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## TRANSPARENCY COMMITTEE

Opinion  
20 November 2013

### PROTOPIC 0.03 PER CENT, ointment

Tube of 30 g (CIP: 34009 359 221 9 9)

### PROTOPIC 0.1 PER CENT, ointment

Tube of 30 g (CIP: 34009 359 223 1 1)

Applicant : ASTELLAS PHARMA S.A.S.

INN	Tacrolimus monohydrate
ATC code (2013)	D11AH01 (drugs for dermatitis, calcineurin inhibitor)
Reason for the review	<b>Renewal of inclusion</b>
List(s) concerned	<b>National Health Insurance</b> (French Social Security Code L.162-17)
Indication(s) concerned	<p>➤ <b>PROTOPIC 0.03%, ointment:</b></p> <p><b>"Flare treatment:</b> Treatment of severe atopic dermatitis* in adults who are not adequately responsive to or are intolerant of conventional therapies, such as topical corticosteroids.</p> <p>Treatment of severe atopic dermatitis* in children (2 years of age and above) who failed to respond adequately to conventional therapies, such as topical corticosteroids."</p> <p>➤ <b>PROTOPIC 0.1%, ointment:</b></p> <p><b>"Flare treatment:</b> Treatment of severe atopic dermatitis* in adults who are not adequately responsive to or are intolerant of conventional therapies, such as topical corticosteroids."</p> <p>*: PROTOPIC is not reimbursable for the treatment of moderate forms.</p>

<p><b>Actual Benefit</b></p>	<ul style="list-style-type: none"> <li>- In children (2 years old and over): Insufficient AB in the treatment of skin eruptions in severe atopic dermatitis which has not responded adequately to conventional treatments, such as topical corticosteroids.</li> <li>- In adults and adolescents (16 years old and over): Low AB flares in severe atopic dermatitis in patients who are inadequately responsive to or are intolerant of conventional therapies, such as topical corticosteroids.</li> <li>- Continuation of the insufficient AB in the treatment of flares in moderate atopic dermatitis in adults and children and in the maintenance treatment.</li> </ul>
<p><b>Therapeutic Use</b></p>	<p>PROTOPIC is a second-line treatment for flares in severe atopic dermatitis in adults who are intolerant of or not adequately responsive to topical corticosteroids.  PROTOPIC has no role in the therapeutic strategy for atopic dermatitis in children.</p>

## 01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	<p>Date of Marketing Authorisation: 28 February 2002 (centralised procedure)</p> <p>Dates of principal amendments to the Marketing Authorisation:</p> <ul style="list-style-type: none"> <li>- 19 May 2004: major changes to the sections Posology, Warnings and precautions for use, Undesirable effects (see Opinion of 27 October 2004);</li> <li>- 10 June 2005: Undesirable effects (addition of rosacea);</li> <li>- 12 June 2006: changes to the sections Indications, Posology, Warnings and precautions for use and Undesirable effects following the re-assessment of topical calcineurin inhibitors by the EMEA;</li> <li>- 3 May 2007: pharmacokinetics in children under the age of 2, preclinical safety data;</li> <li>- 26 February 2009: extension of indication in the maintenance treatment.</li> </ul>
Prescribing and dispensing conditions / special status	<p>List I Medicinal product requiring close monitoring during treatment. Prescription restricted to dermatologists and paediatricians. <b>Exceptional drug status</b></p>

ATC Classification	<p>D: Dermatologicals D11: Other dermatological preparations D11A: Other dermatological preparations D11AH: Agents for dermatitis, excluding corticosteroids D11AH01: Tacrolimus</p>
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## 02 BACKGROUND

Examination of the records of PROTOPIC proprietary medicinal products registered for a 5-year period starting on 15/05/2008 (Official Gazette of 14/04/2009).

PROTOPIC is currently the only medicinal product in the calcineurin inhibitor class that is available in France with an indication for the treatment of atopic dermatitis. Pimecrolimus (ELIDEL), which the Transparency Committee approved (low AB), is not on the market.

In its Opinion of 11 September 2002 relative to PROTOPIC, the Committee had issued a number of comments concerning efficacy and safety data which justified a low AB in children and a moderate AB in adults:

- Efficacy:
  - The inclusion criteria for patients in the studies presented did not correspond with those in the indication (inadequate response to or intolerance of conventional therapies).
  - The comparator in the study in children was a mild topical corticosteroid. The results did not allow for the exclusion of a favourable response to a topical corticosteroid with greater potency.
  - About 50% patients experienced a recurrence 15 days after discontinuing the treatment.
  - Efficacy was not assessed in the event of a secondary infection.

- Safety:

- The effect of the treatment on the immune system had not been established the risk of skin infections or cancers linked to local immunosuppression is unknown beyond 2 years of treatment.
- The safety had not been assessed in the event of a secondary infection.

In its conclusions, the Committee had asked to be regularly informed of the results of studies conducted by the company at the request of the European Medicines Agency:

- the effect of tacrolimus on cellular immunity
- safety (skin and systemic infections and cancers)
- data on usage in children under the age of 2

and requested additional data concerning:

- efficacy following discontinuation of the treatment and in the event of a secondary infection
- the effect of tacrolimus on the response to vaccines of children.

At the previous renewal of the registration of PROTOPIC in 2008, the company provided additional data on efficacy (efficacy versus a potent corticosteroid in adults and children, particularly in patients who were not adequately responsive to topical corticosteroids or conventional therapies, the effect of tacrolimus on cellular immunity in children, a pharmacokinetics study in children under the age of 2, the maintenance of efficacy after the discontinuation of treatment) and safety (the long-term risk of skin infections and cancers).

The conclusions regarding these data were as follows:

"In adults suffering from moderate to severe atopic dermatitis who had failed to respond to or been intolerant of topical corticosteroids, tacrolimus was superior to fluticasone (a potent topical corticosteroid, with application on the face and neck) and hydrocortisone (butyrate 0.1%, a potent topical corticosteroid on the trunk and limbs and acetate 1% with weak activity on the face and neck). No data were supplied on the efficacy of tacrolimus in the event of a secondary infection.

In children from the age of 2 years old suffering from moderate to severe atopic dermatitis (at all locations), tacrolimus was not inferior to fluticasone.

Data on the effect of tacrolimus on the response to vaccines were not able to answer the question regarding the immunosuppressant effect at skin, local or locoregional levels. Pharmacokinetic data in children under the age of 2 were insufficient to recommend the use of tacrolimus in this age group.

Long-term safety data (1 to 4 years) evidenced a safety profile in line with what was expected, particularly in terms of the risk of skin infections. The risk of cancers linked to tacrolimus, particularly skin cancers, could be ruled out although it appeared to be low at that time according to the data available. Additional longer-term safety data (10 years) were expected, as were the results of an assessment performed by the AFSSAPS on pharmacovigilance data since tacrolimus was put on the market."

The Committee had given approval and maintained its assessment of the AB, which was low in children and moderate in adults, but only in severe forms in the event of resistance (and intolerance in adults) to conventional therapies, such as topical corticosteroids, whilst awaiting the results of the studies under way:

- study on the conditions of use requested in the Opinion of 11 September 2002
- assessment by the AFSSAPS (ANSM) of pharmacovigilance data since marketing
- interim results of the prospective review over 10 years (APPLES study).

In October 2011, the Transparency Committee did not recommend the registration of PROTOPIC for the extension of its indication to the maintenance treatment of atopic dermatitis, owing to the absence of any comparison with an active treatment (topical corticosteroids), uncertainties regarding long-term safety and the risk of misuse or poor patient compliance as shown by an observational study.

The application for the renewal of registration does not apply to this indication.

In addition, interim results of the APPLES study had been provided by the company. However, the duration of patient follow-up (1.5 patient years) was considered insufficient to be able to reach any conclusions on the results presented.

The pharmacovigilance data presented (from 01/10/08 to 31/03/2009) had not revealed any new reports.

Since the last review of PROTOPIC by the Transparency Committee, the SPC has been amended several times (European decisions of 21 February 2011, 23 June 2011, 29 June 2012 and 30 August 2012), in particular in order to mention additional information on the use of tacrolimus in children, precautions for use in the event of abnormalities in the skin barrier and the occurrence of cutaneous T-cell lymphoma (see changes in the Appendix).

The company is now requesting a the renewal of registration in the indications that are currently reimbursed to patients by National Health Insurance:

- PROTOPIC 0.03%, ointment:

Flare treatment:

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 of age and above) who failed to respond adequately to conventional therapies, such as topical corticosteroids".

- PROTOPIC 0.1%, ointment:Flare treatment:

Treatment of severe atopic dermatitis in adults who are inadequately responsive to or intolerant of conventional therapies, such as topical corticosteroids."

## 03 THERAPEUTIC INDICATIONS

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### **PROTOPIC 0.03%, ointment:**

"PROTOPIC 0.03% ointment is indicated in adults, adolescents and children from the age of 2 years.

Flare treatment:

*Adults and adolescents (16 years of age and above)*

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.

*Children (2 years of age and above)*

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.

Maintenance treatment:

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 4 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). "

### **PROTOPIC 0.1%, ointment:**

"PROTOPIC 0.1% ointment is indicated in adults and adolescents (16 years of age and above).

### Flare treatment:

#### *Adults and adolescents (16 years of age and above)*

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. "

### Maintenance treatment:

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 4 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). "

## 04 DOSAGE

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"PROTOPIC 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 because this method of administration has not been studied in patients.

PROTOPIC should not be used in children aged below 2 years until further data are available.

Specific studies have not been conducted in older people. However, the clinical experience available in this patient population has not shown the necessity for any dosage adjustment.

### Flare treatment

PROTOPIC can be used for short-term and intermittent long-term treatment. Treatment should not be continuous on a long-term basis.

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 if appropriate (see below). At the first signs of recurrence (flares) of the disease symptoms, treatment should be re-initiated.

#### ***Adults and adolescents (16 years of age and above)***

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.

#### ***Elderly patients***

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.

#### ***Paediatric population***

Children (2 years of age and above) should use the lower strength PROTOPIC 0.03% ointment. Treatment should be started twice a day for up to three weeks. Afterwards the frequency of applications should be reduced to once a day until clearance of the lesions.

PROTOPIC should not be used in children aged below 2 years until further data are available.

### 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.

### **Adults and adolescents (16 years of age and above)**

Adult patients should use PROTOPIC 0.1% ointment.

PROTOPIC ointment should be applied once a day twice weekly (e.g. Monday and Thursday) to areas commonly affected by atopic dermatitis to prevent a progression to flares. Between applications there should be 2–3 days without PROTOPIC treatment.

After 12 months of treatment, and in the absence of safety data on maintenance treatment beyond 12 months, a review of the patient's condition should be conducted by the physician and a decision taken whether to pursue this maintenance treatment.

If signs of a flare recur, twice daily treatment should be re-initiated (see section on flare treatment, above).

### **Elderly patients**

Specific studies have not been conducted in elderly patients (see section on flare treatment, above).

### **Paediatric population**

Children (2 years of age and above) should use the lower strength PROTOPIC 0.03% ointment.

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.

A review of the child's condition after 12 months of treatment should include the suspension of treatment in order to assess the need to continue this regimen and to evaluate the course of the disease.

PROTOPIC should not be used in children aged below 2 years until further data are available."

## **05 THERAPEUTIC NEED**

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### **In children**

According to the recommendations of the French Society of Dermatology<sup>1</sup> the therapeutic management of atopic dermatitis in children is based on adjuvant measures and the prevention of recurrences (regular application of emollients, hygiene measures, suppression of factors irritating the skin and allergic factors, therapeutic education) and symptomatic treatment when flares occur: topical corticosteroid therapy, tacrolimus 0.03%, phototherapy). Bacterial, viral or fungal secondary infections affecting atopic dermatitis lesions should be treated.

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1

Société Française de Dermatologie [French Society of Dermatology]. Consensus Conference. Prise en charge de la dermatite atopique de l'enfant. Ann Dermatol Venereol 2005;132:1S19-33.

Topical corticosteroid therapy is the standard treatment for the acute phase of atopic dermatitis. The potency of topical corticosteroids should be adapted to the age of a child, the severity of dermatitis, the site of lesions and the surface area to be treated. The duration of treatment should be as short as possible so as to limit the potential risk of local and systemic adverse effects. Thus:

- highly potent topical corticosteroids are contraindicated in infants and young children, on the face, flexure areas, and bottom; potent topical corticosteroids should be restricted to short-term courses of treatment for highly inflammatory or very lichenified forms affecting the extremities. In practical terms, few practitioners use these potent topical corticosteroids in children because of local and systemic safety problems; moderate topical corticosteroids should be used with caution on the face, skin folds and genital areas and in infants care, for short courses of treatment and making sure to avoid the eyelids; mild topical corticosteroids have a minor role in therapeutic strategy.

If there is no response to topical corticosteroids, the reason should be determined, such as poor patient compliance, incorrect application or corticophobia. Therapeutic education may then allow the patient to pursue topical corticosteroid treatment with success.

Studies have shown that in children, a potent topical corticosteroid used after failure to respond to, or intolerance of, conventional therapies, such as topical corticosteroids, was non-inferior to tacrolimus.

Tacrolimus 0.03% has a second-line Marketing Authorisation in children of 2 years old and over who have not responded adequately to topical corticosteroids. In practical terms, its use remains restricted because of the low frequency of failures with corticosteroid therapy, the ointment formulation which makes dressing children difficult, and local reactions (irritations, burns).

UVA-UVB and UVB narrow band phototherapy can only be used in exceptional circumstances for the treatment of severe atopic dermatitis in children from the age of 12 years. Administration conditions require visits to a suitably equipped dermatologist several times a week. The serious cumulative toxicity involves a mutagenic/carcinogenic risk and limits access and use over the long term.

### **In adults**

In adults, there are currently no official or consensual recommendations in France concerning the treatment of atopic dermatitis. An international consensus conference published its guidelines in 2003<sup>2</sup> and the European Academy of Dermatology and Venereology also published its guidelines.<sup>3</sup>

As in children, the treatment of atopic dermatitis combines adjuvant measures with those to prevent recurrences (regular application of emollients, hygiene measures, suppression of factors irritating the skin and allergic factors, therapeutic education) and symptomatic treatment when flares occur: topical corticosteroids, tacrolimus, phototherapy and cyclosporine.

Bacterial, viral or fungal secondary infections affecting atopic dermatitis lesions should be treated.

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2

Ellis C. et al. International Consensus Conference on Atopic Dermatitis II (iccad II): clinical update and current treatment strategies. Br J Dermatol, 2003; 148(S63): 3-10.

3

Hanifin JM et al. Guidelines of care for atopic dermatitis. Journal of the American Academy of Dermatology, 2004; 50(3): 391-404.



Topical corticosteroids constitute the standard symptomatic therapy:

- the potency of topical corticosteroids should be adapted to the severity, the site and the surface area to be treated, and the duration of treatment should be as short as possible;
- because of the chronic nature of the disease and its lengthy progression, adults are more sensitive to corticosteroid-induced atrophy than children; topical corticosteroids with moderate or potent activity should only be applied for very short periods in the treatment of atopic dermatitis of the face and neck. This is because of short-term and long-term safety problems: corticosteroid-induced rosacea, peri-oral dermatitis, a risk of atrophy and telangiectasia, corticosteroid-induced slapped cheek syndrome, eye involvement.

If there is no response to topical corticosteroids, the cause should be determined, such as poor patient compliance, incorrect application or corticophobia. Therapeutic education can then allow the successful pursuit of treatment with a topical corticosteroid.

In studies comparing tacrolimus with topical corticosteroids in adults whose previous topical corticosteroid treatment had failed, the percentage of responders among patients treated again with topical corticosteroids, although inferior to that observed with tacrolimus, was relatively significant.

Tacrolimus, phototherapy and cyclosporine are second-line treatments. In practice, because of the difficult application of this ointment formulation, tacrolimus is used in the case of lesions that are little extensive and refractory corticosteroids, mainly on the face and neck.

Phototherapy and cyclosporine are restricted to severe and widespread forms, more frequently refractory to corticosteroids than in children. These are short-term treatments, to be used sparingly because of their potentially serious adverse effects: risk of skin cancers with phototherapy, and kidney disease and hypertension in particular with cyclosporine.

### **Prevention of recurrences**

Preventing recurrences of atopic dermatitis is based on the regular application of emollients, hygiene measures, the suppression of factors irritating the skin and allergic factors and therapeutic education. The prevention of relapses may also involve the use of topical corticosteroids in an intermittent regimen (2 applications a week).

## **06 CLINICALLY RELEVANT COMPARATORS**

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### **Medicinal products**

PROTOPIC is the only medicinal product in its pharmaco-therapeutic class (calcineurin inhibitor) with an indication in severe atopic dermatitis if patients have failed to respond to topical corticosteroids.

Other drug treatments are topical corticosteroids, which are indicated as a first-line treatment. In adults, the cyclosporine capsules and oral solution may be used if phototherapy and/or photochemotherapy have failed or are contraindicated.

## Other health technologies

Phototherapy and photochemotherapy are used as second-line treatments in severe and widespread forms in adults.

### ► Conclusion

**There is no clinically relevant comparator for PROTOPIC. However, topical corticosteroids can be considered as comparators insofar as studies have shown that a potent topical corticosteroid used after patients have failed to respond to or been intolerant of conventional therapies, was non-inferior to tacrolimus in children. In adults, the percentage of responders was also considerable even though inferior to that observed with tacrolimus.**

## 07 SUMMARY OF PREVIOUS ASSESSMENTS

<b>Date of opinion</b>	<b>11 September 2002</b>
<b>Reason for request</b>	<b>Inclusion</b>
<b>Indication</b>	<p><u>PROTOPIC 0.03%, ointment:</u> "Treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies.</p> <p>Treatment of moderate to severe atopic dermatitis in children (2 years old and over) who have not responded adequately to conventional therapies. "</p> <p><u>PROTOPIC 0.1%, ointment:</u> "Treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies. "</p>
<b>AB</b>	<p>Atopic dermatitis is a chronic, frequent, relapsing and itchy skin disorder which, apart from psychosocial repercussions, may cause secondary skin infections.</p> <p>Efficacy:</p> <ul style="list-style-type: none"> <li>- The inclusion criteria for patients in the studies presented do not correspond with those in the indication (inadequate response or intolerance to conventional therapies).</li> <li>- The comparator in the study in children is a mild topical corticosteroid. The results do not allow for the exclusion of a favourable response to a topical corticosteroid with greater potency.</li> <li>- About 50% of patients regressed 15 days after discontinuing the treatment.</li> <li>- Efficacy has not been assessed in the event of secondary infection.</li> </ul> <p>Safety:</p> <ul style="list-style-type: none"> <li>- The effect of the treatment on the immune system has not been established. The risk of skin infections or cancers linked to local immunosuppression is unknown beyond 2 years of treatment.</li> <li>- Safety has not been assessed in the event of secondary infection.</li> </ul> <p>The efficacy/adverse effects ratio is:</p> <ul style="list-style-type: none"> <li>- <u>low</u> in children</li> <li>- <u>moderate</u> in adults.</li> </ul> <p>This proprietary medicinal product is intended as curative therapy. This is a second-line treatment. Alternative medicinal products exist.</p> <p>The actual benefit of this proprietary medicinal product is:</p> <ul style="list-style-type: none"> <li>- <u>low</u> in children</li> <li>- <u>moderate</u> in adults.</li> </ul>

<b>IAB</b>	<p>In the clinical record presented, and with regard to patients treated with first-line treatment (the only data available to the Committee), tacrolimus (PROTOPIC 0.1%-0.03%) does not provide any improvement in actual benefit compared with local corticosteroids (off-label use).</p> <p><b>In the context of the indications of tacrolimus (PROTOPIC 0.1% - 0.03%), the Committee does not have any data which allows it to quality the degree of improvement in actual benefit.</b></p>
<b>Studies requested</b>	<p>The Committee must be regularly informed of the results of studies conducted by the company at the request of the European Medicines Agency:</p> <ul style="list-style-type: none"> <li>- the effect of tacrolimus on cellular immunity</li> <li>- safety (skin and systemic infections and cancers)</li> <li>- data on usage in children under the age of 2.</li> </ul> <p>The Committee requests additional data on:</p> <ul style="list-style-type: none"> <li>- efficacy following discontinuation of the treatment in the event of a secondary infection</li> <li>- the effect of tacrolimus on the response to vaccines in children.</li> </ul> <p>The case will be re-examined within a period of one year. On this occasion, the company must provide data on conditions of use for tacrolimus proprietary medicinal products (PROTOPIC 0.03% - 1%).</p>

<b>Date of opinion</b>	<b>28 May 2008</b>
<b>Reason for review</b>	<b>Renewal of inclusion</b>
<b>Indication</b>	<p><u>PROTOPIC 0.03%, ointment:</u>          "Treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies, <b>such as topical corticosteroids.</b></p> <p>"Treatment of moderate to severe atopic dermatitis in children (2 years of age or above) who have not responded adequately to conventional therapies, <b>such as topical corticosteroids.</b> "</p> <p><u>PROTOPIC 0.1%, ointment:</u>          "Treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies, <b>such as topical corticosteroids.</b> "</p>
<b>AB</b>	<p>Atopic dermatitis is a chronic, inflammatory, itchy, relapsing skin disorder, with the patient experiencing flare-ups. It is often associated with infectious complications. The severe recalcitrant forms are incapacitating and the impact on quality of life is considerable.</p> <p>These proprietary medicinal products fall under the category of symptomatic treatment.</p> <p>Given the similar efficacy of tacrolimus to that of potent topical corticosteroids after the failure of conventional therapies, including topical corticosteroids, but also the persistent uncertainties surrounding the immunosuppressive effect of tacrolimus on the skin and the potentially associated risk of skin cancer, particularly in children, the efficacy/safety ratio is low in children and moderate in adults.</p> <p>These proprietary medicinal products are second-line treatments indicated in moderate to severe forms in patients who are inadequately responsive to or intolerant of conventional therapies, such as topical corticosteroids.</p> <p>In children, the role of tacrolimus 0.03% is limited to severe forms due to the low frequency of treatment failures with topical corticosteroids and, moreover, the</p>

	<p>ointment formulation of tacrolimus which makes dressing children difficult, and local reactions (irritations, burns). In adults, tacrolimus can be useful in severe forms which are little extensive and refractory to topical corticosteroids, mainly on the face and neck.</p> <p>There are treatment alternatives. If there is no response to topical corticosteroids, the cause should be determined, such as poor patient compliance, incorrect application or corticophobia. Therapeutic education can then allow the successful pursuit of treatment with a topical corticosteroid. Studies have shown that a potent topical corticosteroid used after patients had failed to respond to or been intolerant of conventional therapies was as effective as tacrolimus in children. In adults, the percentage of responders was also considerable albeit lower than that observed with tacrolimus. Cyclosporine and phototherapy are also used as second-line treatments in severe and widespread forms in adults.</p> <p>In children, the actual benefit of PROTOPIC 0.03% ointment is low in severe atopic dermatitis if they are not adequately responsive to or are intolerant of conventional therapies, such as topical corticosteroids, and insufficient in moderate forms.</p> <p>In adults, pending assessment by the AFSSAPS of the pharmacovigilance data collected since PROTOPIC 0.03% and 0.1% ointment were put on the market, the actual benefit of these proprietary medicinal products is moderate in severe atopic dermatitis in patients who are not adequately response to or are intolerant of conventional therapies, such as topical corticosteroids; it is insufficient in moderate forms.</p>
<b>IAB</b>	<p>PROTOPIC 0.03% and PROTOPIC 0.1% ointment provides a minor improvement in actual benefit (level IV) in the therapeutic strategy in adult patients suffering from severe atopic dermatitis of the face and neck.</p>
<b>Studies requested</b>	<p>The Committee is awaiting the results of studies under way:</p> <ul style="list-style-type: none"> <li>- study on conditions of use requested in the Opinion of 11 September 2002,</li> <li>- assessment by the AFSSAPS of pharmacovigilance data since market introduction,</li> <li>- interim results of the prospective study over a 10-year period.</li> </ul>

<b>Date of opinion</b> <b>Reason for the review</b>	<p><b>05 October 2011</b> <b>Extension of indication</b> <b>Review of results for the post-inclusion observational study</b></p>
<b>Indication</b>	<p>"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 4 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)."</p>
<b>AB</b>	<p>Atopic dermatitis is a chronic, inflammatory, itchy, relapsing skin disorder, with the patient experiencing flare-ups. It is often associated with infectious complications. The severe recalcitrant forms are incapacitating and the impact on quality of life is considerable.</p> <p>These proprietary medicinal products come within the framework of symptomatic and preventive treatment to delay the onset of new flares.</p> <p><u>Public health benefit:</u> Atopic dermatitis is a common condition, that is usually benign. Relapsing forms can be regarded as having a certain functional severity. The burden</p>

of the disease is low from a public health point of view.

Emollient treatments and topical corticosteroids are recommended as first-line treatments in the prevention of flares.

In the trials presented, in patients suffering from moderate to severe dermatitis, the impact in terms of the morbidity of PROTOPIC treatment to prevent relapses is moderate, as much in adults as in children. However, this impact largely depends on the methods of use of PROTOPIC and on associated treatments, as well as on treatment compliance. The transposability of experimental results to clinical practice is not guaranteed.

In addition, there remains doubt about long-term safety, particularly in the context of maintenance treatment.

As a result, no public health benefit is expected for the proprietary medicinal product PROTOPIC used in the maintenance treatment of moderate to severe atopic dermatitis.

Within the context of maintenance treatment for preventing new flares, and pending long-term safety data (at least 10 years of follow-up) on the risk of cancer, the efficacy/safety ratio of tacrolimus in this indication cannot be assessed.

The prevention of recurrences of atopic dermatitis is based on the regular application of emollients, hygiene measures, the suppression of factors irritating the skin and allergic factors and therapeutic education. The prevention of recurrences may also involve the use of topical corticosteroids in an intermittent regimen (2 applications a week). Due to the absence of a comparison with an active treatment (topical corticosteroids), uncertainties concerning the long-term safety and risks of misuse or poor patient compliance shown in an observational study, PROTOPIC proprietary medicinal products do not currently have a role in therapeutic strategy for the prevention of relapses of atopic dermatitis.

As a result, the actual benefit of PROTOPIC 0.03% in children and adults and PROTOPIC 0.1% in adults is **insufficient** for extension of the indication to maintenance treatment for atopic dermatitis, as it is worded in the Marketing Authorisation, and thus to justify its reimbursement by social security.

## 08 ANALYSIS OF AVAILABLE DATA

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### 08.1 Efficacy

The company provided two efficacy studies from the literature comparing tacrolimus with pimecrolimus (ELIDEL, not marketed in France) in patients with atopic dermatitis previously treated with topical corticosteroids.

These two studies will not be described below insofar as the Kirsner study (2010) is a retrospective analysis of the combined results of 3 studies including adult and child patients with mild to very severe atopic dermatitis, and the Abramovits study (2008) is a retrospective analysis of the results obtained in a sub-group of patients with moderate atopic dermatitis.

### 08.2 Adverse effects

#### 8.2.1 Observational studies

##### **Arana study (2010)<sup>4</sup>**

This retrospective study compared the incidence of cancers in the general population and in patients with atopic dermatitis. It focused on a cohort of 4,456,008 patients with no history of cancer from "The Health Improvement Network" (THIN) database, representative of the population of the United Kingdom. Among these patients, 66,258 (1.5%) had atopic dermatitis. Patient follow-up was on average 6.78 years for the total cohort and 3.16 years for the patients suffering from atopic dermatitis.

The cancer cases reported were 129,972 in number in the total cohort, which corresponds to an incidence of 42.4 per 10,000 patient years (95% CI [42.18; 42.64]). The overall risk of cancer, adjusted according to age and sex, was higher in atopic dermatitis than in non-atopic dermatitis (RI = 1.49; 95% CI [1.39; 1.61]). Considering lymphomas in isolation, the risk was increased in patients suffering from atopic dermatitis with an RI adjusted according to age and sex of 2.21 (95% CI [1.65; 2.98]). As for melanomas and skin cancers, the risk was also increased with an RI of 1.74 (95% CI [1.25; 2.41]) and 1.46 (95% CI [1.27; 1.69]) respectively.

This study showed a higher incidence of skin cancers in atopic patients, but it did not make it possible to establish a link between skin cancer and treatment for atopic dermatitis.

##### **Hui study (2009)<sup>5</sup>**

A retrospective cohort of 953,064 patients with atopic dermatitis or eczema, treated or not with topical calcineurin inhibitors (tacrolimus and pimecrolimus), was monitored between 2001 and 2004. Among these patients, only 4% (n = 38,682) were exposed to a topical calcineurin inhibitor, 11,898 of them to tacrolimus alone and 4,068 to tacrolimus and pimecrolimus. The median follow-up of patients was 2.4 years for tacrolimus, 1.9 years for pimecrolimus and 2.6 years for unexposed patients.

Among the 11,961 cancer cases reported between 2001 and 2005, no difference, for all cancers combined, was observed between patients exposed or not exposed to calcineurin inhibitors after adjustment according to age and sex.

A post-hoc analysis identified 16 cases of T-cell lymphoma. Among these lymphomas, 13 were cutaneous T-cell lymphomas (80% instead of the 30% expected). Among these 13 cases, 4 were re-classified as existing prior to the application of tacrolimus. After adjustment according to age and sex, an increased risk of occurrence of T-cell lymphoma was shown for patients treated with

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<sup>4</sup> Arana A., et al., Incidence of cancer in the general population and in patients with or without atopic dermatitis in the UK. *British Journal of Dermatology* 2010; 163: 1036-43

<sup>5</sup> Hui RL et al., Association between exposure to topical tacrolimus or pimecrolimus and cancers. *Ann Pharmacother* 2009; 43: 1956-63

tacrolimus (HR = 5.04;  $<_{95\%}$  CI [2.39-10.63];  $p < 0.001$ ). After reviewing the records of all the exposed patients with T-cell lymphoma and adjustment that took into account confounding factors, the risk of T-cell lymphoma among patients exposed to topical tacrolimus was 3.1 ( $_{95\%}$  CI = [1.4; 6.9];  $p = 0.005$ ) compared to unexposed patients. It should be noted that the exposure to topical tacrolimus was very low in patients diagnosed with T-cell lymphoma; indeed, the median accumulated quantities of ointment applied were 75 g (that is 2.5 tubes) for the 0.1% dosage form and 105 g (that is 3.5 tubes) for the 0.03% dosage form. These accumulated quantities of tacrolimus ointment were not statistically different from those in patients who did not have T-cell lymphoma.

### **Schneeweiss study (2009)<sup>6</sup>**

A cohort of 1,252,300 patients, 31% of whom were children, was monitored between January 2002 and June 2006 so as to assess the risk of lymphomas during treatment with tacrolimus, pimecrolimus or corticosteroids. The patients were monitored, on average, for 1.5 years for those treated with tacrolimus and pimecrolimus and 1.4 years for those treated with topical corticosteroids. In total, 10 cases of lymphomas were identified among 29,870 patients who had been treated with topical tacrolimus, that is an incidence rate of 25/100,000 patient years. Similar incidence rates were obtained for the patients who had been treated with topical pimecrolimus and for those treated with topical corticosteroids.

Compared to the general population, these three treatments were associated with an increased risk of occurrence of lymphoma:

- RR for tacrolimus: 2.82 ( $_{95\%}$  CI = [1.08; 7.39])
- RR for pimecrolimus: 2.89 ( $_{95\%}$  CI [1.32; 6.32])
- RR for topical corticosteroids: 2.10 ( $_{95\%}$  CI = [1.01; 4.33])

Compared to the patients suffering from atopic dermatitis but not treated, the three treatments were not associated with an increased risk of lymphoma:

- RR for tacrolimus: 1.97 ( $_{95\%}$  CI = [0.87; 4.50])
- RR for pimecrolimus: 1.79 ( $_{95\%}$  CI = [0.92; 3.48])
- RR for topical corticosteroids: 1.33 ( $_{95\%}$  CI = [0.73; 2.38]).

## **8.2.2 Pharmacovigilance data**

International pharmacovigilance data covering the period from 1 April 2009 to 31 March 2012 showed the occurrence of 247 cases of cancer of all types. In 216 cases, confounding factors (duration of inflammatory pathologies associated with atopic dermatitis, treatment with other immunosuppressant drugs, other suspected co-prescribed drugs, pre-existing tumours) did not enable a link to be made with exposure to tacrolimus. In the remaining 31 cases with no previously prescribed immunosuppressant treatment, and in the absence of confounding factors, apart from 3 cases, the time to onset of the tumour compared with the start of treatment (that is an exposure of at least one year) meant that the causal relationship with tacrolimus was not very plausible.

In the absence of any evidence of a link between the development of cancers and exposure to tacrolimus, and because of insufficient long-term data, the carcinogenic risk still needs to be evaluated in the risk management plan.

The ANSM and the Midi-Pyrénées Regional Pharmacovigilance Centre (CRPV), in collaboration with the Groupement Français d'Etudes des Lymphomes Cutanés [French Study Group on Cutaneous Lymphomas] (GFELC) performed an analysis comparing, from the period 1 January 2006 to 31 December 2010, the number of cases of cutaneous T-cell lymphomas observed compared to the number of cases expected. The results of this analysis were presented to the French National Pharmacovigilance Commission in January 2012.

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Schneeweiss S et al., Topical treatments with pimecrolimus, tacrolimus and medium- to high-potency corticosteroids, and risk of lymphoma. *Dermatology* 2009;216: 7-21

Patients were identified from the Échantillon Généraliste de Bénéficiaires (EGB) [General Sample of Beneficiaries], a permanent sample that is representative of the population protected by French National Health Insurance schemes. During the period, exposure to tacrolimus (all dosage forms combined) was 388,155 patient years. Four cases of cutaneous lymphomas were notified. Only the cases for which the diagnosis of cutaneous lymphoma was confirmed were considered, that is 2 cases.

Given that the risk of occurrence of cutaneous lymphoma in patients suffering from atopic dermatitis is the same as that in the general population (0.5/100,000 inhabitants) (hypothesis 1), the number of cases expected was estimated at 1.90. Assuming the risk of occurrence of cutaneous lymphoma in patients suffering from atopic dermatitis is twice as high as that of the general population (hypothesis 2), , , the number of expected cases would be 3.90.

Given the notification rate of 100% and 50%, and regardless of the hypothesis, the analysis did not show a significant difference between the number of cases observed and the number of cases expected. The usefulness of this study was limited because its results were based on assumptions.

### 8.2.3 Wording in the SPC

Since the last review of PROTOPIC by the Transparency Committee, the SPC has been changed several times (European decisions of 21 February 2011, 23 June 2011, 29 June 2012 and 30 August 2012), in particular in order to mention additional information on the use of tacrolimus in children, precautions for use in the event of abnormalities in the skin barrier and the occurrence of cutaneous T-cell lymphomas (see changes in the appendix).

In the section Special warnings and precautions for use, it is stated that, in the long-term (that is in a few years' time), any risk of skin infections or cancers linked to local immunosuppression is unknown. In transplanted patients, prolonged systemic exposure to potent immunosuppression, following systemic administration of calcineurin inhibitors, is linked to an increased risk of developing lymphomas and malignant skin lesions. In patients treated with tacrolimus ointment, cases of malignant conditions, including cutaneous lymphomas (cutaneous T-cell lymphomas to be precise) and other types of lymphomas and skin cancers were reported.

## 08.3 Data on use/prescription

According to IMS data (moving annual total as at November 2012), 43,000 prescriptions for PROTOPIC were issued, of which 24,000 (56.6%) were for 0.01% ointment and 19,000 (43.4%) were for 0.03% ointment.

PROTOPIC 0.1% was prescribed in adolescents (from the age of 16) and in adults in 97.5% of cases, and in 2.5% of cases in children from 5 to 15 years of age, under conditions that did not comply with the Marketing Authorisation.

The main diagnoses for which PROTOPIC 0.1% was prescribed were dermatitis (39.7%), atopic dermatitis (20.6%), vitiligo (15.2%), lichen simplex chronicus or prurigo (6.6%) and seborrhoeic dermatitis (5.5%).

PROTOPIC 0.03% was prescribed in 97.9% of cases in children from the age of 5 and in adults, and in 2.1% of cases in children under 2 years of age, under conditions that did not comply with the Marketing Authorisation.

The main diagnoses for which PROTOPIC 0.03% was prescribed were dermatitis (37.9%), atopic dermatitis (36.1%), lichen simplex chronicus or prurigo (6.7%), vitiligo (6.2%).

To recap, a post-marketing study was requested by the Transparency Committee in its Opinion of 11 September 2002, the main objective being to describe the use of PROTOPIC in outpatients and to assess the impact of treatment on the affected population. The company conducted a prospective, observational study on 565 patients recently treated with PROTOPIC. This study was assessed by the Transparency Committee in 2011 (see its Opinion of 5 October 2011).



The results obtained in these real clinical practice conditions confirmed the efficacy of PROTOPIC on the lesions of atopic dermatitis and in terms of quality of life. However, relapses were frequent, appearing rapidly after the discontinuation of treatment. In addition, these results showed that PROTOPIC was prescribed in severe forms in only 47.3% of cases, in patients who had not failed under treatment with topical corticosteroids 21.9% of cases, or in combination with a topical corticosteroid in 27.2% of cases. Moreover, the 0.1% dose, restricted to adults, was prescribed in 22.3% of children, 65% of whom were 12 years of age and over.

## 08.4 Summary & discussion

The company did not conduct new clinical studies to assess the efficacy of tacrolimus in the treatment of atopic dermatitis and no relevant clinical data have been published since the previous opinions from the Committee (28 May 2008 and 5 October 2011).

Three published observational studies assessed the carcinogenic risk on large cohorts of patients.

An initial study showed a higher incidence of cancer, particularly cutaneous T-cell lymphomas, melanomas and skin cancers in patients suffering from atopic dermatitis. However, this study did not analyse the potential link to exposure to tacrolimus.

In a second retrospective study in 953,064 patients treated for atopic dermatitis or eczema, 4% of whom (n = 38,682) had been exposed to a topical calcineurin inhibitor, the risk of T-cell lymphoma for patients exposed to topical tacrolimus was more significant compared to unexposed patients: HR = 3.1 (95% CI = [1.4; 6.9]; p = 0.005).

In a third study on a cohort of 1,252,300 patients, including 31% children, the risk of lymphomas was assessed during treatment with tacrolimus, pimecrolimus or corticosteroids. The results showed an increased risk of lymphoma for the three treatments in comparison to the general population, but not compared to the population of patients suffering from atopic dermatitis and untreated patients with a RR of 1.97 (95% CI = [0.87; 4.50]) for tacrolimus.

However, it should be noted that the follow-up of patients in these studies was short (2.6 years maximum) and there was difficulty in interpreting these results due to confounding factors (duration of inflammatory pathologies associated with atopic dermatitis, treatment with other immunosuppressants, other suspected co prescribed drug, pre-existing tumours).

Pharmacovigilance data did not establish causal link between the development of cancers and exposure to tacrolimus, due to the additional issues of insufficient long-term data and confounding factors.

The SPCs have been updated, in particular to include references to additional information on the use of tacrolimus in children (not recommended in children under the age of 2), the precautions for use in the event of abnormalities in the skin barrier and the occurrence of cutaneous T-cell lymphomas.

Despite the recommendations in the SPC, PROTOPIC 0.03% is still prescribed in children under the age of 2 as seen in the prescription data (IMS, 2012: 2.1% of PROTOPIC 0.03% prescriptions) and PROTOPIC 0.1% prescriptions have also been prescribed in children and adolescents from 5 to 15 years of age (2.5%).

## 08.5 Planned studies

### **APPLES study**

This observational study envisages the monitoring over 10 years of 8,000 children under 16 years of age at the initiation of tacrolimus treatment for atopic dermatitis. Inclusions ended in August 2012, that is a total of 8,037 children including 209 in France. The final report of the study is expected in late 2022. At the time of submission of this dossier by the company, the average duration of exposure was 2.25 patient years. Long-term data are still insufficient for any conclusions to be reached regarding any carcinogenic effects of tacrolimus, particularly in terms of skin cancers.

### **JOELLE study (PROTOPIC JOint European Longitudinal Lymphoma and skin cancer Evaluation)**

Given the protopathic bias<sup>7</sup> and the methodological limits of published studies on the risk of lymphoma associated with the use of topical calcineurin inhibitors, the company has suggested, in the context of the "Follow-Up Measures" in its Marketing Authorisation, implementing a study with the objective of having both sufficient sample size and follow-up duration to assess, in children and adults, the incidence of skin cancers and lymphomas in patients treated with tacrolimus, pimecrolimus and topical corticosteroids, or not treated with one or other of these drugs.

The study population will be constituted from European databases that provide access to information on prescriptions and reimbursement: the General Practice Research Database (GPRD) in the United Kingdom, the PHARMO Linkage System in the Netherlands, and the national Danish and Swedish databases.

The study will be conducted in two phases: the first will run from the date when tacrolimus and pimecrolimus became available to each study population until 31 December 2011; the second will consist of a follow-up of populations from 1 January 2012 until a date which will be set according to the usage rates of the drugs and estimated statistical power, as a function of the results of phase 1.

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Protopathic bias is frequently advanced in the assessment of the safety of PROTOPIC with regard to the occurrence of cutaneous T-cell lymphoma, given the difficulty of diagnosing it as recognised by the French National Committee for Pharmacovigilance (CNPV) in its minutes of the meeting of November 2011: *"The difficulty of differential diagnosis between atopic dermatitis and cutaneous lymphoma was confirmed by clinicians. It is even more difficult to establish it in the initial form of the disease. The implementation of systematic biopsies before the start of treatment is not possible in practice."* (AFSSAPS. Commission Nationale de Pharmacovigilance [French National Committee for Pharmacovigilance]. Compte rendu de la réunion du 22 novembre 2011 [Minutes of the meeting of 22 November 2011]. Available at: <http://www.ansm.sante.fr>).

As a result, tacrolimus treatment might be initiated on the basis of an erroneous diagnosis of atopic dermatitis whereas it is actually an initial form of cutaneous T-cell lymphoma, the manifestations of which are similar.

## 09 THERAPEUTIC USE

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PROTOPIC retains a role as second-line treatment in the treatment of flares in severe atopic dermatitis in adults and adolescents (16 years old and over) who are inadequately responsive to or intolerant of conventional therapies, such as topical corticosteroids; However, the risk of skin cancer is not being ruled out and is still being assessed under the European risk management plan.

In adults, tacrolimus can be useful in severe forms which are refractory to topical corticosteroids and which are not very widespread, mainly on the face and neck.

In children (2 years old and over), because of the limitations highlighted in previous assessments:

- low frequency of treatment failures with topical corticosteroids,
  - local reactions (irritations, burns),
  - the ointment formulation of tacrolimus which makes dressing children difficult,
- and because of the new safety data:

- observation of skin cancer cases with tacrolimus ointment even though a formal link with tacrolimus has not been clearly established,
- increased risk of systemic absorption in the event of damage to the skin barrier or occlusion, and the detection of a risk of skin cancer in patients subject to lengthy exposure to tacrolimus administered systemically,

and in light of non-severe nature of the disease, PROTOPIC no longer has any role in the therapeutic strategy for atopic dermatitis in children, whatever its severity.

PROTOPIC has no place in maintenance treatment to prevent recurrences of atopic dermatitis.

## 010 TRANSPARENCY COMMITTEE CONCLUSIONS

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

### 010.1 Actual benefit

#### ➤ Treatment of flares:

Atopic dermatitis is a chronic, inflammatory, itchy, relapsing skin disorder, with the patient experiencing flares. It is often associated with infectious complications. Severe recalcitrant forms are incapacitating and the impact on quality of life is considerable.

These proprietary medicinal products fall under the category of symptomatic treatment.

In view of the similar efficacy of tacrolimus and that of potent topical corticosteroids after the failure of other conventional therapies including topical corticosteroids, as well as the potentially associated risk of skin cancer, particularly in children, the efficacy/safety ratio is low.

In adults, these proprietary medicinal products are second-line treatments indicated in severe forms for patients who are intolerant of or inadequately responsive to conventional therapies, such as topical corticosteroids. In adults, tacrolimus can be useful in severe forms which are resistant to topical corticosteroids and which are not very widespread, mainly on the face and neck. In children, because of the limitations highlighted in previous assessments:

- low frequency of treatment failures with topical corticosteroids,
  - local reactions (irritations, burns),
  - the ointment formulation of tacrolimus, which makes dressing children difficult,
- and because of the new safety data:
- observation of skin cancer cases with tacrolimus ointment even though a formal link with tacrolimus has not been clearly established,
  - increased risk of systemic absorption in the event of damage to the skin barrier or occlusion, and the detection of a risk of skin cancer in patients subject to lengthy exposure to tacrolimus administered systemically,
- and in light of the non-severe nature of the disease, PROTOPIC no longer has any role in the therapeutic therapy for atopic dermatitis in children, whatever its severity.

Alternative treatments are available. If there is no response to topical corticosteroids, the cause should be determined, such as poor patient compliance, incorrect application or corticophobia. Therapeutic education can then allow the successful pursuit of topical corticosteroid treatment. Studies have shown that a potent topical corticosteroid used after patients have failed to respond to or been intolerant of conventional therapies was as effective as tacrolimus in children. In adults, the percentage of responders was also considerable albeit lower than that observed with tacrolimus. Cyclosporine and phototherapy can also be used as second-line treatments in severe and widespread forms in adults.

□ Public health benefit:

Atopic dermatitis is a common, generally benign condition. Moderate to severe relapsing forms may assume a certain functional severity and damage the quality of life of patients who are afflicted. The burden of this disease is considered low from the public health point of view.

The management of atopic dermatitis is not a public health need. However, there is a therapeutic need.

Data on the conditions of use of PROTOPIC show that compliance with the recommendations is not optimum. In the absence of new efficacy data, the impact of PROTOPIC on the morbidity and quality of life of treated patients is not quantifiable. A negative impact cannot be ruled out, notably because of the potential risk of cancer. PROTOPIC treatment does not have an impact on the organisation of care. PROTOPIC does not therefore provide a response an identified therapeutic need.

Overall, no public health benefit is rendered by PROTOPIC in the treatment of flares of moderate to severe atopic dermatitis in adults and children.

**In children (2 years old and over):**

**In view these points, the Committee considers that the actual benefit of PROTOPIC 0.03% ointment is insufficient in the treatment of severe atopic dermatitis in children (2 years old and over) who did not respond adequately to conventional therapies, such as topical corticosteroids. It remains insufficient in moderate forms.**

**In adults and adolescents (16 years old and over):**

**In view of these points, the Committee considers that the actual benefit of PROTOPIC 0.03% and 0.1% ointments is low in the treatment of severe atopic dermatitis in adults and children (16 years old and over) who are inadequately responsive to conventional therapies, such as topical corticosteroids. It remains insufficient in moderate forms.**

➤ **Maintenance treatment:**

**In the absence of new data, the actual benefit remains insufficient in this indication.**

**The Committee does not recommend the continued registration of PROTOPIC on the list of medicines reimbursed by National Health Insurance schemes and on the list of medicines approved for hospital use in the treatment of flares of severe atopic dermatitis in children (2**

years old and over) who are inadequately responsive to conventional therapies, such as topical corticosteroids..

The Committee recommends the registration of PROTOPIC on the list of medicines reimbursed by National Health Insurance schemes and on the list of medicines approved for hospital use in the treatment of flares of severe atopic dermatitis in adults and adolescents (16 years old and over) who are not adequately responsive to conventional therapies, such as topical corticosteroids.

□ **Proposed reimbursement rate: 15%**

In addition, the Committee does not recommend the registration of PROTOPIC on the list of medicines reimbursable by National Health Insurance schemes and on the list of medicines approved for hospital use in:

- the treatment of flares of moderate atopic dermatitis in children (2 years old and over) who have not responded adequately to conventional therapies, such as topical corticosteroids;
- the treatment of flares of moderate atopic dermatitis in adults and adolescents (16 years old and over) who are not adequately responsive to or are intolerant of conventional therapies, such as topical corticosteroids;
- the maintenance treatment of moderate to severe atopic dermatitis in order to prevent flares and prolong flare-free intervals in patients experiencing a high frequency of disease exacerbations (i.e. occurring 4 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).

## 011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

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### ► Packaging

Appropriate for the prescription conditions as regards the indication, dosage and treatment duration.

### ► Specific requests inherent to reimbursement

Exception drug status

### ► Requests for data

The Committee requests to be kept informed of the progress of the APPLES and JOELLE studies and the results of the interim analyses planned in the protocol, pending definitive results.

## APPENDIX: Changes made to the SPC since the previous renewal of inclusion

Section concerned	EC Decision of 07 April 2009	EC Decision of 21 February 2011
<p>4.4 Special warnings and precautions for use</p> <p>The following sentence has been changed.</p>	<p>The effect of treatment with PROTOPIC ointment on the developing immune system of children, particularly in young children, has not yet been established, and this should be taken into account when prescribing in this age group (see section 4.1).</p>	<p>The effect of treatment with PROTOPIC ointment on the developing immune system of children aged below 2 years has not been established (see section 4.1).</p>
<p>4.5 Interactions</p> <p>The following sentence has been changed.</p>	<p>The potential interactions between vaccines and the application of PROTOPIC ointment have not been assessed. Because of the potential risk of vaccine failure, it should be carried out before the start of treatment, or after a period of 14 days following the last application of PROTOPIC. In the case of live attenuated vaccines, this period will be extended to 28 days, or the use of other types of vaccines should be envisaged.</p>	<p><i>Paediatric population</i> An interaction study with protein-conjugated vaccine against <i>Neisseria meningitidis</i> serogroup C has been investigated in children aged 2-11 years. No effect on the immediate response to vaccination, the generation of immune memory, or humoral and cell-mediated immunity has been observed (see section 5.1).</p>
<p>4.6 Fertility, pregnancy and lactation</p> <p>The following sentence has been added.</p>		<p><i>Fertility</i> There are no fertility data available.</p>
<p>4.8 Undesirable effects</p> <p>The following sentence has been added.</p>		<p><i>Paediatric population</i> The frequency, type and severity of adverse reactions in children are similar to those reported in adults.</p>
<p>5.1 Pharmacodynamic properties</p> <p>The following sentence has been added.</p>		<p>A seven-month, double-blind, randomised, parallel group study of paediatric patients (2-11 years) with moderate to severe atopic dermatitis was performed. In one arm patients received PROTOPIC 0.03% ointment (n=121) twice a day for 3 weeks and thereafter once a day until clearance. In the comparator arm patients received 1% hydrocortisone acetate ointment (HA) for the head and neck and 0.1% hydrocortisone butyrate ointment for the trunk and limbs (n=111) twice a day for 2 weeks and subsequently HA twice a day to all affected areas. During this period all patients and control subjects (n=44) received a primary immunisation and a rechallenge with a protein-conjugate vaccine against <i>Neisseria</i></p>

		<p><i>meningitidis</i> serogroup C.</p> <p>The primary endpoint of this study was the response rate to vaccination, defined as the percentage of patients with a serum bactericidal antibody (SBA) titre <math>\geq 8</math> at the week 5 visit. Analysis of the response rate at week 5 showed equivalence between the treatment groups (hydrocortisone 98.3%, tacrolimus ointment 95.4%; 7-11 years: 100% in both arms). The results in the control group were similar.</p> <p>The primary response to vaccination was not affected.</p>
5.2 Pharmacokinetic properties	The following sentence has been added.	<p><i>Paediatric population</i></p> <p>The pharmacokinetics of tacrolimus after topical application are similar to those reported in adults, with minimal systemic exposure and no evidence of accumulation (see above).</p>

- **Decision of the European Commission of 23 June 2011:**

The main changes made since the previous decision are indicated in the table below.

Section concerned	EC Decision of 21 February 2011	EC Decision of 23 June 2011
<p>4.4 Special warnings and precautions for use</p> <p>The following sentence has been changed.</p> <p>The following sentence has been changed.</p> <p>(It should be noted that the section 4.8 Undesirable effects already included</p>	<p>Treatment with PROTOPIC may be associated with an increased risk of herpes viral infections (herpes simplex dermatitis [eczema herpeticum], herpes simplex [cold sores], Kaposi's varicelliform eruption).</p> <p>The use of PROTOPIC ointment in patients with a congenital skin barrier defect, such as Netherton's syndrome, is not recommended. These skin conditions may permanently increase systemic absorption of tacrolimus. The safety of PROTOPIC ointment has not been established in patients with generalized erythroderma.</p>	<p>Treatment with PROTOPIC may be associated with an increased risk of folliculitis and herpes viral infections (herpes simplex dermatitis [eczema herpeticum], herpes simplex [cold sores], Kaposi's varicelliform eruption) (see section 4.8).</p> <p>The use of tacrolimus ointment is not recommended in patients with a skin barrier defect, such as Netherton's syndrome, lamellar ichthyosis, generalized erythroderma or cutaneous Graft Versus Host Disease. These skin conditions may increase the systemic absorption of tacrolimus. The oral use of tacrolimus is also not recommended to treat these skin conditions. Post-marketing cases of increased tacrolimus blood levels have been reported with these disorders.</p>

folliculitis)		
<p>4.8 Undesirable effects</p> <p>Presentation of the undesirable effects in the form of a table with subsequent adverse effects added in the table, of unknown frequency (cannot be evaluated from the available data)</p>		<p>Application site oedema</p> <p>Elevation of blood tacrolimus levels (see section 4.4)</p>

Section concerned	EC Decision of 23 June 2011	Favourable Opinion of 29 June 2012
<p>4.4 Special warnings and precautions for use</p> <p>Sentences have been moved to improve understanding.</p> <p>The following sentence has been added.</p>		<p>Caution should be exercised if applying PROTOPIC to patients with extensive skin involvement over an extended period of time, especially in children (see section 4.2). Patients, and particularly paediatric patients, should be evaluated continuously during treatment with PROTOPIC with respect to the response to treatment and the continuing need for treatment. After 12 months this evaluation should include the suspension of PROTOPIC treatment in paediatric patients (see section 4.2).</p>



Section concerned	Favourable Opinion of 29 June 2012	EC Decision of 30 August 2012
<p>4.4 Special warnings and precautions for use</p> <p>The following sentence has been changed.</p>	<p>In patients using tacrolimus ointment, cases of malignancies, including cutaneous and other types of lymphoma, and skin cancers have been reported (see section 4.8).</p>	<p>In patients using tacrolimus ointment, cases of malignancies, including cutaneous (i.e. cutaneous T Cell lymphomas) and other types of lymphoma, and skin cancers have been reported (see section 4.8).</p>
<p>4.8 Undesirable effects</p> <p>The following sentence has been changed.</p>	<p><u>Post-marketing</u> Cases of malignancies, including cutaneous and other types of lymphoma, and skin cancers, have been reported in patients using tacrolimus ointment (see section 4.4).</p>	<p><u>Post-marketing</u> Cases of malignancies, including cutaneous (i.e. cutaneous T cell lymphomas) and other types of lymphoma, and skin cancers, have been reported in patients using tacrolimus ointment (see section 4.4).</p>