HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

18 December 2013

MYCOSTER 10 mg/g, shampoo

B/1 bottle of 60 ml (CIP: 34 009 368 640 0 9)

Applicant: PIERRE FABRE DERMATOLOGIE

INN	ciclopirox
ATC code (2012)	D01AE14 (Antifungals for topical use)
Reason for the request	**Inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indications concerned	**"Treatment of seborrhoeic dermatitis of the scalp."**

Actual Benefit	**Moderate**
Improvement in Actual Benefit	**MYCOSTER 10 mg/g shampoo provides no improvement in actual benefit (level V, non-existent) in comparison with other topical antifungals (KETODERM 2% sachets, SEBIPROX 1.5% shampoo) used in the treatment of seborrhoeic dermatitis of the scalp.**
Therapeutic use	**MYCOSTER 10 mg/g shampoo may be offered as first-line treatment as an alternative to other topical antifungals (KETODERM 2% sachets, SEBIPROX 1.5% shampoo) used in the treatment of seborrhoeic dermatitis of the scalp.**
Recommendations	

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date initiated (licensing procedure): 16 May 2005 Amendment to the Marketing Authorisation: 30 October 2013 (replacement of parabens with sodium benzoate)
Prescribing and dispensing conditions / special status	Non-prescription medicine.

ATC Classification	2012	
	D:	Dermatologicals
	D01:	Antifungals for dermatological use
	D01A:	Antifungals for topical use
	D01AE:	Other antifungals for topical use
	D01AE14:	ciclopirox

02 BACKGROUND

This is a request for inclusion of MYCOSTER 10 mg/g shampoo, which has had Marketing Authorisation for the treatment of seborrhoeic dermatitis of the scalp since 16 May 2005, on the lists of medicines refundable by National Health Insurance and approved for hospital use.

The Marketing Authorisation for this proprietary medicinal product was modified on 30 October 2013 due to a change in preservatives, i.e. parabens were replaced with sodium benzoate, and consequent analytical changes which are unlikely to affect the quality, safety and efficacy of the product.

A comparison table showing the initial Marketing Authorisation and the amendment of 30 October 2013 is attached as an appendix.

03 THERAPEUTIC INDICATIONS

“MYCOSTER® 10 mg/g shampoo is indicated in the treatment of seborrhoeic dermatitis of the scalp.”

04 DOSAGE

“For cutaneous use.
For the initial treatment of symptoms of seborrhoeic dermatitis, MYCOSTER® 10 mg/g shampoo is applied to the scalp once or twice per week, depending on the severity of the condition, for 4 weeks.

Then, as a preventative measure, treatment may be continued for a further 12 weeks.
Wet hair and apply one capful (approximately 5 ml) of MYCOSTER® 10 mg/g shampoo, then work to a lather by thoroughly massaging the scalp. For hair that is longer than shoulder length, use up to 2 capfuls (approximately 10 ml). Leave MYCOSTER® 10 mg/g shampoo to act for 3 minutes then rinse thoroughly with water.
This product has not been studied in children.

Ongoing use of MYCOSTER® 10 mg/g shampoo is limited to a maximum duration of 16 weeks."

05 THERAPEUTIC NEED

Seborrhoeic dermatitis is a common and benign chronic condition which most often affects the face and scalp. Following a chronic course, it may affect quality of life through discomfort, aesthetic embarrassment and the frequency of episodes.

Seborrhoeic dermatitis of the scalp (or dandruff)[1]
In the majority of mild cases, patients do not consult a doctor but use over-the-counter antidandruff shampoos. These contain antifungal or anti-inflammatory ingredients such as zinc pyrithione, piroctone olamine or selenium sulfide, with or without keratolytic agents (salicylic acid, ichthyol, etc.).

In more severe cases requiring medical treatment, the options are:
- ketoconazole 2% foaming gel applied twice a week for 4 weeks;
- ciclopirox olamine shampoo applied twice a week for 4 weeks.

Maintenance treatment is recommended to prevent rapid recurrence. This involves twice-monthly applications of the antifungal used to treat the episode.

There is a therapeutic need to improve the management of this condition due to the modest efficacy of the medicinal products available.

[1] Quéreux G. La dermatite séborrhéique. In: Bouvenot G, Caulin C. Guide du bon usage du médicament. 2nd ed. Médecine Sciences Publications, Paris, 2012, pp. 418-425.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

Medicinal products in the same pharmacotherapeutic class

NAME (INN) *Company*	Indication	Date of last opinion	AB	IAB (Wording)
SEBIPROX (ciclopirox olamine) 1.5%, shampoo 100 ml bottle STIEFEL	Treatment of seborrhoeic dermatitis in adults.	15 March 2006	moderate	Not applicable
KETODERM (ketoconazole) 2%, gel in sachet (B/8) and generics JANSSEN CILAG SA	Treatment of seborrhoeic dermatitis in adults.	19 March 2008	moderate	Not applicable

Other comparator medicines
Dermocorticosteroids and keratolytics.

06.2 Other health technologies

Not applicable

Conclusion

The most relevant comparators are the proprietary medicinal products SEBIPROX and KETODERM, which belong to the same pharmacotherapeutic class.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Marketing Authorisation obtained abroad (European Union, United States, Australia, Japan, Canada)

Date obtained	Country	Dosages, forms and pack sizes	Indications	Prescribing and dispensing conditions	Marketed (yes/no)
22/10/2002	Germany	10 mg/g shampoo, 30 ml, 60 ml and 2x60 ml	Treatment of seborrhoeic dermatitis of the scalp.	Medical prescription only	Yes
27/06/2006	Austria	10 mg/g shampoo, 30 ml, 60 ml and 2x60 ml	"	Non-prescription medicine	Yes
31/08/2005	Cyprus	10 mg/g shampoo, 30 ml, 60 ml and 2x60 ml	"	Medical prescription only	Yes
24/08/2005	Czech Republic	10 mg/g shampoo, 30 ml, 60 ml and 2x60 ml	"	Medical prescription only	No
16/02/2006	Spain	10 mg/g shampoo, 30 ml, 60 ml and 2x60 ml	"	Medical prescription only	No
04/05/2005	Hungary	10 mg/g shampoo, 30 ml, 60 ml and 2x60 ml	"	Non-prescription medicine	No
28/04/2008	Italy	10 mg/g shampoo, 30 ml, 60 ml and 2x60 ml	"	Medical prescription only	Yes
10/05/2005	Netherlands	10 mg/g shampoo, 30 ml, 60 ml and 2x60 ml	"	Medical prescription only	No
29/04/2005	Poland	10 mg/g shampoo, 30 ml, 60 ml and 2x60 ml	"	Medical prescription only	No
12/05/2005	Slovakia	10 mg/g shampoo, 30 ml, 60 ml and 2x60 ml	"	Non-prescription medicine	No

Reimbursement in the European Union

- Germany: 10% of the sales price in the community.

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

The clinical development of MYCOSTER 10 mg/g for seborrhoeic dermatitis involved two phase III studies:
- one study evaluating ciclopirox 1% versus excipients (Study 301); [2]
- one non-inferiority study evaluating ciclopirox 1% versus ketoconazole 2% (Study 302). [3]

In these studies, the clinical signs and symptoms of seborrhoeic dermatitis of the scalp were evaluated using the following ordinal scales (or scores) (from 0 to 5):
- Overall evaluation of seborrhoeic dermatitis status:
  - 0: none; complete absence of signs or symptoms
  - 1: mild; minor presence of signs or symptoms
  - 2: mild plus; mild but evident
  - 3: moderate; easily observable
  - 4: pronounced; obvious
  - 5: severe; extreme
- Overall evaluation of the change in seborrhoeic dermatitis (0 to 5);
- Itching score (0 to 5);
- Desquamation score (0 to 5);
- Inflammation score (0 to 5);
- Sum of itching, desquamation and inflammation scores (0 to 15).

8.1.1 Study 301: A study of the efficacy and safety of ciclopirox 1% shampoo in the treatment of seborrhoeic dermatitis of the scalp and in the prevention of recurrence[4]

- **Study methodology**

Objective

The objective of the study was to demonstrate the efficacy, safety and tolerability of ciclopirox 1% shampoo in the treatment (acute treatment) and prevention (maintenance treatment) of seborrhoeic dermatitis of the scalp.

Study design

This was a randomised, controlled, double-blind study versus placebo shampoo (excipients without the active substance) that consisted of an acute treatment phase with ciclopirox 1% shampoo or placebo (once or twice per week) for 4 weeks (Segment A of the study), followed by a maintenance treatment (prophylaxis) phase lasting 12 weeks in responsive patients (Segment B of the study). After selection, patients underwent a 2-week pre-inclusion period where they were treated with a mild shampoo (Prell shampoo) at least twice per week.

[2] Sam Shuster, Jean Meynadie, Helmut Kerl and Siegfried Nolting. A randomized, double blind, multinational, multi-center study of the efficacy and safety of ciclopirox shampoo in the treatment and prophylaxis of seborrhoeic dermatitis dandruff of the scalp. Arch Dermatol. 2005; 141: 47-52.
[3] Unpublished study.
[4] The study was conducted between 23 April 1997 and 22 June 1998 in 45 centres in Austria (n=3), France (n=15), Germany (n=19) and the United Kingdom (n=8).

Inclusion and non-inclusion criteria

Male or female patients aged 18 to 88 years with stable or worsening seborrhoeic dermatitis of the scalp, with a score greater than or equal to 3 in the majority of cases (70% or more) on the "seborrhoeic dermatitis status", "inflammation" and "desquamation" scales.
Patients with psoriasis, asthma or diabetes were not included in the study.

Population and treatments:

Segment A

A total of 1,000 patients were selected and 949 were randomised (2:2:1 ratio) to receive either 1 or 2 applications per week of ciclopirox 1% shampoo (5 to 10 ml depending on length of hair) or 1 application per week of excipient shampoo for 4 weeks (acute treatment).

Segment B

Patients who were successfully treated in segment A (responders, N=428) were randomised (1:1:1 ratio) to receive prophylactic maintenance treatment for 12 weeks with either ciclopirox 1% shampoo (once/week or once every 2 weeks) or excipient shampoo (once/week).

The complete study lasted for about 5 months for each patient (6 weeks for Segment A patients plus 12 weeks for Segment B patients).

Efficacy endpoints

Segment A

Primary efficacy endpoint: "effectively treated" patients, defined as a score of 0 (or 1 if the score on inclusion was ≥ 3) for symptoms of the disease ("seborrhoeic dermatitis status", "desquamation" and "inflammation").

Secondary endpoint: "asymptomatic" patients, defined as a score of 0 for the following symptoms: "seborrhoeic dermatitis status", "desquamation", "inflammation" and "itching".

Segment B

Primary efficacy endpoint: recurrence, defined by an increase of 2 points or more in the "seborrhoeic dermatitis status" score in comparison with inclusion (start of the Segment B study).

- **Study results**

Segment A

The patients randomised had a median age of 38 years (18 to 88 years). The majority of patients included (about 80%) had "moderate" or "pronounced" seborrhoeic dermatitis (Table 1).

Table 1: Distribution by severity of seborrhoeic dermatitis on inclusion

Evaluation	Ciclopirox 1% Twice/week (n=376)	Ciclopirox 1% Once/week (n=376)	Excipients (n=190)
Mild	46 (12%)	56 (15%)	28 (15%)
Moderate	195 (52%)	195 (52%)	86 (45%)
Pronounced	121 (32%)	113 (30%)	63 (33%)
Severe	14 (4%)	12 (3%)	13 (7%)

On the primary efficacy endpoint ("effectively treated" patients), ciclopirox 1% was superior to excipients. In the ITT analysis, the percentages of "effectively treated" patients in the ciclopirox 1% groups were 45.5% (once-weekly application) and 58.5% (twice-weekly application) versus 31.6% in the excipient shampoo group (Table 2).

Table 2: Results for the primary efficacy endpoint (“effectively treated”)

Population	*Primary efficacy endpoint*	*Ciclopirox 1% twice weekly*	*Ciclopirox 1% once weekly*	*Excipient shampoo*
All patients randomised (LOCF)	Responders: % (n/N)	57.9 (220/380)	45.4 (171/377)	31.3 (60/192)
	OR [95% CI]**	3.025 ([2.096; 4.366])	1.826 ([1.266; 2.634])	-
	p-value**	< 0.0001	0.0007	-
ITT*	Responders: % (n/N)	58.5 (220/376)	45.5 (171/376)	31.6 (60/190)
	OR [95% CI]**	3.056 ([2.114; 4.416])	1.807 ([1.252; 2.609])	-
	p-value	< 0.0001	0.0008	-
PP*	Responders: % (n/N)	58.3 (189/324)	46.4 (149/321)	31.3 (51/158)
	OR [95% CI]**	2.937 ([1.969; 4.382])	1.817 ([1.219; 2.709])	-
	p-value**	< 0.0001	0.0031	-

*** ITT (intention-to-treat) population:** Randomised patients with at least one post-inclusion evaluation of efficacy (withdrawals due to lack of efficacy were included in the ITT population).
*** VC or PP (valid-cases or per-protocol) population:** ITT patients with an evaluation of the primary efficacy endpoint and no major protocol violations.
**** comparison versus excipients**

The percentages of “asymptomatic” patients were also higher in the ciclopirox 1% groups than in the excipient shampoo group:

- Ciclopirox 1% twice weekly: 23.1%;
- Ciclopirox 1% once weekly: 17.0%;
- Excipients: 10.0%.

Segment B

In the ITT population (Table 3), the incidence of recurrence in the ciclopirox 1% groups was 14.7% (twice-weekly application) and 22.1% (once-weekly application) versus 35.5% in the excipient group, with a significant difference in favour of the ciclopirox 1% groups.

Table 3: Primary efficacy endpoint results (recurrence rate defined by an increase of 2 points or more in the seborrhoeic dermatitis status score in comparison with inclusion)

		Ciclopirox 1% Once weekly	*Ciclopirox 1% Once every 2 weeks*	*Excipients Once weekly*
All patients randomised (LOCF)	Recurrence: % (n/N)	15.9 (22/138)	24.2 (36/149)	35.5 (50/141)
	OR [95% CI]*	0.345 ([0.195; 0.611])	0.580 ([0.348; 0.965])	-
	p-value*	< 0.0001	0.0326	-
ITT	Recurrence: % (n/N)	14.7 (20/136)	22.1 (32/145)	35.0 (49/140)
	OR [95% CI]*	0.32 ([0.178; 0.577])	0.526 ([0.311; 0.888])	-
	p-value*	< 0.0001	0.0149	-
PP	Recurrence: % (n/N)	14.4 (14/97)	21.4 (22/103)	36.3 (33/91)
	OR [95% CI]*	0.296 ([0.146; 0.603])	0.477 ([0.253; 0.903])	-
	p-value*	0.0003	0.0196	-

*** comparison versus excipients**

8.1.2 Study 302: A study comparing the efficacy of ciclopirox 1% shampoo to ketoconazole 2% shampoo (unpublished study) [5]

- **Study methodology**

Objective

This was a randomised, controlled, double-blind study aiming to demonstrate the non-inferiority (delta threshold = 10%) of ciclopirox 1% shampoo to ketoconazole 2% shampoo in terms of efficacy in the treatment of seborrhoeic dermatitis of the scalp.

The non-inferiority of ciclopirox 1% shampoo to ketoconazole 2% shampoo was established if the lower limit of the 95% confidence interval (unilateral test) for the difference between response rates was greater than -10% (per-protocol analysis).

Inclusion and non-inclusion criteria

Male or female patients aged 18 to 75 years with stable or worsening seborrhoeic dermatitis of the scalp, with a score ≥ 2 on the "dermatitis status", "inflammation" and "desquamation" scales.
Patients with psoriasis, asthma or diabetes were not included in the study.

Population and treatment

737 of the 781 patients selected were randomised (1:1 ratio) to receive one application (5 to 10 ml) twice weekly of ciclopirox 1% shampoo or ketoconazole 2% shampoo. The duration of treatment was 4 weeks.

Endpoint

Primary efficacy endpoint: response based on the "seborrhoeic dermatitis status" score at the time of individual evaluation, where:

Response = score ≤ 1, or
Improvement from inclusion of ≥ 3 points

Secondary endpoints: response regarding symptoms of "inflammation", "desquamation" and "itching".

- **Study results**

The patients randomised had a median age of 36 years (15 to 75 years).
The distribution of patients by severity of seborrhoeic dermatitis on inclusion showed a slight difference between the groups, in particular in the PP population, with slightly more patients having pronounced or severe seborrhoeic dermatitis in the ciclopirox group than in the ketoconazole group (PP: 27% versus 20%; ITT: 26% versus 22%) (Table 4).

Table 4: Distribution by severity of seborrhoeic dermatitis on inclusion

	ITT		PP	
Evaluation of score on inclusion	**Ciclopirox 1%**	**Ketoconazole 2%**	**Ciclopirox 1%**	**Ketoconazole 2%**
Mild	91 (24.5%)	83 (23.3%)	77 (24.7%)	72 (24.3%)
Moderate	186 (50%)	195 (54.8%)	151 (48.4%)	165 (55.7%)
Pronounced	88 (23.7%)	74 (20.8%)	77 (24.7%)	57 (19.3%)
Severe	7 (1.9%)	4 (1.1%)	7 (2.2%)	2 (0.7%)
Total	372 (100%)	356 (100%)	312 (100%)	296 (100%)

[5] The study was conducted between 1 May 1996 and 25 December 1996 in 75 centres in France (n=23), Germany (n=33) and the United Kingdom (n=19).

Results for the primary efficacy endpoint (response rate)

In the per-protocol (PP) analysis, the response rate was 74.0% (231/312) in the ciclopirox 1% group versus 78.7% (233/296) in the ketoconazole 2% group. The lower limit of the unilateral confidence interval for the difference between the two groups was -10.3%. The non-inferiority hypothesis was not confirmed, since the lower limit of the confidence interval was below the predefined non-inferiority limit of -10%. The intention-to-treat (ITT) analysis showed response rates of 74.2% (276/372) versus 78.9% (281/356); the lower limit of the unilateral confidence interval for the difference = -9.9% (Table 5).

Table 5: Results for the primary efficacy endpoint (response rate)

		ITT **% (n/N)**	**PP** **% (n/N)**
Response rate	**Ciclopirox 1% (p2)**	74.2 (276/372)	74.0 (231/312)
	Ketoconazole 2% (p1)	78.9 (281/356)	78.7 (233/296)
Odds ratio [95% CI]		0.767 [0.544; 1.083]	0.771 [0.529; 1.123]
Non-inferiority test (unilateral test)	Lower limit of 95% CI for p2-p1 difference	-9.9	-10.3
	p-value	0.047	0.061

Results for secondary endpoints

The proportion of "asymptomatic" patients was also higher in the ketoconazole 2% group (38%) than in the ciclopirox 1% group (30%) in the PP analysis (Table 6).

Table 6: Results for secondary endpoints

Secondary response rates			**ITT** **% (n/N)**	**PP** **% (n/N)**
Asymptomatic	Score=0 for symptoms "SD* status", "inflammation", "desquamation", "itching"	**Ciclopirox 1%** **Ketoconazole 2%** OR [95% CI]	29.3 (109/372) 35.7 (127/356) 0.75 [0.55-1.02]	30.1 (94/312) 38.2 (113/296) 0.70 [0.50-0.98]
Effectively treated	Improvement from inclusion ≥ 2 points for symptoms "SD status", "inflammation"	**Ciclopirox 1%** **Ketoconazole 2%** OR [95% CI]	63.2 (235/372) 68.3 (243/356) 0.80 [0.59-1.08]	63.1 (197/312) 66.9 (198/296) 0.85 [0.31-1.18]
Primary endpoint of study 301	Score=0 or 1 for symptoms "SD status", "inflammation", "desquamation"	**Ciclopirox 1%** **Ketoconazole 2%** OR [95% CI]	56.5 (210/372) 61.0 (217/356) 0.83 [0.62-1.12]	55.8 (174/312) 60.1 (178/296) 0.84 [0.61-1.15]
Inflammation	"Inflammation" score = 0 or 1	**Ciclopirox 1%** **Ketoconazole 2%** OR [95% CI]	73.9 (275/372) 78.7 (280/356) 0.77 [0.55-1.09]	74.7 (233/312) 77.4 (229/296) 0.86 [0.59-1.25]
Desquamation	"Desquamation" score = 0 or 1	**Ciclopirox 1%** **Ketoconazole 2%** OR [95% CI]	65.1 (242/372) 71.3 (254/356) 0.75 [0.55-1.02]	65.4 (204/312) 70.9 (210/296) 0.77 [0.55-1.09]
Itching	"Itching" score = 0 or 1	**Ciclopirox 1%** **Ketoconazole 2%** OR [95% CI]	66.9 (249/372) 72.5 (258/356) 0.77 [0.56-1.06]	66.7 (208/312) 73.6 (218/296) 0.72 [0.50-1.02]

* SD = seborrhoeic dermatitis

Results stratified by severity on inclusion (Post-hoc analysis)[6]

A post-hoc analysis performed according to severity on inclusion showed a reduction in response depending on the severity of the seborrhoeic dermatitis and suggested similar efficacy between the two groups (Table 7).

[6]Available in the study report

Table 7: Results for the primary efficacy endpoint (response rate), post-hoc analysis stratified by severity

Score on inclusion	ITT		PP	
	Ciclopirox 1%	**Ketoconazole 2%**	**Ciclopirox 1%**	**Ketoconazole 2%**
Mild	90.1% (82/91)	86.7% (72/83)	88.3% (68/77)	87.5% (63/72)
Moderate	75.3% (140/186)	82.6% (161/195)	77.5% (117/151)	82.4% (136/165)
Pronounced or Severe	56.8% (54/95)	61.5% (48/78)	54.8% (46/84)	57.6% (34/59)
Total	74.2% (276/372)	78.9% (281/356)	74.0% (231/312)	78.7% (233/296)
Non-inferiority test	p=0.020		p=0.016	

08.2 Safety/Adverse effects

8.2.1 Study 301: A study of the efficacy and safety of ciclopirox 1% shampoo in the treatment of seborrhoeic dermatitis of the scalp and in the prevention of recurrence

During acute treatment lasting 4 weeks: Among the patients randomised (N=949, 2:2:1 randomisation), adverse events were reported in 43 patients (11%) in the ciclopirox 1% twice weekly group and 54 patients (14%) in the ciclopirox 1% once weekly group versus 23 patients (12%) in the excipient group. The adverse events were primarily skin disorders and the most common were seborrhoea (n=12) and rhinitis (n=9). Only 12 patients (1%) stopped treatment due to adverse events.

Adverse events considered as possibly related to the study treatments were reported in 19 patients (2%). The majority were skin disorders, and none was judged to be serious. The distribution of these adverse events was similar in all three treatment groups.

Serious adverse events were reported in 3 patients (shock, anxiety and skin ulcer). Abnormal changes in laboratory test values were reported in 41 cases (including an increase in liver enzymes in 33 cases). None of these events was considered to be linked to the medicinal product studied.

During maintenance treatment (prophylaxis) lasting 12 weeks: Among the patients randomised (N=428), adverse events were reported in 16 patients (12%) in the ciclopirox 1% once weekly group and 31 patients (21%) in the ciclopirox 1% once/2 weeks group versus 25 patients (18%) in the excipient group. The adverse events were primarily skin disorders and the most common were seborrhoea (n=7) and eczema (n=6). No difference was observed between the groups. Only 10 patients (2.3%) stopped treatment due to adverse events, with a higher incidence in the group using shampoo once every 2 weeks (4%).
Adverse events considered as possibly related to application of the study treatment were reported in 15 patients (3.5%). The majority were skin disorders and none was judged to be serious. The distribution of these adverse events was similar in all three treatment groups.
Abnormal changes in laboratory test values were reported in 16 cases (including an increase in liver enzymes in 11 cases) and were not considered to be treatment related.

The aesthetic acceptability and local tolerance of the shampoo were judged to be good by the majority of patients.

8.2.2 Study 302: A study comparing the efficacy of ciclopirox 1% shampoo with ketoconazole 2% shampoo (unpublished study)

During active treatment, a total of 119 adverse events were reported in 91 patients (12.3%), with a similar distribution in both treatment groups (48 patients in the ciclopirox 1% group and 43 patients in the ketoconazole 2% group).
About half of the adverse events were skin disorders, including pruritus (11 patients) and rash (10 patients).

Adverse events considered as related to the study treatment were reported in 15 patients (4%) in the ciclopirox 1% group versus 6 patients (1.6%) in the ketoconazole 2% group. The majority were skin disorders and none was judged to be serious.

Five patients (ciclopirox 1%: 3 patients; ketoconazole 2%: 2 patients) stopped treatment due to moderate to severe adverse events. Three of these adverse events, reported in 2 patients (both in the ciclopirox 1% group), were considered as probably related to application of the medicinal product (seborrhoea, pruritus, rash).
Abnormal changes in laboratory test values (liver enzymes) were reported in 12 patients in the ketoconazole 2% group and 3 patients in the ciclopirox 1% group.

8.2.3 Adverse effects (extract from the SPC)

"Within each frequency group, the adverse effects are listed below in decreasing order of severity.

- **Skin and subcutaneous tissue disorders**

Uncommon (≥ 1/1,000, < 1/100): skin reactions at the application site such as irritation and eczema, subjective discomfort such as burning and itching, hair disorders such as mild hair loss or mild discoloration, dull and matted hair, slightly dry hair.

- **Immune system disorders**

  Rare (≥ 1/10,000 and < 1/1,000): allergic contact dermatitis may occur."

08.3 Other data from the literature

The company submitted four publications[7,8,9,10] of placebo-controlled clinical trials (versus excipients) which reinforce the efficacy and safety of ciclopirox 1% shampoo.

[7] Vardy DA, Zvulunov A, Rchetov T, Biton A and Rosenman D. A double-blind, placebo-controlled trial of a ciclopirox olamine 1% shampoo for the treatment of scalp seborrheic dermatitis. J Dermatol Treatment 2000, 11, 73-11.
[8] Abeck D. Rationale of frequency of use of ciclopirox 1% shampoo in the treatment of seborrheic dermatitis: results of a double-blind, placebo-controlled study comparing the efficacy of once, twice, and three times weekly usage. Internat J Dermatol 2004, 43, 13-16.
[9] Lebwohl M, Plott T. "Safety and efficacy of ciclopirox 1% shampoo for the treatment of seborrheic dermatitis of the scalp in the US population: Results of a double-blind, vehicle-controlled trial". Internat J Dermatol 2004, 43, 17-20.
[10] Altmeyer P and Hoffmann K. Efficacy of different concentrations of ciclopirox shampoo for the treatment of seborrheic dermatitis of the scalp: results of a randomized, double-blind, vehicle-controlled trial. Internat J Dermatol 2004, 43, 9-12.

08.4 Summary & discussion

The clinical development of ciclopirox 1% (MYCOSTER 10 mg/g) for seborrhoeic dermatitis involved two controlled phase III studies (Study 301 and Study 302), using four symptoms of the disease (seborrhoeic dermatitis status, desquamation, inflammation and itching) as efficacy endpoints, together with two other derived endpoints: “effectively treated” and “asymptomatic” patients.
In Study 301, after 4 weeks of treatment, ciclopirox 1% shampoo (1 or 2 applications per week) was superior to excipient shampoo (shampoo with no active substance), with response rates (“effectively treated” patients)[11]in the ciclopirox 1% group of 45.5% (once-weekly application) and 58.5% (twice-weekly application) versus 31.6% in the placebo shampoo group. The percentages of “asymptomatic” patients in the ciclopirox 1% groups were 23.1% (twice-weekly application) and 17.0% (once-weekly application) versus 10% in the placebo shampoo group (a statistically significant difference favouring ciclopirox 1%). In addition, continuing the treatment for 12 further weeks as prophylaxis (maintenance treatment) led to fewer recurrences: the recurrence rate in the ciclopirox 1% group was 14.7% (application once every 2 weeks) and 22.1% (once-weekly application) versus 35.5% (50/141) when a shampoo with no active substance was used (a statistically significant difference favouring the ciclopirox 1% groups).

Study 302 is a non-inferiority study (with the non-inferiority margin defined as -10%) which compared the efficacy of ciclopirox 1% with another shampoo containing ketoconazole 2%, both applied twice a week for 4 weeks, using similar efficacy endpoints. In the per-protocol (PP) analysis, the response rates (“effectively treated” patients)[12]were 74.0% (231/312) in the ciclopirox 1% group versus 78.7% (233/296) in the ketoconazole 2% group. The lower limit of the unilateral confidence interval for the difference between the two groups was -10.3%. The non-inferiority hypothesis was not confirmed, since the lower limit of the confidence interval was below the predefined non-inferiority limit of -10%. The intention-to-treat (ITT) analysis showed response rates of 74.2% (276/372) versus 78.9% (281/356); the lower limit of the unilateral confidence interval for the difference = -9.9%. The proportion of “asymptomatic” patients (secondary endpoint) was also higher in the ketoconazole group than in the ciclopirox 1% group (30% versus 38%) in the PP analysis. On the secondary endpoint of “effectively treated” patients, defined by a score of 0 (or 1 if the score on inclusion was ≥ 3) (the primary endpoint from study 301), the response rates were 56.5% (210/372) in the ciclopirox 1% group versus 61.0% (217/356) in the ketoconazole 2% group, which is similar to the effect size observed with ciclopirox 1% (applied twice weekly) in Study 301.

Overall, the treatment was well tolerated. The adverse effects that occurred during the clinical trials were primarily skin disorders (including pruritus and rash) and were mild or moderate in severity. In both comparative studies, the incidence of adverse effects was low (2% to 4%).

08.5 Planned studies

Not applicable

09 THERAPEUTIC USE

MYCOSTER 10 mg/g shampoo may be offered as first-line treatment as an alternative to other topical antifungals (KETODERM 2% sachets, SEBIPROX 1.5% shampoo) used in the treatment of seborrhoeic dermatitis of the scalp.

[11] Primary efficacy endpoint: “effectively treated” patients, defined as a score of 0 (or 1 if the score on inclusion was ≥ 3) for symptoms of the disease (“seborrhoeic dermatitis status”, “desquamation” and “inflammation”).
[12] The primary efficacy endpoint was the response rate based on the “seborrhoeic dermatitis status” score at the time of individual evaluation, where: Response = score ≤ 1 or improvement from inclusion of ≥ 3 points.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗Seborrhoeic dermatitis is a common and benign chronic condition which most often affects the face and scalp. **Following a chronic course, it may affect quality of life through discomfort, aesthetic embarrassment and the frequency of episodes.**
◗This medicinal product is intended as symptomatic treatment for seborrhoeic dermatitis of the scalp.
◗The efficacy/adverse effects ratio of this medicinal product in this indication is modest.
◗This medicinal product is a first-line therapy.
◗Alternative medicinal products exist.

◗Public health benefit:
Although this condition is fairly common, the public health burden of seborrhoeic dermatitis of the scalp is small.

There is a therapeutic need to improve the management of this condition due to the modest efficacy of the medicinal products available, particularly in the more severe forms that require medical treatment, but this is not a public health need.

Taking into account the availability on the market of another ciclopirox-based proprietary medicinal product and in view of the results of the non-inferiority study versus ketoconazole 2% discussed, this proprietary medicinal product is not expected to have any impact on morbidity. In addition, due to the current lack of data, the proprietary medicinal product MYCOSTER cannot be presumed to have any impact on the quality of life of patients treated.

Consequently, in view of these elements, it is not expected that the proprietary medicinal product MYCOSTER 10 mg/g shampoo will benefit public health.

Taking account of these points, the Committee considers that the actual benefit of MYCOSTER 10 mg/g shampoo is moderate in the Marketing Authorisation indication.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication and at the dosages in the Marketing Authorisation.

◗Proposed reimbursement rate: 30%

010.2 Improvement in actual benefit (IAB)

MYCOSTER 10 mg/g shampoo provides no improvement in actual benefit (level V) in comparison with other topical antifungals (KETODERM 2% sachets, SEBIPROX 1.5% shampoo) used in the treatment of seborrhoeic dermatitis of the scalp.

010.3 Target population

The target population consists of patients with seborrhoeic dermatitis of the scalp.
Seborrhoeic dermatitis is a common skin complaint (1% to 3% of the French population, i.e. 600,000 to 1,800,000 patients) occurring primarily in young adults and more commonly in men. It

has a chronic course punctuated with episodes and periods of remission, which may be spontaneous or follow treatment.[13]

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

Packaging

Appropriate for the prescription conditions in terms of the indication, dosage and treatment duration.

[13]Transparency Committee opinion of 18 December 2002 on the proprietary medicinal product SEBIPROX.

Appendix 1: MYCOSTER® 10 mg/g, shampoo (Main changes to the Marketing Authorisation dated 30/10/2013)

Former SPC dated 22/03/2012 Initial Marketing Authorisation of 16/06/2005	New SPC Amended Marketing Authorisation of 30/10/2013
1. NAME **MYCOSTER 10 mg/g, shampoo**	**1. NAME** Unchanged
2. QUALITATIVE AND QUANTITATIVE COMPOSITION Ciclopirox ..... 10 mg Per 1 g of shampoo. For the full list of excipients, see section 6.1.	**2. QUALITATIVE AND QUANTITATIVE COMPOSITION** One gram of shampoo contains 10 mg of ciclopirox Excipient(s) with known effect: Benzoic acid (E210) and sodium benzoate (E211) For the full list of excipients, see section 6.1.
3. PHARMACEUTICAL FORM Shampoo. Translucent, almost colourless to light yellow solution.	**3. PHARMACEUTICAL FORM** Unchanged
4. CLINICAL PARTICULARS **4.1. Therapeutic indications** MYCOSTER ® 10 mg/g shampoo is indicated in the treatment of seborrhoeic dermatitis of the scalp.	**4. CLINICAL PARTICULARS** **4.1 Therapeutic indications** Unchanged
4.2. Posology and method of administration For cutaneous use. For the initial treatment of symptoms of seborrhoeic dermatitis, MYCOSTER 10 mg/g shampoo is applied to the scalp once or twice per week, depending on the severity of the condition, for 4 weeks.	**4.2. Posology and method of administration** Unchanged

Then, as a preventative measure, treatment may be continued for a further 12 weeks. Wet hair and apply one capful (approximately 5 ml) of MYCOSTER 10 mg/g shampoo, then work to a lather by thoroughly massaging the scalp. For hair that is longer than shoulder length, use up to 2 capfuls (approximately 10 ml). Leave MYCOSTER 10 mg/g shampoo to act for 3 minutes then rinse thoroughly with water. This product has not been studied in children. Ongoing use of MYCOSTER 10 mg/g shampoo is limited to a maximum duration of 16 weeks.	
4.3. Contraindications MYCOSTER 10 mg/g shampoo should not be used in cases of known hypersensitivity to ciclopirox, ciclopirox olamine, parabens or to any of the excipients.	**4.3. Contraindications** MYCOSTER 10 mg/g shampoo should not be used in cases of known hypersensitivity to ciclopirox, ciclopirox olamine ~~parabens or to any of the excipients~~ or to any of the excipients listed in section 6.1.
4.4. Special warnings and precautions for use Avoid contact with the eyes when using MYCOSTER 10 mg/g shampoo. In case of accidental contact, the eyes must be rinsed liberally with water. This medicinal product contains parabens and paraben esters and may therefore provoke immediate or delayed hypersensitivity reactions. Benzoic acid may cause mild irritation of the skin, eyes and mucosa. In case of irritation or sensitisation after prolonged use, the medicinal product should be stopped and another treatment started.	**4.4. Special warnings and precautions for use** Avoid contact with the eyes when using MYCOSTER 10 mg/g shampoo. In case of accidental contact, the eyes must be rinsed liberally with water. ~~This medicinal product contains parabens and paraben esters and may therefore provoke immediate or delayed hypersensitivity reactions.~~ ~~Benzoic acid may cause mild irritation of the skin, eyes and mucosa.~~ As it contains benzoic acid and sodium benzoate, this medicinal product may cause irritation of the skin, eyes and mucosa. In case of irritation or sensitisation after prolonged use, the medicinal product should be stopped and another treatment started.
4.5. Interaction with other medicinal products and other forms of interaction To date, no interactions have been reported between ciclopirox and other medicinal products.	**4.5. Interaction with other medicinal products and other forms of interaction** Unchanged
4.6. Pregnancy and lactation **<u>Pregnancy</u>** No clinical data on the use of ciclopirox in pregnant women are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development and parturition. However, there are insufficient data regarding possible long-term effects on postnatal development (see section 5.3). As a precautionary measure, MYCOSTER 10 mg/g shampoo should not be used during	**4.6. Pregnancy and lactation** Unchanged

pregnancy. **<u>Breast-feeding</u>** It is unknown whether ciclopirox is excreted in human milk. Consequently, MYCOSTER 10 mg/g shampoo should not be used during breast-feeding.	
4.7. Effects on ability to drive and use machines Not applicable.	**4.7. Effects on ability to drive and use machines** Unchanged
4.8. Undesirable effects • **<u>Immune system disorders</u>** Rare (< 1/10,000 and < 1/1,000): allergic contact dermatitis may occur. • **<u>Skin and subcutaneous tissue disorders</u>** Uncommon (> 1/1,000; < 1/100): hair disorders such as dull and matted hair, slightly dry hair, mild hair loss and mild discoloration, and skin reactions during use such as irritation and eczema as well as subjective discomfort such as burning and itching. Parabens can cause allergic reactions, which may be delayed.	**4.8. Undesirable effects** Within each frequency group, the adverse effects are listed below in decreasing order of severity. • **<u>Skin and subcutaneous tissue disorders</u>** Uncommon (≥ 1/1,000, < 1/100): skin reactions at the application site such as irritation and eczema, subjective discomfort such as burning and itching, hair disorders such as mild hair loss or mild discoloration, dull and matted hair, slightly dry hair. ~~hair disorders such as dull and matted hair, slightly dry hair, mild hair loss and mild discoloration, and skin reactions during use such as irritation and eczema as well as subjective discomfort such as burning and itching.~~ ~~Parabens can cause allergic reactions, which may be delayed.~~ • **<u>Immune system disorders</u>** Rare (≥ 1/10,000 and < 1/1,000): allergic contact dermatitis may occur. **<u>Reporting of suspected adverse reactions</u>** Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: French National Medicines and Health Products Safety Agency (ANSM) and network of Regional Pharmacovigilance Centres. Website: www.ansm.sante.fr

4.9. Overdose No data regarding overdose of preparations containing ciclopirox are available. However, no significant systemic effects are expected following overly frequent use of MYCOSTER 10 mg/g shampoo. In case of accidental ingestion, appropriate treatment should be given.	**4.9. Overdose** Unchanged
5. PHARMACOLOGICAL PROPERTIES	**5. PHARMACOLOGICAL PROPERTIES**
5.1. Pharmacodynamic properties Pharmacotherapeutic group: **ANTIFUNGALS.** ATC code: **D01AE14 (other antifungals for topical use).** Ciclopirox is a broad spectrum N-hydroxypyridone antifungal agent which is active against pathogenic dermatophytes, moulds and yeasts, including *Pityrosporum* ovale which is considered to be the main cause of seborrhoeic dermatitis. Preclinical studies have shown a dose-response curve with a very steep gradient, indicating not only fungistatic but also fungicidal activity, a favourable optimum pH, a long duration of action, low influence of proteins on inhibitory concentrations, good penetration into the deep layers of the epidermis, and additional antibacterial activity on aerobic Gram-positive and Gram-negative bacteria. The impact of a ciclopirox-based medicated shampoo on the viability of *Pityrosporum* ovale was studied in a pig dorsal skin model, showing that the shampoo is active even after short periods of treatment. Experiments looking at penetration into the stratum corneum of dorsal skin excised from pigs have shown that a short period of contact with a ciclopirox-based medicated shampoo is sufficient to reach active concentrations of the product even in the deeper layers of the stratum corneum. In vivo studies have confirmed that ciclopirox is effective on dermatophytoses in guinea pigs. Ciclopirox has demonstrated a clear dose-dependent effect on infections with *microsporum canis and trichophyton mentagrophytes.* A rapid onset of action was observed. The mechanism of action is very complex, targeting various metabolic processes in the fungal cell. Unlike most antifungal agents, ciclopirox does not affect sterol biosynthesis. The primary mechanism of action within the fungal cell derives from the high affinity of ciclopirox for trivalent metal cations such as Fe^{3+}. Trapping this essential enzyme cofactor has an inhibitory effect on enzymes such as cytochromes, which play a role in the transport of electrons involved in energy production in the mitochondria. In addition, the activity of catalases and peroxidases, which are responsible for the intracellular degradation of toxic peroxides, is strongly reduced by the active substance. Consequently, ciclopirox impairs the fungal metabolism by affecting the transport mechanisms located in the fungal cell membrane. This particular mechanism of action of ciclopirox suggests that there is a low risk of developing resistance and minimises the	**5.1. Pharmacodynamic properties** Unchanged

risk of cross-resistance with other antifungal agents such as azole antifungals and allylamines. Ciclopirox has anti-inflammatory properties. *In vitro* studies have shown that ciclopirox inhibits production of cyclooxygenase and 5-lipoxygenase inflammatory mediators. *In vivo,* ciclopirox has also shown an anti-inflammatory effect in animals, confirmed in UV-induced erythema in human volunteers. This anti-inflammatory effect may facilitate healing from some fungal skin infections, such as seborrhoeic dermatitis. A total of 1,189 patients with seborrhoeic dermatitis were treated for 4 weeks in three controlled double-blind studies, using four symptoms of the disease (status, desquamation, inflammation and itching) as efficacy endpoints, together with two other derived endpoints: “effectively treated” and “asymptomatic” patients. After use of the shampoo, 17.2% (once-weekly application) and 21.3% (twice-weekly application) of patients became completely asymptomatic. The percentages of “effectively treated” or “asymptomatic” patients were 44.2% (once-weekly application) and 52.5% (twice-weekly application). In addition to the results described above for acute treatment of the disease, a clinical study has shown that maintenance treatment once a week resulted in recurrence of the disease in only 16% of patients compared with 36% of those who were using a shampoo with no active substance. In a randomised, double-blind study, a total of 737 patients were randomised to compare the efficacy of ciclopirox 1%-based shampoo with another shampoo containing ketoconazole 2%, both applied twice a week, using similar efficacy endpoints. After 4 weeks of treatment, about 74% of the ciclopirox group and 78.7% of the ketoconazole group had responded (non-inferiority statistical analysis: ITT population, p = 0.047; per-protocol (PP) population, p = 0.061). When the higher number of more severe cases on inclusion in the ciclopirox 1% group was taken into account, non-inferiority statistical analysis gives: p = 0.014 (PP) and p = 0.021 (ITT).	
5.2. Pharmacokinetic properties During three clinical studies of the 1% formulation, urine and serum concentrations of ciclopirox were measured in patients with seborrhoeic dermatitis of the scalp. In the first study, patients were treated twice a week for 4 weeks. In the second study, patients were treated under exaggerated use conditions, for example, patients washed their hair	**5.2. Pharmacokinetic properties** Unchanged

with the ciclopirox-based shampoo every day for 29 days, increasing the contact time from 3 minutes to 6 minutes after 15 days. In a phase III study, serum and urine levels of ciclopirox were measured after 4 weeks of treatment once or twice a week, then after an additional 12 weeks of prophylactic treatment applied once a week or once every 2 weeks. After 4 weeks of treatment, serum levels were detected in 21 out of 293 patients, with maximum serum levels of between 13.2 and 39.0 µg/l. After 12 weeks of prophylactic treatment, ciclopirox levels were detected in 2 out of 94 patients (max. 14.4 µg/l). In chronic oral toxicity studies, the no-observed-adverse-effect levels of ciclopirox and its metabolites were 2,210-2,790 µg/l in rats and 1,500-3,500 µg/l in dogs, revealing a high margin of safety. When urinary elimination of ciclopirox was measured, excretion peaks were obtained in the first 4 hours following administration and then fell rapidly. Given that more than 98% of absorbed ciclopirox is eliminated by the kidneys, urinary excretion is a reliable parameter for measuring the quantity of product absorbed during shampooing. In these studies, the median urinary elimination ranged from 0.42% to 1.36% of the dose administered. **5.3. Preclinical safety data** Preclinical data reveal no evidence of toxicity up to an oral dose of 10 mg/kg based on conventional studies of repeated dose toxicity, and no evidence of genotoxicity and carcinogenicity. A reduced fertility index was found in rats at ciclopirox doses of 5 mg/kg. No embryotoxicity, fetotoxicity or teratogenicity was observed in rats and rabbits. There is no evidence of perinatal or postnatal toxicity; however, possible long-term effects on offspring have not been studied. In a skin tolerance study in rabbits, MYCOSTER 10 mg/g shampoo showed no irritant effects. In a mucosal tolerance study in rabbits, the shampoo caused ocular irritation. To date, no studies have been conducted into irritant potential following repeated local use or into sensitisation.	**5.3. Preclinical safety data** Unchanged
6. PHARMACEUTICAL PARTICULARS **6.1. List of excipients** • Sodium dodecyl-di(oxyethylene) sulfate, 27% solution.* • Disodium dodecyl-poly(oxyethylene)-3-2-sulfosuccinate, 33% solution.** • Macrogol lauryl ether. • Sodium chloride. • Purified water. *Consisting of: Sodium dodecyl-di(oxyethylene) sulfate; purified water; benzoic acid (E210).	**6. PHARMACEUTICAL PARTICULARS** **6.1. List of excipients** Sodium dodecyl-di(oxyethylene) sulfate, 27% solution;* Disodium dodecyl-poly(oxyethylene)-3-2-sulfosuccinate, 33% solution;** Macrogol lauryl ether; Sodium chloride; Purified water. * Consisting of: Sodium dodecyl-di(oxyethylene) sulfate; purified water; benzoic acid (E210). ** Consisting of: Disodium dodecyl-poly(oxyethylene)-3-2-sulfosuccinate; ~~phenoxyethanol; isobutyl parahydroxybenzoate; butyl parahydroxybenzoate;~~ sodium benzoate (E211); purified water; ~~methyl~~

Consisting of: disodium dodecyl-poly(oxyethylene)-3-2-sulfosuccinate; phenoxyethanol; isobutyl parahydroxybenzoate; butyl parahydroxybenzoate; purified water; methyl parahydroxybenzoate (E218); ethyl parahydroxybenzoate (E214); propyl parahydroxybenzoate (E216). **6.2. Incompatibilities Not applicable **6.3. Shelf life** 2 years. After first opening the bottle, the shampoo should be stored for a maximum of 8 weeks. **6.4. Special precautions for storage** Do not store above 30°C. **6.5. Nature and contents of container** This medicinal product is supplied in low density polyethylene (LDPE) bottles with a polypropylene (PP) screw cap: • Box of 1 30 ml bottle; • Box of 1 or 2 60 ml bottles. Not all pack sizes may be marketed. **6.6. Special precautions for disposal and other handling** No special requirements.	~~parahydroxybenzoate (E218); ethyl parahydroxybenzoate (E214); propyl parahydroxybenzoate (E216).~~ **6.2. Incompatibilities** Unchanged **6.3. Shelf life** 2 years. After first opening the bottle, the shampoo ~~should~~may be ~~stored for a maximum of~~used for up to 8 weeks. **6.4. Special precautions for storage** Unchanged **6.5. Nature and contents of container** This medicinal product is supplied in low density polyethylene (LDPE) bottles with a polypropylene (PP) ~~screw~~ cap: • Box of 1 30 ml bottle; • Box of 1 or 2 60 ml bottles. Not all ~~pack sizes~~pack sizes may be marketed. **6.6. Special precautions for disposal and other handling** No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.