TRANSPARENCY COMMITTEE

OPINION

18 March 2009

TOCTINO 10 mg, soft capsule
Box of 30 (CIP: 389 600-8)
TOCTINO 30 mg, soft capsule
Box of 30 (CIP: 389 602-0)

Applicant: BASILEA

Alitretinoin
ATC code: D11AX19

List I

Prescribed only by or under the supervision of dermatologists or doctors with a full understanding of the risks associated with the use of systemic retinoids and the monitoring this requires.

Medicine requiring special monitoring during treatment.

For women of childbearing age (see Pregnancy Prevention Programme):

- The patient's consent to care and contraception must be obtained prior to prescription
- Prescriptions are limited to one month of treatment, and a new prescription is required for continuation
- Dispensing must occur within a maximum of 7 days of the prescription
- Dispensing may take place only after a check has been carried out to ensure that the following mandatory information appears on the prescription:
  - For the first prescription:
    Signature of the care and contraception agreement
    Use of an effective method of contraception for at least one month
    Evaluation of the patient's level of understanding
    Date of the latest pregnancy test
  - For subsequent prescriptions:
    Continuation of effective contraception
    Evaluation of the patient's level of understanding
    Date of the latest pregnancy test

Date of the decentralised Marketing Authorisation: 16 October 2008

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

Medical, Economic and Public Health Assessment Division

---

1 because of the teratogenic effects of TOCTINO, the Committee recommends that it should be prescribed only by dermatologists
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Alitretinoin

1.2. Novel aspects
First oral treatment for adults with severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids.

1.3. Indication
"TOCTINO is indicated for use in adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids. Patients in whom the eczema has predominantly hyperkeratotic features are more likely to respond to treatment than those in whom the eczema predominantly presents as pompholyx (See section 5.1 “Pharmacodynamic properties”)."

1.4. Dosage
"Prescriptions of TOCTINO for women of childbearing potential should be limited to 30 days of treatment and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing of TOCTINO should occur on the same day. Dispensing of TOCTINO should occur within a maximum of 7 days of the prescription.
The recommended dose range for TOCTINO is 10 mg-30 mg once daily.
The recommended start dose for TOCTINO is 30 mg once daily. A dose reduction to 10 mg once daily may be considered in patients with unacceptable adverse reactions to the higher dose. In studies investigating 10 mg and 30 mg daily doses, both doses resulted in clearing of the disease. The 30 mg dose provided a more rapid response and a higher response rate. The 10 mg daily dose was associated with fewer adverse events (see section 4.4 “Special warnings and precautions for use” and section 5.1 “Pharmacodynamic Properties”).
A treatment course of TOCTINO may be given for 12 to 24 weeks depending on response. Discontinuation of therapy should be considered for patients who still have severe disease after the initial 12 weeks of treatment. In the event of relapse, patients may benefit from further treatment courses of TOCTINO.
The capsules should be taken with a meal once daily.
TOCTINO should not be prescribed if the patient's eczema can be adequately controlled by standard measures, including skin protection, avoidance of allergens and irritants, and treatment with potent topical corticosteroids.
Children
TOCTINO is not recommended for use in patients under 18 years of age."
2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

D : Dermatologicals
D11 : Other dermatological preparations
D11A : Other dermatological preparations
D11AX : Other dermatologicals
D11AX19 : Alitretinoin

2.2. Medicines in the same therapeutic category

No systemic retinoid is indicated in eczema.

2.3. Medicines with a similar therapeutic aim

No other medicinal product is indicated in the treatment of severe chronic hand eczema after failure to respond to potent topical corticosteroids.

Some medicinal products are indicated in atopic dermatitis, including as second-line therapy in patients who do not respond adequately to or who do not tolerate conventional treatments such as topical corticosteroids. These are immunosuppressants:

- Oral: Ciclosporin: NEORAL, SANDIMMUM (adults)
- Topical:
  - Tacrolimus: PROTOPIC 0.03% (adults and children) and 0.1% (adults)
  - Pimecrolimus: ELIDEL 1% (not included on the list of medicines reimbursed by National Health Insurance and approved for hospital use)

Phototherapy and PUVA therapy can be used, and some medicinal products (retinoids, calcipotriol, immunosuppressants) are used on an off-label basis.
The efficacy and tolerance of TOCTINO were analysed in the course of 3 clinical studies:

- A double-blind, randomised study comparing alitretinoin versus placebo in 1,032 patients with severe chronic hand eczema (BAP00089)
- An extension phase of study BAP00089 in 360 patients assigned to two cohorts (BAP00091):
  - Cohort A: Randomised, double-blind study comparing alitretinoin versus placebo in patients who had initially responded to alitretinoin or placebo but then relapsed during the follow-up period of study BAP00089
  - Cohort B: Non-comparative phase which evaluated the efficacy of alitretinoin 30 mg in patients who initially failed to respond to alitretinoin or placebo
- A non-comparative study in 249 patients, intended to supplement the tolerance data (BAP00626)

The dossier also includes one dose-finding (10, 20 or 40 mg) study (BAP00003) and a pharmacokinetics study (10 or 30 mg) which will not be elaborated upon in this opinion.

### 3.1. Efficacy

**Methodology common to both studies**

The inclusion criteria included:

- Patients aged between 18 and 75 years of age with severe chronic hand eczema according to the Physician Global Assessment\(^2\) (PGA)

- All types of chronic hand eczema were concerned, including hyperkeratosis, vesicular eczema (dyshidrosis - pompholyx) and fingertip dermatitis

- The eczema had to have persisted for more than 6 months and be refractory* to hygiene measures (including the use of emollients and barrier protection) and despite the elimination of environmental irritants and allergens

- Women had to be postmenopausal, have had a hysterectomy or be using two methods of contraception

*: The eczema was considered refractory if there was no response, an inadequate or transient response or poor tolerance of at least 8 weeks of treatment with the most potent topical corticosteroids, including re-treatments (in 4-week periods according to the SPCs) in the course of the previous 6 months.

The exclusion criteria included:

- patients whose disease was controlled by hygiene measures and topical corticosteroid treatment, but in whom a relapse had occurred after discontinuation of treatment

- systemic corticosteroids, retinoids or immunosuppressants in the 4 weeks prior to the start of the study (the use of inhaled steroids was permitted)

- UVB or PUVA phototherapy in the 4 weeks prior to the start of the study

- allergic contact dermatitis demonstrated by a positive patch test and patients for whom allergens could not be removed from the environment

- psoriasis (including palmoplantar psoriasis)

- atopic dermatitis "requiring medical treatment"

\(^2\) PGA score measured using a 5-point assessment scale: hands clear, almost clear, mild, moderate and severe lesions (cf. Annex 1)
- acute episodes of dyshidrosis (pompholyx) or contact dermatitis
- infection of the hands caused by a bacterial, fungal or viral agent
- other dermatological condition likely to interfere with the implementation of the study or with its results
- other serious condition, including chronic heart failure, chronic kidney failure, hypothyroidism, chronic biliary insufficiency, immunodepression and uncontrolled diabetes
- score of >20 on the CES-D scale or history of major psychiatric disorders (major depression, generalised anxiety syndrome, bipolar I and II disorder or schizophrenia)

**Study BAP00089**

Randomised, double-blind study versus placebo which evaluated the efficacy and tolerance of alitretinoin (TOCTINO) after 12 or 24 weeks of treatment in 1,032 patients with severe chronic hand eczema who had no response or a transient response (initial improvement and worsening of the condition despite continuation of treatment) to potent topical corticosteroids or who did not tolerate these topical corticosteroids.

**Treatment:**
- Placebo (n = 205)
- Alitretinoin 10 mg (n = 418)
- Alitretinoin 30 mg (n = 409)

The treatments were administered once daily initially for 12 weeks and then continued if necessary for up to 24 weeks if the symptoms had not cleared / almost cleared after 12 weeks. No dose reduction was permitted. After the end of treatment (12 or 24 weeks), the patients were followed up for a period of 24 weeks.

Note: It would have been desirable to have access to a study comparing alitretinoin with an active treatment (potent topical corticosteroid, phototherapy) and/or evaluating the efficacy of alitretinoin in combination.

**Primary efficacy endpoint:** PGA response rate (hands clear or almost clear) at the end of the treatment (cf. Annex 1).

**The secondary endpoints included:** Modified Total Lesion Syndrome Score\(^4\) (mTLSS) response rate (cf. Annex 2).

**Results:**

- **Initial patient characteristics:**
The most represented form of severe chronic hand eczema was hyperkeratosis (cf. Table 1). The time since diagnosis was around 9 years (whatever the treatment group) and the time since the start of the current episode was around 29 months in the two alitretinoin groups and 32 months in the placebo group.

---


\(^4\) Score ranging between 0 and 21 evaluating 7 symptoms on a 4-point scale
Table 1: Initial characteristics of patients with severe chronic hand eczema
(study BAP00089)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Alitretinoin 10 mg</th>
<th>Alitretinoin 30 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 205</td>
<td>N = 418</td>
<td>N = 409</td>
</tr>
<tr>
<td><strong>Average age (years)</strong></td>
<td>47.9</td>
<td>47.3</td>
<td>48.5</td>
</tr>
<tr>
<td><strong>Gender</strong> (% women / % men)</td>
<td>41 / 59</td>
<td>43.1 / 56.9</td>
<td>45.5 / 54.5</td>
</tr>
<tr>
<td><strong>Type of lesion: N (%) of patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>170 (82.9%)</td>
<td>362 (86.6%)</td>
<td>349 (85.3%)</td>
</tr>
<tr>
<td>Dyshidrosis</td>
<td>55 (26.8%)</td>
<td>111 (26.6%)</td>
<td>111 (27.1%)</td>
</tr>
<tr>
<td>Fingertip dermatitis</td>
<td>101 (49.3%)</td>
<td>180 (43.1%)</td>
<td>196 (47.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>29 (14.1%)</td>
<td>61 (14.6%)</td>
<td>55 (13.4%)</td>
</tr>
<tr>
<td><strong>History of previous treatments: % of patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory to previous treatments</td>
<td>100</td>
<td>100</td>
<td>99.8</td>
</tr>
<tr>
<td>Transient response</td>
<td>59</td>
<td>53.1</td>
<td>48.7</td>
</tr>
<tr>
<td>No response</td>
<td>39.5</td>
<td>43.3</td>
<td>48.2</td>
</tr>
<tr>
<td>Did not tolerate the previous treatment</td>
<td>1</td>
<td>1.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Treated with potent topical corticosteroids</td>
<td>96.6</td>
<td>96.7</td>
<td>97.1</td>
</tr>
</tbody>
</table>

The previous treatments included notably corticosteroids (99.3%), emollients (37%), topical immunosuppressants (15%), PUVA therapy (5.1%), immunosuppressants (2.8%), systemic retinoids (2.5%) and topical retinoids (2%).

- **Study drop-outs:**
  In the placebo group, 33.2% of the patients (68/205) dropped out of the study, mainly owing to an inadequate response to treatment (20.5%).
  In the alitretinoin 10 mg group, 23.7% of the patients (99/418) dropped out of the study (24 patients because of adverse events and 35 owing to an inadequate response).
  In the alitretinoin 30 mg group, 25.9% of the patients (106/409) dropped out of the study (39 patients because of adverse events and 32 owing to an inadequate response).

- **Primary efficacy endpoint (ITT):**
  After 12 and 24 weeks, the PGA response rate observed in the alitretinoin 10 and 30 mg groups was higher than that observed in the placebo group. The patients in whom the eczema had predominantly hyperkeratotic features (sub-group analysis) responded better to the treatment (cf. Table 2).
Table 2: PGA response / non-response rate (study BAP00089)

<table>
<thead>
<tr>
<th></th>
<th>Placebo N = 205</th>
<th>Alitretinoin 10 mg N = 418</th>
<th>Alitretinoin 30 mg N = 409</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PGA response rate after 12 or 24 weeks (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (hands clear and almost clear)</td>
<td>16.6% [11.8; 22.4]</td>
<td>27.5%* [23.3; 32.1]</td>
<td>47.7%** [42.7; 52.6]</td>
</tr>
<tr>
<td>Hands clear (disappearance of symptoms)</td>
<td>2.9%</td>
<td>9.3%</td>
<td>22.0%</td>
</tr>
<tr>
<td>Hands almost clear (symptoms almost disappeared)</td>
<td>13.7%</td>
<td>18.2%</td>
<td>25.7%</td>
</tr>
<tr>
<td><strong>PGA non-response rate after 12 or 24 weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild lesions²</td>
<td>19.5%</td>
<td>22.0%</td>
<td>14.4%</td>
</tr>
<tr>
<td>Moderate lesions³</td>
<td>30.2%</td>
<td>29.9%</td>
<td>21.5%</td>
</tr>
<tr>
<td>Severe lesions</td>
<td>33.2%</td>
<td>18.9%</td>
<td>16.7%</td>
</tr>
<tr>
<td><strong>PGA response rate according to type of lesion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkeratosis (64%)</td>
<td>12%</td>
<td>30%</td>
<td>54%</td>
</tr>
<tr>
<td>Hyperkeratosis / dyshidrosis (22%)</td>
<td>12%</td>
<td>23%</td>
<td>33%</td>
</tr>
<tr>
<td>Dyshidrosis (5%)</td>
<td>30%</td>
<td>22%</td>
<td>33%</td>
</tr>
</tbody>
</table>

(* p=0.004, **p<0.001 versus placebo)

➢ Secondary endpoint (ITT): mTLSS

After 24 weeks, the average reduction in the mTLSS compared with the baseline value (15 on a scale of 0 to 21) was around 37% in the placebo group, 51% in the alitretinoin 10 mg group and 61% in the alitretinoin 30 mg group.

The percentage of patients who relapsed during the 24-week follow-up period after discontinuation of treatment, i.e. those with a mTLSS of >75% of the baseline value prior to treatment, was 44.1% in the placebo group, 29.6% in the alitretinoin 10 mg group and 37.4% in the alitretinoin 30 mg group.

Note: The Committee regrets that the duration of remission after discontinuation of treatment has not been evaluated.

² the patients with mild or moderate lesions were included in Cohort B of study BAP00091
Study BAP00091: Extension phase of study BAP00089

Study conducted in 360 patients with severe chronic hand eczema unresponsive to potent topical corticosteroids and previously treated with alitretinoin or placebo during study BAP00089. These patients were assigned to two cohorts:

- **Cohort A (n = 117)**
  Randomised, double-blind study of alitretinoin versus placebo in patients who initially responded (hands clear or almost clear according to the PGA) and who relapsed (mTLSS ≥ 75% of the baseline value) during the 24-week follow-up period of study BAP00089.

**Treatment:**
The patients were randomised to different groups depending on the treatment received during study BAP00089.

- Patients initially treated with placebo:
  - placebo (n = 13)
- Patients initially treated with alitretinoin 10 mg:
  - alitretinoin 10 mg (n = 21)
  - placebo (n = 10)
- Patients initially treated with alitretinoin 30 mg:
  - alitretinoin 30 mg (n = 49)
  - placebo (n = 24)

The treatments were administered once daily for 12-24 weeks (depending on the response to treatment).

**Primary efficacy endpoint:** PGA response rate (hands clear, almost clear) at the end of the treatment (12 or 24 weeks).

**Results:**

- **Study drop-outs**
  Of the 117 patients included in Cohort A, 24 patients (20.5%) dropped out of the study (14 in the placebo group, 4 in the alitretinoin 10 mg group and 6 in the alitretinoin 30 mg group). The main reason leading to discontinuation of the study was lack of efficacy for 8 out of 14 patients in the placebo group and the occurrence of adverse events for 3 out of 10 patients in the alitretinoin groups.

- **Results (ITT):**
  - Of the 13 patients in the placebo group who initially responded to placebo in study BAP00089, 9 responded a second time (PGA)
  - Of the patients who relapsed after initial treatment with alitretinoin 10 mg, the difference between the response rates among the patients treated with alitretinoin 10 mg and those receiving placebo was not statistically significant
  - Of the 195 patients who responded to treatment with alitretinoin 30 mg during study BAP00089, 73 patients (37.4%) relapsed (49 randomised to the alitretinoin 30 mg group and 24 in the placebo group)

After a second period of treatment, around 80% (39/49) of the patients re-treated with alitretinoin 30 mg responded to treatment a second time compared with 8% (2/24) in the placebo group (statistically significant difference) (cf. Table 3).
Table 3: PGA response rate (study BAP00091, Cohort A)

<table>
<thead>
<tr>
<th>Initial treatment (study BAP00089)</th>
<th>Placebo</th>
<th>Alitretinoin 10 mg</th>
<th>Alitretinoin 30 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (study BAP00091)</td>
<td>N = 13</td>
<td>N = 21</td>
<td>N = 49</td>
</tr>
<tr>
<td>Total (hands clear and almost clear)</td>
<td>69.2% (9/13)</td>
<td>47.6%* (10/21)</td>
<td>79.6%** (39/49)</td>
</tr>
<tr>
<td>Hands clear (disappearance of symptoms)</td>
<td>23.1% (3/13)</td>
<td>9.5% (2/21)</td>
<td>42.9% (21/49)</td>
</tr>
<tr>
<td>Hands almost clear (symptoms almost disappeared)</td>
<td>46.2% (6/13)</td>
<td>38.1% (8/21)</td>
<td>36.7% (18/49)</td>
</tr>
<tr>
<td>Placebo</td>
<td>N = 10</td>
<td>N = 49</td>
<td>N = 24</td>
</tr>
<tr>
<td>10% (1/10)</td>
<td>10% (1/10)</td>
<td>79.6%** (39/49)</td>
<td>8.3% (2/24)</td>
</tr>
<tr>
<td>8.3% (2/24)</td>
<td>8.3% (2/24)</td>
<td>8.3% (2/24)</td>
<td>8.3% (2/24)</td>
</tr>
</tbody>
</table>

(* NS, ** p<0.001 versus placebo)

Note: The significance of these results is limited insofar as this was an extension study which selected the relapsed patients from study BAP00089 and the randomisation for which depended on the initial treatment.

**Cohort B (n = 243)**

Non-comparative phase which evaluated the efficacy of alitretinoin 30 mg in patients who did not initially respond (mild or moderate hand lesions) to alitretinoin or placebo.

**Treatment:**
The patients who did not respond all received alitretinoin 30 mg.

**Primary efficacy endpoint:** PGA response rate (hands clear or almost clear) at the end of the treatment.

**Results:**

- **Study drop-outs**

Of the 243 patients in Cohort B, 48 patients (19.8%) dropped out of the study, 13 (5.3%) owing to an inadequate response to treatment and 11 (4.5%) because of adverse events.

- **Results (ITT):**

Overall, all the treatments combined, 47.3% of the patients who did not respond and who had mild or moderate hand lesions during study BAP00089 responded to re-treatment with alitretinoin 30 mg.

Continuing treatment with alitretinoin 30 mg for 24 weeks or increasing the dose from 10 to 30 mg produced a response to treatment in 39.1% of the patients who did not respond to initial treatment with 30 mg alitretinoin and in 50.4% of the patients who did not respond to initial treatment with 10 mg alitretinoin (cf. Table 4).
Table 4: PGA response rate (study BAP00091, Cohort B)

<table>
<thead>
<tr>
<th>Initial treatment (study BAP00089)</th>
<th>Placebo</th>
<th>Alitretinoin 10 mg</th>
<th>Alitretinoin 30 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (study BAP00091) N = 243</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alitretinoin 30 mg N = 57</td>
<td>50.9%</td>
<td>50.4%</td>
<td>39.1%</td>
</tr>
<tr>
<td>Hands clear (disappearance of symptoms)</td>
<td>31.6%</td>
<td>21.4%</td>
<td>18.8%</td>
</tr>
<tr>
<td>Hands almost clear (symptoms almost disappeared)</td>
<td>31.6%</td>
<td>29.1%</td>
<td>20.3%</td>
</tr>
</tbody>
</table>

Study BAP00626:
Non-comparative study conducted in 249 adults with severe chronic hand eczema, refractory to topical corticosteroids, the main objective of which was to evaluate the tolerance of alitretinoin 30 mg. The evaluation of efficacy was a secondary objective. Efficacy and tolerance were evaluated every 4 weeks for a period of 24 weeks and then for 4 weeks after the end of the treatment.

Treatment:
The patients received alitretinoin at a dosage of 30 mg per day. Discontinuation of treatment or a dose reduction of 10 mg alitretinoin per day were permitted temporarily depending on the occurrence of adverse events.

The demographic and clinical characteristics of the patients (91.2% had hyperkeratosis) were similar to those observed in the previous studies. The time (mean interval) since diagnosis was around 9 years and the time since the start of the current episode was around 21 months.

Of the 249 patients, 59 (23.7%) dropped out of the study prematurely, 21 because of adverse events and 17 owing to an inadequate response.

Results for the PGA response rate (secondary endpoint):
The response rate (lesions disappeared or almost disappeared) was 46.6% (including 25.9% of patients without any hand lesions). These results were similar to those obtained in the alitretinoin group at the same dosage (30 mg/day) in study BAP00089.
3.2. Adverse effects

**Study BAP00089**

The percentage of patients who experienced an adverse event was around 50% in the placebo group (101/203), 52% in the alitretinoin 10 mg group (216/418) and 59% in the alitretinoin 30 mg group (244/410).

The percentage of patients who experienced a serious adverse event was 1.5% in the placebo group (3/203), 4.1% in the alitretinoin 10 mg group (17/418) and 2.7% in the alitretinoin 30 mg group (11/410).

One patient in the alitretinoin 10 mg group died of myocardial infarction which was considered not attributable to the treatment.

The adverse events observed most frequently in the patients treated with alitretinoin were headache, dry skin and dry lips.

Increases in cholesterol, triglyceride and creatine kinase concentrations and decreases in TSH and free T4 levels were observed. ECG monitoring did not reveal any clinically relevant changes.

**Study BAP00091**

The percentage of patients who experienced an adverse event was around 45% (26% with placebo and between 43 and 39% with alitretinoin).

Serious adverse events were reported only in patients treated with alitretinoin (10 patients, i.e. 2.8%). Two (4%) of these serious events (worsening of an abdominal aortic aneurysm and exacerbation of coronary artery disease) were linked to treatment with alitretinoin 30 mg in Cohort A.

One patient in the alitretinoin 10 mg group died of myocardial infarction which was considered not attributable to treatment.

Seventeen patients (4.7%) dropped out of the study because of an adverse event (mainly headache and dizziness).

The adverse events reported most frequently (≥1%) were infections (rhinopharyngitis, bronchitis), dermatological conditions (erythema, dry skin), headache and gastrointestinal disturbances.

Most of the adverse events were of mild-to-moderate severity.

**Study BAP00626**

An adverse event was report in around 50% of the patients (135/248).

The adverse events observed most frequently in the patients treated with alitretinoin were headache, vasomotor flushes, rhinopharyngitis and dry skin and mucous membranes.

Serious adverse events were reported in 3 patients (1.2%), including one case of angioneurotic oedema in a 22-year-old woman which was considered to be treatment-related. Increases in cholesterol and triglyceride levels and decreases in TSH levels were observed.

The dose was reduced from 30 mg to 10 mg on one or more occasions in 41 patients (16%) because of clinical (33 patients) or biochemical (5 patients) adverse events or rapid improvement in symptoms (3 patients).
**Teratogenic risk**
Because of the teratogenic risk associated with retinoids, a pregnancy prevention plan has been put in place including measures and tools to provide better supervision of prescribing and dispensing and to inform the patients and professionals concerned.

### 3.3. Conclusion
The 3 aforementioned studies were conducted in adults with chronic hand eczema which was severe according to the PGA and which had failed to respond to potent topical corticosteroids.

After 12 or 24 weeks of treatment, alitretinoin (10 or 30 mg) was more effective than placebo, with a statistically significant difference, in terms of the proportion of patients who responded to treatment (hands clear or almost clear according to the PGA). The response rate was 16.6% (including 2.9% with clear hands) with placebo, 27.5% (including 9.3% with clear hands) with alitretinoin 10 mg and 47.7% (including 22% with clear hands) with alitretinoin 30 mg. The patients in whom the eczema had predominantly hyperkeratotic features (sub-group analysis) responded better to the treatment.

It would have been desirable to have access to a study comparing alitretinoin with an active treatment (potent topical corticosteroid, phototherapy) and/or evaluating the efficacy of alitretinoin in combination.

The adverse events reported most frequently (>1 /100) during studies were headache, vasomotor flushes and changes in biochemical parameters. Most of these adverse events were of mild-to-moderate severity. Because alitretinoin is teratogenic, a pregnancy prevention plan has been put in place.
4.1. Actual benefit

Chronic hand eczema is a common, recurrent inflammatory skin condition which has a relapsing-remitting course and which has psycho-social consequences. Its causes are various and it takes different forms.

These medicinal products are intended as symptomatic therapy.

In terms of public health, although it is a fairly common condition, severe chronic hand eczema represents a low burden.

A therapeutic need exists to improve the management of chronic hand eczema, notably the severe forms which are refractory to existing treatments but which do not constitute a public health priority.

In view of the data from the available clinical trials, it is expected that this medicinal product will have a moderate impact in terms of morbidity. However, the data are insufficient to evaluate the impact of the medicinal product TOCTINO on quality of life and on the social and professional consequences of eczema for these patients.

In addition, the transferability of the results to clinical practice is not guaranteed insofar as, notably:

- the profile of the patients treated in real practice is likely to differ from that of the patients from the studies (where the exclusion criteria were numerous)
- uncertainty exists regarding the consequences of the tolerance profile with regard to the maintenance of treatment

Furthermore, a risk of misuse (use without effective contraception), and therefore a teratogenic risk, cannot be ruled out in women of childbearing age.

Consequently, in view of these different factors, the expected public health benefit of the medicinal product TOCTINO cannot be evaluated.

The efficacy/adverse effects ratio is modest because of the teratogenic nature of alitretinoin.

This is a second-line therapy restricted to the treatment of severe chronic hand eczema in adults in the absence of a response to potent topical corticosteroids. Patients in whom the eczema had predominantly hyperkeratotic features seemed to respond better to the treatment.

Few treatment alternatives are available.

The actual benefit of TOCTINO 10 and 30 mg, soft capsules, is substantial.
4.2. Improvement in actual benefit (IAB)
In the absence of a comparison with an active treatment, TOCTINO does not provide an improvement in actual benefit by comparison with the therapeutic measures used in the current management of severe chronic hand eczema which does not respond to treatment with potent topical corticosteroids (IAB V).

TOCTINO constitutes an additional therapeutic measure which is a useful component of treatment.

4.3. Therapeutic use
There are no official recommendations in France concerning the treatment of chronic hand eczema.
Treatment is essentially local, using potent topical corticosteroids combined with emollients. It is usually intermittent and long-term.
If allergens and irritants are found to be implicated in this eczema, elimination and management of the environment are carried out where possible.
If potent topical corticosteroids prove ineffective or are poorly tolerated or contra-indicated, few alternatives are available (phototherapy or PUVA therapy). Some medicinal products are used on an off-label basis (retinoids, calcipotriol, immunosuppressants).
Systemic antihistamines may be used occasionally in order to reduce itching. The use of antibiotics is justified only in cases of proven secondary infection.
In adult patients with severe chronic hand eczema which does not respond to properly managed treatment with potent topical corticosteroids, treatment with alitretinoin may be considered as a second-line therapy subject to strict compliance with the prescribing and dispensing conditions.

4.4. Target population
The target population for TOCTINO is represented by adult patients with severe chronic hand eczema which does not respond to treatment with potent topical corticosteroids.
In the absence of a French epidemiological study, the target population is estimated on the basis of the following data\(^6\) and estimates:
- a hand eczema prevalence of around 10% in the general population
- chronic and severe forms representing 5%-7% of patients with hand eczema
- although the percentage of adults who do not respond to potent topical corticosteroids cannot be specified owing to a lack of epidemiological data, the proportion of patients with severe chronic hand eczema which is refractory to topical treatments can be estimated at between 2 and 4% of patients with hand eczema
- 78% of the population was over 18 years of age on 1 January 2008\(^7\)

On this basis, around 6.4 million people are likely to have hand eczema in France. Of these patients, around 333,000-450,000 people are likely to have a chronic and severe form.
Around 130,000-255,000 patients with severe chronic hand eczema are likely to be resistant to topical treatments.
In relation to adults over 18 years of age, the target population can be estimated to be 100,000-200,000 patients.

### 4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for use by hospitals and various public services in the indication and at the dosages in the Marketing Authorisation.

Because of the teratogenic effects of TOCTINO, the Committee recommends that it should be prescribed only by dermatologists.

The Committee wishes to have access to the results of a long-term follow-up study of patients with severe chronic hand eczema treated with TOCTINO. The objectives of this study are to document, under real treatment conditions:

- the characteristics of the patients treated: gender, age, socio-professional group, case history, whether or not the cause of the eczema was occupational, type of eczema, severity (mTLSS and PGA scores), associated sites, frequency and course of exacerbations in relation to the treatments, previous treatments including phototherapy, hygiene practices

- the conditions of use of this medicinal product: dosage, frequency and duration of treatment, associated treatments, hygiene practices

- the conditions for monitoring the treatment, particularly with regard to effective contraception in women of childbearing age

- the impact of the treatment on morbidity, quality of life and social and/or professional impact of these lesions

- the frequency of treatment discontinuations and reasons for this. The impact of adverse effects on the maintenance of treatment

Should the studies which are planned or under way, notably within the scope of the European Risk Management Plan, fail to answer all the questions posed by the Committee, a specific study must be conducted.

The duration of the study must be justified by an independent scientific committee.

#### 4.5.1 Packaging: Appropriate for the prescription conditions

#### 4.5.2 Reimbursement rate: 65%
ANNEX 1: Physician Global Assessment (PGA): Description of the degrees of severity of chronic hand eczema

The PGA criteria are based on all the clinical signs and symptoms associated with severe chronic hand eczema

<table>
<thead>
<tr>
<th>Severity criteria</th>
<th>Symptoms</th>
<th>Intensity</th>
<th>Area involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Erythema, scaling, hyperkeratosis, lichenification</td>
<td>At least one sign/symptom: moderate or severe</td>
<td>&gt;30% of the affected hand surface</td>
<td></td>
</tr>
<tr>
<td>Vesiculation, oedema, fissures, pruritus, pain</td>
<td>At least one sign/symptom: severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate Erythema, scaling, hyperkeratosis, lichenification</td>
<td>At least one sign/symptom: mild or moderate</td>
<td>10-30% of the affected hand surface</td>
<td></td>
</tr>
<tr>
<td>Vesiculation, oedema, fissures, pruritus, pain</td>
<td>At least one sign/symptom: moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild Erythema, scaling, hyperkeratosis, lichenification</td>
<td>At least one sign/symptom: mild</td>
<td>&lt;10% of the affected hand surface</td>
<td></td>
</tr>
<tr>
<td>Vesiculation, oedema, fissures, pruritus, pain</td>
<td>At least one sign/symptom: mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almost clear Erythema, scaling, hyperkeratosis, lichenification</td>
<td>At least one sign/symptom: mild</td>
<td>&lt;10% of the affected hand surface</td>
<td></td>
</tr>
<tr>
<td>Vesiculation, oedema, fissures, pruritus, pain</td>
<td>Absent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear Erythema, scaling, hyperkeratosis, lichenification</td>
<td>Absent</td>
<td>No surface affected</td>
<td></td>
</tr>
<tr>
<td>Vesiculation, oedema, fissures, pruritus, pain</td>
<td>Absent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ANNEX 2: mTLSS *(modified Total Lesion Syndrome Score)*

4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe) which is used to evaluate 7 signs or symptoms of severe chronic hand eczema. All the signs and symptoms contributing to the overall evaluation of the PGA are included in the mTLSS. The mTLSS corresponds to the sum of 7 subscores (between 0 and 21). The change in mTLSS is the percentage difference between the scores recorded at the start and end of treatment.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Degree of severity and description of lesions</th>
</tr>
</thead>
</table>
| Erythema                        | 0 = absent  
1 = faint erythema  
2 = prominent redness  
3 = deep intense red colour                                      |
| Scaling                         | 0 = absent  
1 = slight flaking over limited areas, mostly fine scales  
2 = flaking over widespread area(s), coarser scales  
3 = desquamation covering >30% of the hand with thick, coarse scales |
| Lichenification / hyperkeratosis | 0 = absent  
1 = mild thickening with exaggerated skin lines over limited area(s)  
2 = palpable thickening over widespread area(s)  
3 = prominent thickening over widespread area(s)                              |
| Vesiculation                    | 0 = absent  
1 = scattered vesicles affecting up to 10% of hand without erosion  
2 = scattered or clustered vesicles affecting up to 30% of hand, without visible erosion or excoriation  
3 = high density of vesicles extending over large area(s) or with erosion or excoriation |
| Oedema                          | 0 = absent  
1 = dermal swelling over <10% of hand  
2 = definite dermal swelling over more than 10% of hand  
3 = dermal swelling with skin induration over widespread area(s)             |
| Fissures                        | 0 = absent  
1 = cracked skin affecting a small area of the hand  
2 = cracked skin affecting multiple areas of the hand and causing pain  
3 = one or more deep fissures and causing bleeding or severe pain                |
| Pruritus / pain                 | 0 = absent  
1 = occasional, slight discomfort a few times a day  
2 = intermittent, causing discomfort frequently during the day  
3 = persistent or interfering with sleep                                           |