HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

5 October 2011

PROTOPIC 0.03%, ointment
Tube of 30 g (CIP code: 359 221-9)

PROTOPIC 0.1%, ointment
Tube of 30 g (CIP code: 359 223-1)

Applicant: ASTELLAS PHARMA SAS

tacrolimus monohydrate
ATC code: D11X14

List I
Medicine requiring special monitoring during treatment.
Prescription restricted to dermatologists and paediatricians.
Exceptional drug status

Date of Marketing Authorisation: 28 February 2002 (centralised procedure)

Date of principal amendments to the Marketing Authorisation:

- 19 May 2004: significant amendments to the Posology, Special warnings and precautions for use and Undesirable effects sections (see opinion dated 27 October 2004);
- 10 June 2005: undesirable effects (addition of rosacea);
- 12 June 2006: amendments to Indications, Posology, Special warnings and precautions for use and Undesirable effects sections following the re-assessment of topical calcineurin inhibitors by the EMA;
- 3 May 2007: pharmacokinetics in children under 2 years, pre-clinical safety data;
- 26 February 2009: extension of the indication to include maintenance treatment.

Reason for the request:

- Inclusion on list of products reimbursed by National Health Insurance and approved for hospital use for the extension of the indication to cover "Maintenance treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals in patients experiencing a high frequency of disease exacerbations (i.e. occurring four or more times per year) who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected)".
- Examination of the results of the post-marketing study performed at the request of the transparency Committee.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Tacrolimus monohydrate

1.2. Indications

PROTOPIC 0.03%, ointment:
"Treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids.

"Treatment of moderate to severe atopic dermatitis in children (2 years of age and above) who failed to respond adequately to conventional therapies such as topical corticosteroids."

PROTOPIC 0.1%, ointment:
"Treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids."

New indication for the two forms:
"Treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals in patients experiencing a high frequency of disease exacerbations (i.e. occurring four or more times per year) who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected)."

1.3. Dosage

"PROTOPIC treatment should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis.
PROTOPIC can be used for short-term and intermittent long-term treatment. Treatment should not be continuous on a long-term basis.
PROTOPIC ointment should be applied as a thin layer to affected or commonly affected areas of the skin. PROTOPIC ointment may be used on any part of the body, including face, neck and flexure areas, except on mucous membranes. Protopic ointment should not be applied under occlusion.
PROTOPIC ointment should not be used in children aged below 2 years until further data are available.
Specific studies have not been conducted in elderly patients. However, the clinical experience available in this patient population has not shown the necessity for any dosage adjustment.

Treatment
PROTOPIC treatment should begin at the first appearance of signs and symptoms. Each affected region of the skin should be treated with PROTOPIC until lesions are cleared, almost cleared or mildly affected. Thereafter, patients are considered suitable for maintenance treatment (see below). At the first signs of recurrence (flares) of the disease symptoms, treatment should be re-initiated.

Paediatric population (2 years of age and above)
Treatment should be started twice a day for up to three weeks. Afterwards the frequency of application should be reduced to once a day until clearance of the lesions.

Adults and adolescents (16 years of age and above)
PROTOPIC is available in two strengths, PROTOPIC 0.03% and PROTOPIC 0.1% ointment. Treatment should be started with PROTOPIC 0.1% twice a day and treatment should be continued until clearance of the lesions. If symptoms recur, twice daily treatment with PROTOPIC 0.1% should be restarted. An attempt should be made to reduce the frequency of application or to use the lower strength, PROTOPIC 0.03% ointment, if the clinical condition allows.

Generally, improvement is seen within one week of starting treatment. If no signs of improvement are seen after two weeks of treatment, further treatment options should be considered.

Maintenance treatment
Patients who are responding to up to 6 weeks treatment using tacrolimus ointment twice daily (lesions cleared, almost cleared or mildly affected) are suitable for maintenance treatment.
PROTOPIC ointment should be applied once a day twice weekly (e.g. Monday and Thursday) to areas commonly affected by atopic dermatitis to prevent progression to flares. Between applications there should be 2–3 days without PROTOPIC treatment.
Adult patients (16 years of age and above) should use PROTOPIC 0.1% ointment; children (2 years of age and above) should use the lower strength PROTOPIC 0.03% ointment. If signs of a flare reoccur, twice daily treatment should be re-initiated. After 12 months treatment, a review of the patient's condition should be conducted by the physician and a decision taken whether to continue maintenance treatment in the absence of tolerance data for maintenance treatment beyond 12 months. The review of the child's condition after 12 months treatment should include suspension of treatment to assess the need to continue this regimen and to evaluate the course of the disease."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

D	Dermatologicals
D11	Other dermatological preparations
D11X	Other dermatologicals
D11X14	Tacrolimus

2.2. Medicinal products in the same pharmacotherapeutic category

2.2.1. Strictly comparable medicinal products

PROTOPIC is the only topical calcineurin inhibitor immunosuppressant medicinal product that is indicated as second-line treatment for moderate to severe atopic dermatitis and the prevention of recurring atopic dermatitis.

2.2.2. Not strictly comparable medicinal products

Not applicable.

2.3. Medicinal products with the same therapeutic objective

Topical treatment: topical corticosteroids indicated as first-line treatment.

FLIXOVATE 0.05% cream and 0.005% ointment (fluticasone propionate, potent topical corticosteroid) are the only fist-line medicinal products indicated for the prevention of recurrences of atopic dermatitis in adults or children aged 1 year and older.

Systemic treatments:
- Children: oral corticosteroid therapy
- Adults: oral corticosteroid therapy, phototherapy, photo-chemotherapy, cyclosporine capsules and oral solution (if phototherapy and/or photo-chemotherapy have failed or are contraindicated).

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy and safety of 0.1% and 0.03% tacrolimus ointments used as maintenance treatment with two applications per week was evaluated in two phase III clinical trials with similar protocols; one was carried out on adults (FG 506-06-40) and the other on children (FG 506-06-41).

During these two randomised, double-blind studies tacrolimus was compared over a 12-month period with a PROTOPIC excipient mainly comprised of vaseline which has its own emollient property.

These studies were designed into three phases:

Phase 1: Monitoring of enrolled patients for one week, without treatment.

Phase 2: Phase of the initial flare treatment, with tacrolimus applied without blinding, for all patients enrolled, twice daily (normal flare treatment regimen) over a minimum of 8 days and a maximum of 6 weeks.
If the "Investigator's Global Assessment" (IGA[1]) score was ≤2 after 6 weeks of treatment, the patients were randomised to receive either tacrolimus, or its excipient, being applied once daily, 2 days per week.
Patients with an IGA score that was not ≤2 at the end of 6 weeks were not included in the comparative maintenance phase.

Phase 3: after randomisation, a period of double-blind maintenance treatment during which the patients received two applications per week to previously treated areas. The patients were assessed at the end of week 2, month 2 then every 2 months for 12 months.
If a new flare occurred during the period (IGA score >2), treatment with tacrolimus (two applications/day) was introduced until an IGA score ≤2 was regained at which time the original randomized maintenance treatment was reinitiated.
Furthermore, patients in both of the two groups could use a topical emollient if necessary.

The 0.1% strength tacrolimus formulation was used for adults, and the 0.03% strength ointment was used for children.

The patients included were adults and adolescents aged at least 16 years (study FG 506-06-40) and children aged from 2 to 15 years (study FG 506-06-41) with mild to severe atopic dermatitis (Rajka/Langeland score ≥3).

[1] "Investigation Global Assessment": criteria to determine overall efficacy by the clinical investigator using a score from 0 (disappeared, no sign of inflammation) to 5 (disease very severe, severe erythema and severe papulation / infiltration with oozing / crusting).

Note: the indication of tacrolimus is limited to moderate to severe forms; however, patients with a mild form of atopic dermatitis were also included in the studies.
The principle of an *a posteriori* analysis in the sub-group of patients with a moderate to severe form, which accounted for approximately two-thirds of the total study population, was accepted by EMA given the highly significant difference (p <0.001) observed for the primary efficacy endpoint across the whole population.

Before inclusion, patients had to have stopped all other treatments for atopic dermatitis: topical corticosteroids (for at least 3 days), systemic corticosteroids (for at least 5 days), systemic immunosuppressants such as methotrexate (MTX) or cyclosporine (for at least 2 weeks) and UVA and UVB treatments (for at least 6 weeks).

Primary efficacy endpoint: number of atopic dermatitis flares during the maintenance phase "requiring substantial therapeutic intervention", defined by an IGA score of 3 to 5 (moderate to very severe atopic dermatitis) and the need for recourse to a new twice daily tacrolimus treatment for more than 7 days.

Secondary endpoints:
- time to the occurrence of the first flare "requiring substantial therapeutic intervention"
- time to the appearance of the first flare (including flares not requiring twice daily tacrolimus treatment),
- total number of flares during the control period (including flares not requiring twice daily tacrolimus treatment)
- number of patient without “significant” flare
- percentage of days with a “significant” flare.

Results:
Only the results from the sub-group of patients with moderate to severe atopic dermatitis are presented below.

- **In adults**

Out of a total of 183 patients with moderate to severe atopic dermatitis included in the initial flare treatment phase, 155 patients were randomised for the disease control period: 80 in the tacrolimus group and 75 in the excipient group. Two patients from the excipient group were lost to follow-up and were not included in the statistical analysis.

At the time of inclusion, the mean total Rajka and Langeland severity score was 7.1 for the whole population and the modified EASI score was 3.8% in the tacrolimus group and 4.0% in the excipient group for maintenance treatment. The percentage of body surface area affected was 8.7% on average in the tacrolimus group and 8.6% in the excipient group. On average, atopic dermatitis had been developing for 23 years, and the mean duration of the current active episode was 15 months.

During the 12 months prior to inclusion in the study, 98.8% of patients in the tacrolimus group and 95.9% in the excipient group had been using dermatological preparations, mainly emollients (73.8% and 76.7%) and topical corticosteroids (58.8% and 60.3%).

Premature discontinuations of the study treatment concerned 28/80 patients treated with tacrolimus (2 because of a lack of efficacy, 8 due to IGA > 2 following treatment for a new flare and 7 for a lack of compliance) and 39/73 patients in the excipient group (13 for a lack of efficacy, 5 due to IGA > 2 following treatment of a new flare, 3 for a lack of compliance and 2 because of adverse events).

- Results for the primary efficacy endpoint (ITT population):

During the 12 months of maintenance treatment, the patients treated with tacrolimus experienced significantly fewer flares "requiring substantial therapeutic intervention" compared with those treated with the excipient: a median of 1.0 flare in the group treated with tacrolimus versus 5.3 flares in the group treated with the excipient, or a median difference of -3.1 ($CI_{95\%}$ = [-4.7; -1.9]; p < 0.001).

- Results for the secondary endpoints (ITT population):

The median time to the occurrence of the first "significant" flare was 142 days with tacrolimus versus 15 days with the excipient, or a median increase in the period without a flare "requiring therapeutic intervention'' of 127 days (p <0.001).

The median time to the occurrence of the first flare (all severity included) was 123 days with tacrolimus versus 14 days with the excipient, or a median increase in the period without a flare of 109 days (p <0.001).

The median total number of flares (all severity included) was 1.0 with tacrolimus and 6.8 with the excipient, or a difference of -4.3 ($CI_{95\%}$ = [-5.8; -2.7]).

The percentage of patients without flare "requiring therapeutic intervention" was 48.8% with tacrolimus and 17.8 % with the excipient (p <0.001).

The mean percentage of days with a flare "requiring therapeutic attention" was 16.1% with tacrolimus and 39.0% with the excipient (p <0.001).

- **In children**

Out of a total of 166 patients with moderate to severe atopic dermatitis included in the initial flare treatment phase, 153 patients were randomised for the disease control period: 78 in the tacrolimus group and 75 in the excipient group.

At the time of inclusion, the mean total Rajka and Langeland severity score was 7.0 in the tacrolimus group and 7.1 in the excipient group for maintenance treatment. The mean modified EASI score[2] was 4.5% in the tacrolimus group and 4.9% in the excipient group. The mean percentage of body surface area affected was 8.7% in the tacrolimus group and 8.6% in the excipient group. On average, atopic dermatitis has been developing for 6 years and the mean duration of the current active episode was 13 months.

During the 12 months prior to inclusion in the study, 91% of patients in the tacrolimus group and 86.7% in the excipient group had been using dermatological preparations, mainly emollients (73.1% and 81.3%, respectively) and topical corticosteroids (51.3% and 42.7%, respectively).

Premature discontinuations of the study treatment concerned 24/78 patients treated with tacrolimus (5 because of a lack of efficacy, 7 due to IGA >2 following treatment of a new flare and 1 because of an adverse event) and 73/75 patients in the excipient group (6 because of a lack of efficacy, 4 due to IGA >2 following treatment of a new flare and 2 for a lack of compliance with the protocol).

[2] modified EASI: composite score including an evaluation of symptoms by the clinical investigator and the body surface area affected, and an assessment by the patient of their itching / pruritus; score from 0 to 90 (most marked change in condition).

- Results for the primary efficacy endpoint (ITT population):

During the 12 months of maintenance treatment, patients treated with tacrolimus experienced significantly fewer flares "requiring substantial therapeutic intervention" compared with those treated with the excipient: median of 1.0 flare in the tacrolimus group versus 2.9 flares in the excipient group, or a median difference of -1.1 ($CI_{95\%=}$ [-2.1; -0.3]; p <0.001).

- Results for the secondary endpoints (ITT population):

The median time to the occurrence of the first "significant" flare was 217 days with tacrolimus versus 36 days with the excipient, or a median increase in the period without a flare "requiring therapeutic intervention" of 181 days (p <0.001).

The median time to the occurrence of the first flare (all severity included) was 146 days with tacrolimus and 17 days with the excipient, or a median increase in the period without a flare of 129 days (p<0.001).

The median total number of flares (all severity included) was 1.5 with tacrolimus and 3.5 with the excipient, or a difference of -2.1($CI_{95\%}$ = -3.0; -1.0].

The percentage of patients without flares "requiring therapeutic intervention" was 46.2% with tacrolimus and 21.3% (p<0.001).

The mean percentage of days with a flare "requiring therapeutic attention" was 16.9% with tacrolimus and 29.9% with the excipient (p<0.001).

3.2. Adverse Effects

3.2.1. Tolerance during clinical studies

During the 12-month maintenance treatment phase, the patients applied either tacrolimus or the excipient twice per week. However, in cases of a significant flare, patients in both groups resumed treatment with tacrolimus at a rate of two applications per day until the end of the flare.

In total, the mean exposure of adult patients to tacrolimus during this period was 282 days, with a mean daily consumption of 1.68 ± 1.76 g in the tacrolimus group, and 217 days with a mean daily consumption of 2.20 ± 2.75 g of tacrolimus in the excipient group.

For children, the mean exposure to tacrolimus during this period was 304 days, with a mean daily consumption of 1.29 ± 1.15 g in the tacrolimus group, and 229 days with a mean daily consumption of 1.42 ± 2.63 g of tacrolimus in the excipient group.

- **Treatment-related adverse events in adults (study FG 506-06-40)**

During the 12-month maintenance treatment phase, in the sub-group of patients with moderate to severe atopic dermatitis, 36/80 (45%) of patients in the tacrolimus group and 29/73 (39.7%) in the excipient group experienced a treatment-related adverse event.

These treatment-related adverse events were mainly reactions at the application site (42.5% with tacrolimus versus 38.4% with the excipient). Adverse events not occurring at the application site were observed in 6.3% of patients in the tacrolimus group and 12.3% in the excipient group (see Table 1).

The most common adverse events observed at the application site were: pruritus, folliculitis, irritation, infection, Herpes simplex and impetigo (see Table 1).

Table 1: Most common treatment-related adverse events (study in adults)

Adverse events with an incidence > 3%	**Moderate to severe AD sub-group**		**Total population**	
	Tacrolimus (N = 80)	**Excipient (N = 73)**	**Tacrolimus (N = 116)**	**Excipient (N = 108)**
Adverse events at the application site n (%)				
Pruritus at application site	9 (11.3)	9 (12.3)	13 (11.2)	12 (11.1)
Folliculitis at application site	6 (7.5)	7 (9.6)	6 (5.2)	8 (7.4)
Irritation at application site	4 (5.0)	6 (8.2)	6 (5.2)	7 (6.5)
Infection at application site	5 (6.3)	2 (2.7)	6 (5.2)	2 (1.9)
Herpes simplex	3 (3.8)	3 (4.1)	4 (3.4)	3 (2.8)
Impetigo	2 (2.5)	4 (5.5)	2 (1.7)	4 (3.7)
Adverse events other than at the application site n (%)				
Pruritus	2 (2.5)	4 (5.5)	4 (3.4%)	6 (5.6)

- **Treatment-related adverse events in children (study FG 506-06-41)**

During the 12-month maintenance treatment phase, in the sub-group of patients with moderate to severe atopic dermatitis, 33/78 (42.3%) of children in the tacrolimus group and 27/75 (36.0%) in the excipient group experienced a treatment-related adverse event.

Table 2: Most commonly observed treatment-related adverse events (study in children)

Adverse events with an incidence > 3%	**Moderate to severe AD sub-group**		**Total population**	
	Tacrolimus (N = 78)	**Excipient (N = 75)**	**Tacrolimus (N = 125)**	**Excipient (N = 125)**
Adverse events at the application site n (%)				
Pruritus at application site	8 (10.3)	8 (10.7)	9 (7.2)	12 (9.6)
Impetigo	6 (7.7)	2 (2.7)	7 (5.6)	2 (1.6)
Infection at application site	5 (6.4)	3 (4.0)	5 (4.0)	3 (2.4)
Skin papilloma	2 (2.6)	3 (4.0)	2 (1.6)	4 (3.2)
Adverse events other than at the application site n (%)				
Pruritus	7 (9.0)	2 (2.7)	10 (8.0)	2 (1.6)
Nasopharyngitis	7 (9.0)	5 (6.7)	7 (5.6)	6 (4.8)
Infected eczema	2 (2.6)	4 (5.3)	2 (1.6)	4 (3.2)

The percentages of patients experiencing adverse effects at the application site were 28.2% in the tacrolimus group and 24% in the excipient group, while effects not occurring at the application site concerned 6.3% in the tacrolimus group and 12.3% in the excipient group.

The most common adverse events observed at the application site were: pruritus, folliculitis, irritation, infection including Herpes simplex and impetigo (see Table 2).

Away from the application site, the most commonly observed adverse events were: pruritus, nasopharyngitis and infected eczema (see Table 2).

The tolerance of tacrolimus has not been assessed beyond 12 months of treatment.

- **Risk of neoplasm**

Studies FG 506-06-40 and FG 506-06-41 did not highlight any cases of cancer related to tacrolimus, but such a risk cannot be ruled out insofar as cases of malignant tumours (including skin or other types of lymphoma, and skin cancers) have been observed in patients using tacrolimus since this medicinal product was put on the market.

3.2.2. SPC: risk of immunosuppression and neoplasm

The SPC states that treatment with PROTOPIC may be associated with an increased risk of herpes viral infections (herpes simplex dermatitis [eczema herpeticum], herpes simplex [herpes labialis] and Kaposi's varicelliform eruption). In the presence of these infections, the benefit/risk ratio associated with PROTOPIC use should be evaluated.

The effect of treatment with PROTOPIC ointment on the developing immune system of children, especially of young children, has not yet been established, and this should be taken in to consideration when prescribing for this age range.

In transplant patients, prolonged systemic exposure to intense immunosuppression following systemic administration of calcineurin inhibitors has been associated with an increased risk of developing lymphomas and skin malignancies. In patients treated with PROTOPIC, cases of malignancies, including cutaneous and other types of lymphoma, and skin cancers have been reported. Patients with atopic dermatitis treated with PROTOPIC, have not been found to have significant systemic tacrolimus levels.

PROTOPIC ointment must not be applied to lesions considered as being potentially malignant.

3.2.3. Pharmacovigilance data

The last international safety update report covering the period from 1st October 2008 to 31 March 2009 did not indicate any new signals with respect to safety.

3.2.4. Long-term safety: interim results of the APPLES study

The applicant has provided the interim results at 5 years of a 10-year, prospective, longitudinal epidemiological study (end of inclusions in 2014), implemented at the request of the FDA and EMA (APPLES study).
The aim of this study, which should include approximately 8000 patients by 2014, is to assess, under in real-life conditions of use, the long-term safety of tacrolimus ointment 0.03% or 0.1% in children under 16 years of aged at the time of initial treatment for atopic dermatitis, and notably concerning the occurrence of skin or systemic cancers (such as lymphomas).

The interim report issued in November 2010 and concerning 5872 patients (1342 in Europe and 4530 in the United States) were included by 276 centres (21 in France). At that time, 476 patients had dropped out the study, mainly for consent withdrawn, and the mean duration of monitoring was 1.5 patient-years.
Because of insufficient hindsight, it is not possible to draw any conclusions regarding the long-term safety of tacrolimus and the risk of cancer from the interim results of this study.

3.3. Conclusion

The efficacy and tolerance of tacrolimus as maintenance treatment (two applications per week over 12 months) after flare treatment with tacrolimus were compared with those of the PROTOPIC excipient (placebo group) during two randomised, double-blind trials, in patients with mild to severe atopic dermatitis, one in adults (from the age of 16 years), and the other in children (2 to 15 years).
If a flare occurred during maintenance treatment, patients in both two groups could receive tacrolimus twice daily.

Analyses were performed *a posteriori* on these sub-groups of patients with moderate to severe atopic dermatitis (corresponding to the indication in the Marketing Authorisation) who represent approximately two-thirds of the participants, or 183 adults (155 of whom were analysed) and 166 children (153 of whom were analysed). In both studies, these analyses demonstrated a superiority of tacrolimus over the excipient in terms of the number of flares of atopic dermatitis "requiring substantial therapeutic intervention", defined by an IGA score of

3to 5 and the need for recourse to a new twice daily tacrolimus treatment for at least 7 days. The median number of flares "requiring substantial therapeutic intervention" was:

- In adults, 1.0 in the tacrolimus group versus 5.3 in the excipient group, or a median difference of -3.1 flares ($CI_{95\%}$ = [-4.7; -1.9]).
- In children, 1.0 in the tacrolimus group versus 2.9 in the excipient group, or a median difference of -1.1 flares ($CI_{95\%}$ = [-2.1; -0.3]).

Analyses showed that tacrolimus was also significantly superior to the excipient, , with respect to all secondary efficacy endpoints: time to the occurrence of the first flare "requiring substantial therapeutic intervention", time to the occurrence of the first flare (including flares not requiring tacrolimus treatment twice daily), the total number of flares during the control period (including flares not requiring tacrolimus treatment twice daily), the number of patients without a flare "requiring substantial therapeutic intervention" and the percentage of days with a flare "requiring substantial therapeutic intervention".

The Committee regrets the absence of any comparison with a topical corticosteroid, which would have enabled a clearer assessment of the degree of effect exerted by tacrolimus during maintenance treatment.

Adverse events associated with treatment were primarily local in adults (42.5% of patients in the tacrolimus group versus 38.4% in the excipient group) and children, (28.2% of patients in the tacrolimus group versus 24% in the excipient group): pruritus, folliculitis, irritation, infection, Herpes simplex and impetigo.
Systemic adverse events were observed in 6.3% of patients in the tacrolimus group and 12.3% in the excipient group: nasopharyngitis, influenza infection, viral infection of the respiratory tract, pruritus, pyrexia and cough.
These adverse effects were all expected, however in the tacrolimus group versus the excipient group, a higher proportion of impetigo was seen in children (7.7% versus 2.7%) and a higher proportion of infections at the application site was observed in both adults (6.3% versus 2.7%) and children (6.4% versus 4.0%).
The safety of tacrolimus has not been assessed in clinical studies for a period longer than 12 months.
A prospective, longitudinal epidemiological study over 10 years (end of inclusion in 2014), was implemented at the request of the FDA and EMA (APPLES study). Under real-life conditions of use, its aim is to assess the long-term safety of tacrolimus, and especially the occurrence of skin and systemic cancers (such as lymphomas), in children with atopic dermatitis, under 16 years of aged at the time of initial treatment. Because of insufficient hindsight to date (an average follow-up of 1.5 patient-years after 5 years of the study), no conclusions regarding the long-term safety of tacrolimus or the risk of cancer can be drawn from the interim results of the APPLES study.

The long-term risks associated with PROTOPIC treatment thus remain poorly understood at this time.

4 POST INCLUSION STUDY

A post authorisation study was requested by the Transparency Committee in the opinion it issued on 11/09/2002 (another request by the CEPS for a study on the long-term risk of cancer was included in the amendments dated 18/09/03 and then 03/08/04).

In order to describe the conditions of use of PROTOPIC, the applicant carried out a prospective observational study on 565 patients (500 planned) newly treated with PROTOPIC and recruited by 135 dermatologists (140 planned in the protocol) and 5 paediatricians (20 planned). The protocol for this study was approved by the Transparency

Committee in May 2007. The details regarding the analysis of this study can be found in the appendix of this opinion.

The primary aim of this study was to describe the use of PROTOPIC as an outpatient treatment, and to assess the impact of treatment on the population covered.

Among the 565 patients included, 521 (92.4%) had consulted for atopic dermatitis. A SCORAD[3] was recorded for 313 patients (60% of cases). At the time of inclusion, the severity of atopic dermatitis was: mild: 7 patients (2.2%), moderate: 158 patients (50.5%) and severe: 148 patients (47.3%).

The 0.1% dosage of PROTOPIC was used on 90.2% of adult patients and was prescribed for 22.3% of children, 65% of whom were aged 12 years or older. In 93% of cases, the posology was two applications daily.

PROTOPIC was combined with another treatment in 63.9% of cases: cosmetics, emollients (31.5%) and topical corticosteroids alone or concomitantly (27.2%). Furthermore, 21.9% of patients had previously topical corticosteroids tolerated and efficient.

Total SCORAD went from 44.9 at inclusion to 18.6 after 3 weeks ($p < 0.001$). Regarding the severity of dermatitis, 2.2% of patients were suffering from mild forms at inclusion compared with 49.6% after 3 weeks, 50.5% of moderate forms at inclusion compared with 44.0% after 3 weeks and 47.3% of severe forms at inclusion compared with 6.4% after 3 weeks.

Dermatitis reappeared after treatment discontinuation in 55% of patients, with a mean delay of 15 days.

Compliance assessed at 3 weeks showed that 82.4% of patients stated that they had taken their treatment every day, 4.8% every other day, 11.6% irregularly and 1.2% had never took it.

Conclusion:

These results obtained in real-life conditions of clinical practice confirmed the efficacy of PROTOPIC on atopic dermatitis lesions, and in terms of quality of life, but relapses are common, occurring soon after treatment discontinuation. Furthermore, these results demonstrate the prescription for PROTOPIC for severe forms in only 47.3% of cases, in patients who had not failed under topical corticosteroids in 21.9% of cases and in combination with a topical corticosteroid in 27.2% of cases. In addition, the 0.1% dosage, for use in adults only, was prescribed in 22.3% of children, 65% of whom were aged 12 years or older.

5 TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Actual benefit

Atopic dermatitis is a chronic, itchy, recurrent inflammatory dermatitis that develops in flares. It is often associated with infectious complications. Severe, recurring forms are debilitating and their impact on the quality of life is substantial.

These proprietary medicinal products fall under the category of symptomatic and preventive treatments to delay the occurrence of flares.

[3] Scorad (score from 0 to 103): mild AD if Scorad < 15 / moderate AD if 15 ≤ Scorad ≤ 45 / severe AD if Scorad > 45

Public health benefit:

Atopic dermatitis is a common and generally benign disorder. Recurrent forms can be considered as having a certain severe functional impact. From a public health point of view, the burden of the disease is small.

As preventive treatment for flares, emollients and topical corticosteroids are recommended as first-line therapies.

In the studies presented, conducted in patients with moderate to severe atopic dermatitis, the impact in terms of morbidity of the preventive treatment of relapses with PROTOPIC is moderate, both in adults as well as children. However, as this impact largely depends on the conditions of use for PROTOPIC and on the concomitant treatments, as well as compliance with the treatment regimen, the transferability of experimental results to clinical practice is not proven.

Furthermore, doubts remain regarding long-term safety, particularly in the context of maintenance treatment.

Consequently, a public health benefit is not expected for PROTOPIC when used for maintenance treatment of moderate to severe atopic dermatitis.

In the context of maintenance treatment to prevent flares, and while awaiting long-term safety data (at least 10 years follow up) on the risk of cancer, the efficacy/safety ratio of tacrolimus in this indication cannot be determined.

The prevention of atopic dermatitis relapses relies on the regular application of emollients, good hygiene, the avoidance of skin irritants and allergic factors, and therapeutic education. The prevention of relapses may also involve the intermittent use of topical corticosteroids (two applications per week). Due to the absence of a comparison with an active treatment (topical corticosteroids), the doubts regarding the long-term safety, and the risks of misuse or poor compliance, as highlighted in an observational study, PROTOPIC currently have no role in the therapeutic strategy for preventing atopic dermatitis. relapses.

Consequently, the actual benefit of PROTOPIC 0.03% in children and adults, and by PROTOPIC 0.1% in adults, is insufficient in the extension of the indication for maintenance treatment of atopic dermatitis, as stated by Marketing Authorisation, to justify reimbursed reimbursement by public funds.

5.2. Transparency Committee recommendations

The transparency Committee does not recommend on the list of medicines refundable by National Health Insurance and on the list of medicines approved for use by hospitals and various public services in this extension of its indication.

APPENDIX

PROTOPIC (tacrolimus monohydrate)

Astellas Pharma

FINAL RESULTS OF THE POST-INCLUSION STUDY

OPINION OF ISPEP GROUP OF 08/04/2010

1. CONTEXT

PROTOPIC (tacrolimus) is indicated:

- for the 0.1% form, for the treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to, or are intolerant of, conventional therapies.
- for the 0.03% form, for the treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to, or are intolerant of, conventional therapies, and in the treatment of moderate to severe atopic dermatitis in children (2 years of age and above) who have failed to respond adequately to conventional therapies.

The indications refundable (see FIT, Journal Officiel of 08/08/2008) are limited to severe forms of the disease.[4]

In the Therapeutic Benefits Sheet, severe atopic dermatitis is defined as an atopic dermatitis which impacts quality of life (pruritus, sleep disorders, and social impact), does not respond completely to appropriate treatment, and recurs rapidly (<10 days).

PROTOPIC can only be prescribed by dermatologists and physicians with extensive experience in the use of immunomodulating treatment for atopic dermatitis.

It has the status of “exception drug”, reimbursed at 35%.

A study was requested for this proprietary medicinal product by the Transparency Committee (in its opinion issued on 11/09/02). A further request came from the CEPS (amendments dated 18/09/03 and then 03/08/04). The wording was as follows:

- Opinion of the Transparency Committee of 11/09/02

"The Committee should be kept informed regularly of the results of studies carried out by the company at the request of the European Medicines Agency:
- the effect of tacrolimus on cell-mediated immunity,
- safety (infections and skin and systemic cancers),
- data on use in children before the age of 2 years.

The Committee also requests additional data concerning:
- efficacy after treatment discontinuation in the event of super infection,
- the effect of tacrolimus on the vaccine response in children."

[4] Indications reimbursed:
0.1% strength: treatment of severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids.
0.03% strength:
- Treatment of severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids.
- Treatment of severe atopic dermatitis in children (2 years upwards) who failed to respond adequately to conventional therapies, such as topical corticosteroids.
-

The dossier will be re-examined after one year. On this occasion, the company should provide data on the conditions of use of tacrolimus proprietary medicinal products (PROTOPIC 0.03% - 0.1%).

- CEPS Amendments dated 18/09/03 and of 03/08/04

"The applicant undertakes to study the long-term risk of cancer (6 years) of PROTOPIC by collecting and assessing data on all cancers observed in the French population being treated, or having been treated, with PROTOPIC."

In order to be able to define the conditions of use of PROTOPIC, the company carried out an observational, prospective study on 565 patients (500 planned) newly treated with PROTOPIC and recruited by 135 dermatologists (140 planned in the protocol) and five paediatricians (20 planned). The study protocol was validated by the Committee in May 2007.

The primary aim of this study was to describe the use of PROTOPIC as an outpatient treatment and to assess the impact of the treatment on the population covered.

2. PRINCIPAL RESULTS PRESENTED

2.1. Remarks on the methodology

The minimal participation of paediatricians was linked to the fact that these prescriptions are mainly issued by dermatologists.

The representativeness of the dermatologists was acceptable (see paragraph 2.2). The over-representation of physicians practising in towns of more than 5000 to 100,000 inhabitants, and in the Paris region, does not appear to affect the results of this study.

In order to make the best use of these results, in April 2010 additional information was requested to the company concerning the representativeness of the patients treated with PROTOPIC, the frequency of missing data, the correct use of this proprietary medicinal product and the outcomes of treated patients (a comparison of the efficacy of tacrolimus depending on atopic dermatitis severity, its history and concomitant treatments received (in particular topical corticosteroids), and ideally, a multivariate analysis should be carried out).

Following this request, the company supplied additional information on the first three points (letter dated 8 October 2010), but did not carry out the additional analyses on efficacy that had been requested.

The representativeness of patients was not ideal (see paragraph 2.3).

It is regrettable that the level of missing data, especially regarding the SCORAD score (the values were not recorded for 208 patients out of 521), was significant, especially in light of the fact that in a significant percentage of patients (36%), their assessment at 3 weeks could not be made during a consultation but only via a telephone interview during which any SCORAD changes were not recordable (a point specified in the protocol).

Furthermore, it should be noted that some patients were excluded from the study: six because they were treated with PROTOPIC for a disease other than atopic dermatitis and four because of their poor compliance with the treatment.

2.2. Description of the physicians

The 135 practising dermatologists were predominately female, and under 50 years old. Nearly 56% worked in a group practice and half only in private practice.

The practising dermatologists were representative of all French dermatologists (in terms of age, gender, the method and type of practice), except with regard to the practice environment and the area where they were based: physicians working in towns with between 5000 and 100,000 habitants and in the Paris region were over-represented in this study.

2.3. Reasons for non-inclusion:

A total of 210 patients were not included in the cohort. The reasons for non-inclusion were:

- Inclusion file not available (18.1%)
- Follow-up not possible (11.9%),
- Patient unable to answer questions (9.8%)
- Patient already treated with PROTOPIC (9.8%)
- Indication not covered by the Marketing Authorisation[5] (3.1%, n = 6)
- Poor compliance with the treatment (2.1%, n = 4)
- Few lesions (1.6%, n = 3)
- Patient <16 years (0.3%, n = 1)

2.4. Study of patient representativeness: comparison between patients in the cohort (N = 565) and those registered being treated with tacrolimus (N = 210)

In the cohort, patients living in the Paris region were over-represented compared with those from the Mediterranean, Central-East and Northern regions of France.

There were no statistically significant differences in the gender or age of patients, or the size (number of inhabitants) of the towns where they lived.

On average, patients in the cohort had suffered from AD for longer (15.2 years vs. 11.1 years), the number of AD flares per year was higher (7.4 vs. 5.3), the number of areas affected was greater (3.2 vs. 2.7), and the AD form was more severe (Scored 44.9 vs. 13.9).

There were no statistically significant differences in the efficacy and safety of the topical corticosteroids prescribed prior to the study.

2.5. Baseline patient characteristics

A total of 565 patients were included in the trial between 26/09/2007 and 26/06/2008, 553 of whom were recruited by dermatologists and 12 by paediatricians.

The mean age of the patients included was 27 years (median = 23 years) and 29.4% of them were children (n = 166), 3 of whom were under 2 years when they were put on PROTOPIC. The patients included in the study were mainly female (60.5%).

Among the 565 patients included, 521 (92.4%) had consulted for atopic dermatitis (AD). For the other patients (7.6%), the most common reason for a consultation was another form of eczema (74%).

The mean age of atopic dermatitis onset was 11 years (median = 2.4 years) and in almost one quarter of patients, it had started at around the age of 3 months or in adolescence. The mean history of AD was 15 years. Nearly half of the patients (46.1%) had been followed for less than 6 months by the dermatologist who included them in the study, 8.9% for between 6 to 12 months and 44.1% for longer than 12 months.

On average, the patients presented with 7episodes of AD per year. Trigger factors are known for 73% of patients: these were primarily stress (51%), cold and dry weather (41%) and, less commonly, contact with wool (19.4%), dust mites (18%), pollen (16.7%), pet hair (14.6%) and certain foods (10.6%).

The mean time elapsing since the last AD flare was 5.5 months before inclusion (median = 3).

As for the ongoing flare, it had started on average 2 months previously. The most commonly affected areas of the body were the lower limbs (74%), the torso (63 %), the head (61%), the upper limbs (47%) and the feet (41%). By contrast, fewer than 20% of patients presented with lesions on the scalp or hands. The mean number of areas affected was three.

[5] Absence of AD

SCORAD is used to measure the severity of AD.[6] Scores were recorded for 313 patients (60% of cases). The distribution of AD severity at inclusion was: mild AD: 7 patients (2.2%), moderate AD: 158 patients (50.5%) and severe AD: 148 patients (47.3%).

The data on quality of life could not be exploited because they were based on all the patients included (N = 565), while only 521 patients actually had atopic dermatitis.

More than 68% of patients had a previous family history of atopic allergy, more than half had other forms of atopic allergy (in particular, allergic rhinitis and asthma) and 13% suffered from another dermatological condition, most often acne.

2.6. Conditions of use for PROTOPIC

The initial results showed that:

- The 0.1% strength was used in 90.2% of adult patients
- Although it is only indicated for use in adults, the 0.1% strength product was prescribed for 22.3% of children, 65% of whom were 12 years or older.
- The dosage regimen of two applications per day was used in 93% of cases.
- PROTOPIC was combined with another treatment in 63.9% of cases:
    - 27.2% with topical corticosteroids alone or concomitantly (18.6% of which had previously displayed satisfactory safety and efficacy)
    - 31.5% cosmetics or emollients
- Furthermore, 21.9% of patients had previously used safe and effective topical corticosteroids.

Following the request from the ISPEP group, the company provided an additional synthetic analysis concerning the correct use of PROTOPIC.
The criteria for correct use were as follows:

- prescription for the treatment of atopic dermatitis (AD)
- for moderate to severe AD
- intolerance and/or inefficacy of topical corticosteroids

In children under 16 years old, two additional criteria were added:

- aged more than 2 years old
- PROTOPIC dosage form of 0.03%.

Data were available for 54% of adults (N = 216 out of the 399 adult patients included in the cohort) and for 64% of children (n = 106 out of the 166 children included).
In these patients, all the criteria for the correct use of PROTOPIC were complied with in 67% of adults and 68% of children.

2.7. Follow-up of patients treated with PROTOPIC

In terms of the data available during follow-up, 95% of patients were monitored at 3 weeks (381 patients at the physician practice, 124 by telephone) and 81% (n = 457) were monitored at 12 weeks.

The comparison between patients who were or were not followed at 12 weeks showed a statistically significant difference in terms of gender (males were under-represented 36.8% vs. 50.9%) and a limited significant difference in terms of history of AD (14.1 years vs. 16.7 years, p = 0.06). However, there were no differences in terms of age, the number of episodes and the impact on quality of life.

At 3 weeks, 70% of patients received a repeat prescription of PROTOPIC, often using the same regimen as for the initial prescription, but:

- 57% of adults and 61% of children had a reduction in the number of applications
- 7 children had an increase in their dosage to 0.1%.

The concomitant use of topical corticosteroids remained frequent.

[6] Scorad (score from 0 to 103): mild AD if Scorad < 15 / moderate AD if 15 ≤ Scorad ≤ 45 / severe AD if Scorad > 45

The total Scorad fell from 44.9 at inclusion to 18.6 at 3 weeks ($p<0.001$)

With regards the severity of dermatitis, there were 2.2% of mild forms at inclusion compared with 49.6% after 3 weeks, 50.5% of moderate forms at inclusion compared with 44.0% after 3 weeks and 47.3% of severe forms at inclusion and 6.4% after 3 weeks.

The impact of AD on quality of life showed an improvement across all age ranges:

- in children aged <4 years, the score fell from 8.9 at inclusion to 5.5 at 3 weeks and 4 at 12 weeks;
- in children from 4 to 16 years, these scores were 8.1, 3.6 and 2.8, respectively;
- and in patients older than 16 years, they were 9.4, 4.7 and 3.4.

Dermatitis recurred after treatment discontinuation in 55% of patients, following a mean period of 15 days.

Premature treatment discontinuations were reported in 25.9% of patients; the principal reasons were: recovery (41%), intolerance (23%), inefficacy (13%), restrictive treatment (2.9%) and other reasons (15.2%).

Compliance was assessed at 3 weeks: 82.4% of patients stated that they had used their treatment every day, 4.8% every other day, 11.6% irregularly and 1.2% never.

Among patients eligible for treatment with tacrolimus, comparison of those receiving tacrolimus and those not receiving tacrolimus

For this study, 358 patients were included in the register: 210 patients were treated with tacrolimus (TAC) and 148 were not treated with TAC. These two sub-populations were then compared: patients treated with TAC more commonly lived in North, West and Central-Eastern areas of France compared with those not treated with TAC. They experienced a larger number of AD episodes (52.8% had four episodes or more per year vs. 25.9% for patients not treated with TAC), and had a more severe form of AD on the VAS (5.9+/-2.2 vs. 4.8+/-2.3). Their AD also had a greater impact on the VAS (5.5+/-2.4 vs. 4.5+/-2.2) and the intensity of their spontaneous complaint was more severe (3.9+/-1.7 vs. 3.1+/-1.6). Furthermore, the location of lesions appeared to differ (more lesions on the scalp and head, especially in patients receiving TAC, and more lesions on the limbs for patients not receiving TAC).

Regarding topical corticosteroids, the efficacy of this treatment was judged as being very satisfactory or satisfactory by 26.9% of the patients who received TAC vs. 70.3% of patients who had not received TAC; safety was poorer among patients treated with TAC (it was judged as being less satisfactory in 67.3% of patients treated with TAC vs. 89.1 % of those not treated with TAC). Finally, the treatment prior to consultation differed between these two sub-populations: Among patients not treated with TAC, 87.2% had previously used corticosteroids and 20.3% emollients (the percentages were 9% and 5.2%, respectively, among patients who received TAC).

However, there was no statistically significant difference regarding socio-demographic criteria (gender, age) and history of the disease.

3. CONCLUSION

In general, the presentation of results was fairly clear.

Based on the initial data regarding the conditions of use of PROTOPIC, the indication in the Marketing Authorisation (moderate to severe AD) and the dosage were widely complied with. However, it should be noted that:

- More than 20% of patients treated with PROTOPIC had previously received well-tolerated and effective treatment with topical corticosteroids ;

- PROTOPIC was often combined with topical corticosteroid therapy;
- The 0.1% strength, indicated for use in adults only, was prescribed in 22.3% of children, 65% of whom were aged 12 years or older.

Across all the parameters studied and for all patients for whom data were available, all criteria for the correct use of PROTOPIC were complied with in 67% of adults and 68% of children.

The outcome at 3 weeks in the patients treated was generally favourable, but dermatitis recurred after treatment discontinuation in more than half of patients, after a mean period of 15 days, and compliance with treatment diminished over time.

In the absence of additional analyses on the efficacy, it is not possible to draw any conclusions regarding the true impact of PROTOPIC on the outcome of treated patients, particularly because of its frequent combination with cosmetics, emollients and also topical corticosteroids.