain that the results can be transposed into clinical practice, since some patients among those most likely to benefit from the treatment (individuals aged over 70 and people with uncontrolled diabetes) were excluded from the clinical trial.

Consequently, in view of these various factors, ONYTEC is not expected to have any public health benefit.

The actual benefit of this medicinal product is moderate.

4.2. Improvement in actual benefit (IAB)

The information available indicates that ONYTEC does not provide any improvement in actual benefit (IAB V) compared to MYCOSTER 8% in the management of onychomycosis.

4.3. Therapeutic use

4.3.1. Treatment strategy

Onychomycoses are nail infections that can be caused by dermatophytes, fungi, or more rarely moulds. Dermatophytoses are the most common ungual conditions, especially on the toes.

It is particularly beneficial to treat onychomycosis in patients who are diabetic or immunosuppressed because of the increased risk of bacterial complications (erysipelas, infectious cellulitis).

The choice of treatment depends on identification of the fungal agent. This is essential in order to avoid long and pointless treatment.

Treatment is based on topical antifungals, allowing the active ingredient to be distributed throughout the nail plate ("filmogenic" or occluded-cream formulation) or oral antifungals. Forms for topical use can be combined with surgical or chemical removal of the nail plate.

Treatment with topical antifungals alone should only be considered for patients with a moderate form of the condition, without lunula involvement, and where only a few nails are affected. Other cases generally require extended oral treatment either alone or in combination with topical treatment.

4.3.2. Role of ONYTEC in treatment strategy

ONYTEC has the same active ingredient composition, same dosage and is used for the same indication as MYCOSTER 8% medicated nail lacquer applied once a day.

Nail lacquers (filmogenic solution containing ciclopirox – MYCOSTER 8% and amorolfine LOCERYL) are the products recommended³ for the management of onychomycoses caused by dermatophytes affecting the distal two-thirds of the nail without diffuse underlying hyperkeratosis or significant onycholysis. They are of limited therapeutic efficacy and prolonged treatment is required. Other solutions involve chemical destruction of the nail (Amycor Onychoset).

This type of mycosis does not necessarily require treatment. The decision as to whether to treat the condition depends on how much inconvenience it causes the patient or on the risk of contamination.

ONYTEC is a new treatment option that is an alternative to other filmogenic solutions.

4.4. **Target population**

The target population comprises patients with mild to moderate onychomycosis caused by dermatophytes and/or other ciclopirox-sensitive fungi, without lunula involvement.

Onychomycosis is a frequent and recurrent disease. It mainly affects adults, and is rarely seen in children. The French Dermatology Association estimates the prevalence of onychomycosis among the general population to be 6 to 9%, or 3.90 to 5.85 million individuals.

Fifty-six percent of these individuals have a form of onychomycosis with no lunula involvement⁴.

This means that between two and three million people have that particular form of the condition.

In practice, the number of patients likely to undergo treatment with a filmogenic solution is probably lower, because this type of mycosis does not necessarily require treatment in all circumstances, but only when it causes inconvenience to the patient or there is a risk of contamination.

Data produced by GERS in 2009 indicates that the total number of courses of treatment with filmogenic solutions (LOCERYL 5%, MYCOSTER 8% and its generics) was around 743,000 in 2009 (moving total annual turnover 04/09).

4.5. **Transparency Committee recommendations**

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and/or on the list of medicines approved for use by hospitals and various public services in the indications and at the posology in the marketing authorisation.

4.5.1. Packaging: Appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 35%

³ Guidelines of the French Dermatology Association. Ann Dermatol Venerol 2007 ;134 :5S7-16

⁴ Guibal F, Baran R, Duhard E, Feuilhade de Chauvin M. , Epidemiology and management of onychomycosis in private dermatological practice in France. Ann Dermatol Venerol. 2008 Aug Sep;135(8-9):561-6