STELARA 45 mg, solution for injection
B/1 x 0.5 ml vial (CIP code: 392 586-2)

JANSSEN-CILAG

Ustekinumab
ATC code: L04AC05

List I
Initial six-month hospital prescription.
Initial prescription and renewal reserved for specialists in dermatology or internal medicine.

Date of Marketing Authorisation: 16 January 2009 (centralised procedure)

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital and various public services use.
1.1. Active ingredient
Ustekinumab

1.2. Background
Ustekinumab is a human IgG1κ monoclonal antibody which belongs to a new class of treatments, interleukin IL12 and IL23 inhibitors.

1.3. Indication
“STELARA is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA.”

1.4. Dosage
“STELARA is intended for use under the guidance and supervision of doctors experienced in the diagnosis and treatment of psoriasis.

Dosage
The recommended dose of STELARA is an initial dose of 45 mg administered subcutaneously in week 0, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Consideration should be given to discontinuing treatment in patients who show no response up to 28 weeks of treatment.

- **Patients with body weight > 100 kg**
  For patients with body weight > 100 kg the initial dose is 90 mg administered subcutaneously in week 0, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter. The 45 mg dose has also been shown to be efficacious in patients with a body weight > 100 kg. However, 90 mg resulted in greater efficacy in these patients.

  - **Elderly patients (≥ 65 years)**
    No dose adjustment is needed for elderly patients.

  - **Children and adolescents (< 18 years)**
    STELARA is not recommended for use in children and adolescents below age 18 due to a lack of data on tolerance and efficacy.

  - **Renal and hepatic impairment**
    STELARA has not been studied in these patient populations. No dose recommendations can be made.

Method of administration
STELARA is for subcutaneous injection. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

After proper training in subcutaneous injection technique, patients may self-inject STELARA if their doctor determines that it is appropriate. However, the doctor should ensure appropriate follow-up of patients. Patients should be instructed to inject the full amount of STELARA according to the directions given in the package leaflet. Comprehensive instructions for administration are given in the package leaflet.”
2.1. ATC Classification (2009)

L : Antineoplastic and immunomodulating agents
L04 : Immunosuppressants
L04A : Immunosuppressants
L04AC : Interleukin inhibitors
L04AC05 : Ustekinumab

2.2. Medicines in the same therapeutic category

2.2.1. Strictly comparable medicines in the same therapeutic category

STELARA is the only medicine in its class (interleukin inhibitors) indicated for the treatment of psoriasis.

2.2.2. Not strictly comparable medicines in the same therapeutic category

These consist of other immunosuppressant biotherapies indicated in the treatment of moderate to severe adult plaque psoriasis in cases of failure or contraindication to, or intolerance to, other systemic treatments, including ciclosporin, methotrexate or PUVA treatment:
- ENBREL (etanercept), soluble anti-TNF-alpha receptor,
- REMICADE (infliximab), anti-TNF-alpha chimeric monoclonal antibody
- HUMIRA (adalimumab), anti-TNF-alpha human monoclonal antibody
- RAPTIVA (efalizumab), humanised monoclonal antibody targeting the surface protein of T lymphocytes (LFA-1) (marketing authorisation suspended).

2.3. Medicines in the same therapeutic category

Local treatments: keratolytics (including salicylic acid), powerful dermocorticoids, vitamin D analogues and vitamin A derivatives.

Systemic treatments: SORIATANE (acitretin), NECORAL and SANDIMMUN (ciclosporin), NOVATREX 2.5 mg tablet, METHOTREXATE BELLON, METOJECT (methotrexate)

Other treatments: UVA photochemotherapy (in combination with photosensitising agents), UVB phototherapy.
3 ANALYSIS OF AVAILABLE DATA

The pharmaceutical company has submitted three phase III studies to support its request:
- 2 studies versus placebo (PHOENIX 1 and PHOENIX 2 studies)
- 1 study versus etanercept (ACCEPT study)

3.1. Efficacy

3.1.1. Studies versus placebo

PHOENIX 1 study

Randomised, double-blind study carried out to assess the efficacy and tolerance of ustekinumab versus placebo in patients suffering from moderate to severe plaque psoriasis. The secondary endpoints were assessment of maintenance of response to treatment with ustekinumab and the impact of ustekinumab on patients’ quality of life.

Main inclusion criteria:
- patients aged 18 or over,
- plaque psoriasis present for at least six months (patients with associated psoriatic rheumatism were eligible),
- lesions covering at least 10% of the body surface,
- PASI score\(^1\) ≥ 12,
- suitable for phototherapy or systemic treatment (either never having undergone treatment or with a history of previous treatments),

N.B.: the patients taking part in this study might not have had past treatment with phototherapy or systemic treatments, which does not correspond to the indication specified in the marketing authorisation. However, most of the patients who were randomised had undergone systemic treatment (the same comment applies to the PHOENIX 2 study, see the results).

Main exclusion criteria:
- other forms of psoriasis (erythrodermic, pustular, guttate, etc.),
- drug-induced psoriasis,
- prior use of a drug specifically targeting interleukin 12 or interleukin 23,
- phototherapy or systemic treatment in the four weeks prior to the study which might affect psoriasis and the PASI score grading,
- topical treatments in the two weeks prior to the study which might affect psoriasis and the PASI score grading,
- treatment with a biological drug or experimental drug in the three months prior to the study.

Treatments:
- group 1: ustekinumab 45 mg administered by subcutaneous injection,
- group 2: ustekinumab 90 mg administered by subcutaneous injection,
- group 3: placebo administered by subcutaneous injection.

\(^1\) PASI (Psoriasis Area Severity Index): composite index taking account of values relating to erythema, induration, desquamation and the amount of body surface area affected. It ranges from 0 (no psoriasis) to 72 (maximum severity). However, this score, which is a combination measurement of erythema, induration and area, is valid only if at least 3% of the body surface area is affected. A PASI response of 75 indicates a reduction of at least 75% compared to the baseline PASI score. A PASI response of 100 indicates complete remission.
Injections given in weeks 0 and 4, and every 12 weeks thereafter (every 8 weeks in phases 3 and 4 of the study for some of the partial-responder patients, i.e. those with $50 \leq \text{PASI} \leq 75$, depending on their randomisation).

**Study design:**

This study was divided into four phases:

- **PHASE 1** (weeks 0 to 11): comparative, randomised, ustekinumab 45 mg (group 1) or ustekinumab 90 mg (group 2) versus placebo (group 3). Injections given in weeks 0 and 4.

- **PHASE 2** (weeks 12 to 27): non comparative, all patients were given ustekinumab. The patients in the ustekinumab 45 mg or 90 mg groups (group 1 and 2) continued their treatment (injections in weeks 16 and 28). The patients in the placebo group (group 3) were given ustekinumab injections (45 mg or 90 mg) in weeks 12, 16 and 28.

- **PHASE 3** (weeks 28 to 39): continuation of treatments and adjustment of the interval between injections for partial-responder patients (dose regimen of injections every 8 weeks, not included in the marketing authorisation).

- **PHASE 4** (weeks 40 to 264): long-term open-label phase. Patients in groups 1 and 2 were randomised to continue treatment or to receive the placebo. Patients in group 3 continued to receive the placebo. Patients on placebo who relapsed during this phase were put back on ustekinumab.

**Primary efficacy endpoint:** percentage of responders with a PASI 75 (reduction of at least 75% in the PASI score) after 12 weeks treatment (phase 1).

**Main secondary endpoints:**

- After 12 weeks of treatment (phase 1):
  - responders according to the PGA scale\(^2\) (score 0 “cleared” or 1 “almost cleared”);
  - changes in the quality of life score (DLQI score\(^3\));

- In phase 4 (randomised, starting in week 40), length of PASI 75 maintenance for patients who continued on ustekinumab compared to those transferred to placebo.

**Results:**

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\(^2\) The PGA (Physician global assessment) score represents the physician’s overall assessment of the severity of the condition and has six severity grades. It provides information about the overall status of psoriasis at a given time: lesions are classified on the basis of their duration and extent and the presence of erythema. A higher grade indicates more severe psoriasis. The severity levels in the PGA are:

- 0 = “clear”
- 1 = “minimal”
- 2 = “slight”
- 3 = “moderate”
- 4 = “pronounced”
- 5 = “severe”.

\(^3\) DLQI (Dermatology Life Quality Index): a quality of life score that assesses the impact of the dermatological condition on the patient’s psychosocial, social and sexual functions and on his/her ability to undertake everyday activities. The DLQI questionnaire contains ten questions relating to the impact of the skin condition on six areas: symptoms and self-perception (questions 1 and 2), everyday activities (questions 3 and 4), leisure (questions 5 and 6), work and study (question 7), social interactions and sex life (questions 8 and 9) and treatment (question 10). Patients have four or five possible responses to each question. These are then converted into a figure of 0 to 3. The final score is the sum of the figures attributed to each question. The final score ranges from 0 (no negative impact on quality of life) to 30 (extremely severe negative impact on quality of life). A reduction of 5 or more points in the DLQI is the minimum change recognised as having a relevant clinical impact.
A total of 766 patients were randomised: 255 were allocated to the ustekinumab 45 mg group, 256 to the ustekinumab 90 mg group and 255 to the placebo group.

The characteristics of patients in all groups were similar. Approximately a quarter of the body surface was affected, and the average length of time that patients had been suffering from psoriasis was 20 years. Around 44% of patients had a PGA score of 4 or 5 (pronounced to severe). 95% of patients had previously undergone topical treatments, phototherapy in 65% of cases, conventional systemic treatment in 55% of cases and biotherapies in 50% of cases.

Results for the primary endpoint

After 12 weeks of treatment, the proportion of patients with a PASI 75 response was higher in the ustekinumab 45 mg (67.1%) and ustekinumab 90 mg (66.4%) groups than in the placebo group (3.1%) (p<0.001).

Results for the secondary endpoints

After 12 weeks of treatment, the percentage of patients with a PGA score of 0 or 1 was higher in the ustekinumab 45 and 90 mg groups than in the placebo group (see table 1). The reduction in the DLQI quality of life score was higher in the ustekinumab 45 and 90 mg groups than in the placebo group (see table 1). The differences observed versus placebo were above the threshold regarded as clinically relevant (reduction in the DLQI score of ≥ 5).

Table 1: Results for the main secondary endpoints

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Ustekinumab 45 mg N = 255</th>
<th>Ustekinumab 90 mg N = 256</th>
<th>Placebo N = 255</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGA (% of patients with a score of 0 or 1) in week 12</td>
<td>60.4*</td>
<td>61.7*</td>
<td>3.9</td>
</tr>
<tr>
<td>Baseline DLQI</td>
<td>11.1± 7.1</td>
<td>11.6 ± 6.9</td>
<td>11.8 ± 7.4</td>
</tr>
<tr>
<td>Average change in the DLQI score at week 12</td>
<td>-8.0 ± 6.9**</td>
<td>-8.7 ± 6.5**</td>
<td>-0.6 ± 6.0</td>
</tr>
</tbody>
</table>

* : p < 0.0001 versus placebo
** : p < 0.001 versus placebo

Results for patients treated with ustekinumab for 76 weeks

The median time to loss of PASI 75 response among patients who stopped taking ustekinumab and who were randomised to receive placebo (phase 4) was 15 weeks. No rebound phenomenon was observed.

The PASI 75 response remained stable in percentage terms for 76 weeks among patients who continued to receive ustekinumab until week 76 (n = 77 for ustekinumab 45 mg and n = 82 for ustekinumab 90 mg), as did the percentage of PGA responders (score of 0 or 1).
**PHOENIX 2 study**

Randomised, double-blind study carried out to assess the efficacy and tolerance of ustekinumab versus placebo in patients suffering from moderate to severe plaque psoriasis. The impact of ustekinumab on quality of life was a secondary objective.

**Inclusion and exclusion criteria:** the same as those for the PHOENIX 1 study.

**Treatments:**
- group 1: ustekinumab 45 mg administered by subcutaneous injection,
- group 2: ustekinumab 90 mg administered by subcutaneous injection,
- group 3: placebo administered by subcutaneous injection.

Injections given in weeks 0 and 4, and every 12 weeks thereafter (every 8 weeks in phases 3 and 4 of the study for some of the partial-responder patients, i.e. those with $50 \leq \text{PASI} \leq 75$, depending on their randomisation).

**Study design:**
This study was divided into four phases:

- **PHASE 1** (weeks 0 to 11): comparative, randomised, double-blind, ustekinumab 45 mg (group 1) or ustekinumab 90 mg (group 2) versus placebo (group 3). Injections given in weeks 0 and 4.
- **PHASE 2** (weeks 12 to 27): non comparative, all patients were given ustekinumab. The patients in the ustekinumab 45 mg or 90 mg groups (group 1 and 2) continued their treatment (injections in weeks 16 and 28). The patients in the placebo group (group 3) were given ustekinumab injections (45 mg or 90 mg) in weeks 12, 16 and 28.
- **PHASE 3** (weeks 28 to 51): continuation of treatments and adjustment of the interval between injections for partial-responder patients (dose regimen not included in the marketing authorisation).
- **PHASE 4** (weeks 52 to 239): long-term open-label continuation of the various treatments.

**Primary efficacy endpoint:** percentage of responsive patients with a PASI 75 (reduction of at least 75% in the PASI score) after 12 weeks treatment (phase 1).

**Main secondary endpoints:**
After 12 weeks of treatment (phase 1):
- responders according to the PGA scale (score 0 “cleared” or 1 “almost cleared”);
- changes in the quality of life score (DLQI score).

**Results:**
A total of 1,230 patients were randomised: 409 were allocated to the ustekinumab 45 mg group, 411 to the ustekinumab 90 mg group and 410 to the placebo group. The characteristics of the patients were broadly the same in each group. Approximately a quarter of the body surface was affected, and the average length of time that patients had been suffering from psoriasis was 20 years. Around 40% of patients had a PGA score of 4 or 5 (pronounced to severe). 95% of patients had previously undergone topical treatments, phototherapy in 67% of cases, conventional systemic treatment in 55% of cases and biotherapies in 38% of cases.
Results for the primary endpoint

After 12 weeks of treatment (phase 1), the proportion of patients with a PASI 75 response was higher in the ustekinumab 45 mg (66.7%) and ustekinumab 90 mg (75.7%) groups than in the placebo group (3.7%) (p<0.001).

Results for the secondary endpoints

After 12 weeks of treatment (phase 1), the percentage of patients with a PGA score of 0 or 1 was higher in the ustekinumab 45 and 90 mg groups than in the placebo group (see table 2). The reduction in the DLQI quality of life score was higher in the ustekinumab 45 and 90 mg groups than in the placebo group (see table 2). The differences observed versus placebo were above the threshold regarded as clinically relevant (reduction in the DLQI score of ≥ 5).

Table 2: Results for the main secondary endpoints

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Ustekinumab 45 mg N = 409</th>
<th>Ustekinumab 90 mg N = 411</th>
<th>Placebo N = 410</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGA (% of patients with a score of 0 or 1) in week 12</td>
<td>68.0*</td>
<td>73.5*</td>
<td>4.9</td>
</tr>
<tr>
<td>Baseline DLQI</td>
<td>12.2 ± 7.1</td>
<td>12.6 ± 7.3</td>
<td>12.3 ± 6.9</td>
</tr>
<tr>
<td>Average change in the DLQI score in week 12</td>
<td>-9.3 ± 7.1**</td>
<td>-10.0 ± 6.7**</td>
<td>-0.5 ± 5.7</td>
</tr>
</tbody>
</table>

*: p < 0.0001 versus placebo
**: p < 0.001 versus placebo

Results for patients treated with ustekinumab for 52 weeks

The PASI 75 response remained stable in percentage terms for 52 weeks among patients who continued to receive ustekinumab until week 52 (n = 251 for ustekinumab 45 mg and n = 286 for ustekinumab 90 mg), as did the percentage of PGA responders (score of 0 or 1) and the improvement in quality of life (DLQI).

3.1.2. Studies versus active comparator (etanercept)

ACCEPT study

Randomised, single-blind study (investigator-blinded) with the primary aim of comparing the efficacy and tolerance of ustekinumab to the efficacy and tolerance of etanercept in patients suffering from moderate to severe plaque psoriasis.

Main inclusion criteria:
- patients aged 18 or over,
- diagnosed with psoriasis for six months or more,
- lesions covering at least 10% of the body surface,
- PASI score ≥ 12 and PGA score ≥ 3,
- suitable for phototherapy or systemic treatment,
- lack of response to, contraindication or intolerance to other systemic treatments such as ciclosporin, methotrexate or PUVA treatment.

Main exclusion criteria:
- other forms of psoriasis (erythrodermic, pustular, guttate, etc.),
- drug-induced psoriasis,
- prior use of a drug specifically targeting interleukin 12 or interleukin 23,
- phototherapy or systemic treatment in the four weeks prior to the study which might affect psoriasis and the PASI score grading,
- topical treatments in the two weeks prior to the study which might affect psoriasis and the PASI score grading,
- biotherapy in the three months prior to the study or treatment with an experimental drug in the four weeks prior to the study,
- prior treatment with etanercept.

Treatments:
- group 1: ustekinumab 45 mg administered as subcutaneous injections in weeks 0 and 4, and every 12 weeks thereafter,
- group 2: ustekinumab 90 mg administered as subcutaneous injections in weeks 0 and 4, and every 12 weeks thereafter,
- group 3: etanercept 50 mg administered as subcutaneous injections twice a week (maximum recommended dose specified in the marketing authorisation).

Study design:
The study was divided into three phases:

PHASE 1 (weeks 0 to 11): comparative, single-blind (investigator-blinded), randomised, ustekinumab 45 mg (group 1) or ustekinumab 90 mg (group 2) versus etanercept (group 3)

PHASE 2 (weeks 12 to 39): non-comparative, discontinuation of treatment for responsive patients and continuation or change of treatment for non-responsive patients.
- Patients who were non-responsive (PGA ≥ 3) at week 12 continued with their treatment (group 1 and 2) or changed treatment (group 3) to ustekinumab 90 mg in weeks 16, 20 and 32.
- Patients who were responsive (PGA ≤ 2) discontinued treatment until they relapsed (PGA ≥ 3). They were then put back on ustekinumab treatment (2 subcutaneous injections at a four-week interval, and then every 12 weeks):
  ▪ group 1: ustekinumab 45 mg
  ▪ group 2: ustekinumab 90 mg
  ▪ group 3: ustekinumab 90 mg.

PHASE 3 (weeks 40 to 63): long-term treatment phase.

Primary efficacy endpoint: percentage of responsive patients with a PASI 75 (reduction of at least 75% in the PASI score) after 12 weeks treatment.

Main secondary endpoints:
After 12 weeks of treatment:
- percentage of responsive patients according to the PGA scale (score 0 “cleared” or 1 “almost cleared”);
- percentage of responsive patients with a PASI 90 score;
- percentage of responsive patients with a PASI 75 score in the “combined” group (patients with body weight ≤ 100 kg receiving ustekinumab 45 mg and patients with body weight ≥ 100 kg receiving ustekinumab 90 mg, i.e. patients taking the dose recommended in the marketing authorisation) compared to that observed among patients receiving etanercept 50 mg.

Results:
A total of 903 patients were randomised: 209 were allocated to the ustekinumab 45 mg group, 347 to the ustekinumab 90 mg group and 347 to the etanercept group.
The characteristics of the patients were broadly the same in each group. Approximately a quarter of the body surface was affected, and the average length of time that patients had been suffering from psoriasis was 18 years. Around 44% of patients had a PGA score of 4 or 5 (pronounced to severe). 97% of patients had previously undergone topical treatments, 28% phototherapy, 39% methotrexate, 14% ciclosporin and 22% biotherapy.
Results for the primary endpoint

After 12 weeks of treatment (phase 1), the proportion of patients with a PASI 75 response was higher in the ustekinumab 45 mg and ustekinumab 90 mg groups than in the etanercept group (see table 3).

Table 3: PASI 75 responses after 12 weeks of treatment

<table>
<thead>
<tr>
<th>PASI 75 responders in week 12</th>
<th>Ustekinumab 45 mg N = 209</th>
<th>Ustekinumab 90 mg N = 347</th>
<th>Etanercept 50 mg N = 347</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (%)</td>
<td>67.5</td>
<td>73.8</td>
<td>56.8</td>
</tr>
<tr>
<td>95% CI of the difference between ustekinumab and etanercept</td>
<td>[2.4 ; 19.0]</td>
<td>[10.0 ; 24.0]</td>
<td>-</td>
</tr>
<tr>
<td>p</td>
<td>0.012</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
</tbody>
</table>

Results for the secondary endpoints

After 12 weeks of treatment (phase 1), the percentages of patients with a PGA response (score of 0 or 1) and a PASI 90 response were higher in the ustekinumab 45 and 90 mg groups than in the etanercept group (see table 4).

Table 4: Results for the main secondary endpoints

<table>
<thead>
<tr>
<th>% of patients with a PGA response (score 0 or 1) in week 12</th>
<th>Ustekinumab 45 mg N = 209</th>
<th>Ustekinumab 90 mg N = 347</th>
<th>Etanercept 50 mg N = 347</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>65.1*</td>
<td>70.6*</td>
<td>49.0</td>
</tr>
<tr>
<td>Difference between ustekinumab and etanercept, 95% CI</td>
<td>16.1 [7.6 ; 24.4]</td>
<td>21.6 [14.4 ; 28.6]</td>
<td>-</td>
</tr>
<tr>
<td>% of PASI 90 responses in week 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>36.4*</td>
<td>44.7*</td>
<td>23.1</td>
</tr>
<tr>
<td>Difference between ustekinumab and etanercept</td>
<td>13.3</td>
<td>21.6</td>
<td>-</td>
</tr>
<tr>
<td>RR and 95% CI</td>
<td>1.58 [1.18 ; 2.12]</td>
<td>1.94 [1.55 ; 2.43]</td>
<td>-</td>
</tr>
</tbody>
</table>

*: p < 0.001 versus etanercept

In the “combined” group (patients receiving ustekinumab at the correct dosage specified in the marketing authorisation for their body weight), the percentage of patients with a PASI 75 response was higher than in the etanercept group (69.3% versus 56.8%, p = 0.002).

Results in week 24 for patients treated with ustekinumab or etanercept for 12 weeks

Among responsive patients who stopped treatment after 12 weeks of treatment in phase 1 (i.e. two ustekinumab injections in weeks 0 and 4), the percentage of patients maintaining a PGA score of 0 or 1 until week 24 was higher in the ustekinumab 45 and 90 mg groups than in the etanercept group (see table 5).
Table 5: Percentage of patients with a PGA response in weeks 16, 20 and 24

<table>
<thead>
<tr>
<th>Number of randomised patients with a PGA response in week 12</th>
<th>Ustekinumab 45 mg</th>
<th>Ustekinumab 90 mg</th>
<th>Etanercept 50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with a PGA response in week 16 (95% CI)</td>
<td>89.3 [84.8 ; 93.9]</td>
<td>92.6 [89.7 ; 95.5]</td>
<td>71.9 [66.7 ; 77.2]</td>
</tr>
<tr>
<td>% with a PGA response in week 20 (95% CI)</td>
<td>79.2 [73.2 ; 85.2]</td>
<td>82.6 [78.4 ; 86.8]</td>
<td>45.5 [39.6 ; 51.4]</td>
</tr>
<tr>
<td>% with a PGA response in week 24 (95% CI)</td>
<td>59.9 [52.7 ; 67.1]</td>
<td>71.6 [66.6 ; 76.6]</td>
<td>36.7 [31.0 ; 42.4]</td>
</tr>
</tbody>
</table>

3.2. Adverse effects

3.2.1. Tolerance data versus placebo

Most common adverse events:

The tolerance data available was obtained from the following studies: PHOENIX 1 (results after 76 weeks), PHOENIX 2 (results after 52 weeks) and ACCEPT (results after 24 weeks). The PHOENIX 1 and 2 studies are continuing in order to provide tolerance data after 5 years.

The adverse events most commonly reported by patients receiving ustekinumab 45 or 90 mg in the first 12 weeks of treatment in the PHOENIX 1 study were upper respiratory tract infections (6.3-7.1%), rhinopharyngitis (8.2-10.2%), arthralgia (2.4-2.7%) and headaches (5.1-5.5%). These adverse events were also observed in the placebo group at the same rates, except for headaches which were half as common.

This tolerance profile remained unchanged when treatment continued for 76 weeks.

A similar finding was observed in the PHOENIX 2 study, where skin erythema at the injection site was also frequently seen (1.5% of patients). This was seen in only 0.2% of patients on placebo.

In both studies, most of the adverse events reported were not very severe, not serious and did not require treatment to be discontinued.

The other adverse events which occurred frequently (≥1/100 to <1/10) and which are mentioned in the SPC are: depression, dizziness, headache, pharyngo-laryngeal pain, nasal congestion, diarrhoea, pruritus, back pain, myalgia and fatigue.

Serious adverse events:

The frequency of infections in the comparative phases of the studies was similar to that seen in the placebo group: 1.39 cases of infection per patient-year with ustekinumab and 1.21 per patient-year with placebo. The frequency of serious infections was 0.01 per patient-year (5 serious infections in 407 patient-years) with ustekinumab and 0.02 per patient-year (3 serious infections in 177 patient-years) in the placebo group.

In the comparative and non-comparative phases of the studies, for ustekinumab-treated patients 1.24 cases of infection per patient-year and 0.01 cases of serious infection per patient-year (i.e. 24 cases in 2,251 patient-years) were observed.

In the comparative phases of the studies, the frequency of malignant tumours other than non-melanoma skin cancers was 0.25 per 100 patient-years in the group of patients treated with ustekinumab (1 patient in 406 patient-years) versus 0.57 in the placebo group (1 patient in 177 patient-years).
The incidence of non-melanoma skin cancer was 0.74 per 100 patient-years in the ustekinumab group (3 patients in 406 patient-years) and 1.13 in the placebo group (2 patients in 176 patient-years).

In the comparative and non-comparative phases of the studies the frequency of malignant tumours other than non-melanoma skin cancers was 0.36 per 100 patient-years in the ustekinumab group (8 patients in 2,249 patient-years). These cancers included cancers of the breast, colon, head and neck, kidney, prostate and thyroid. The frequency of malignant tumours affecting patients treated with ustekinumab was similar to that expected in the general population (standardised incidence ratio = 0.68, 95% CI = [0.29; 1.34]). The frequency of non-melanoma skin cancers was 0.80 per 100 patient-years in the ustekinumab group (18 patients in 2,245 patient-years).

**Immunogenicity:**
Approximately 5% of patients treated with ustekinumab developed antibodies against ustekinumab, usually at low concentrations. No apparent correlation was observed between the development of these antibodies and reactions at the injection site. The response to treatment tended to be weaker in patients with antibodies against ustekinumab. However, the SPC points out that the presence of antibodies does not allow any conclusions to be drawn as to the clinical response.

**Hypersensitivity reactions:**
Rashes and urticaria were observed in less than 2% of patients taking part in clinical studies.

3.2.2. **Tolerance data versus etanercept (ACCEPT study)**
The percentage of patients suffering an adverse event in the first 12 weeks of treatment was the same in the ustekinumab 45 and 90 mg group and the etanercept group (69.5% versus 67.4%).

The most common adverse events were: headache (12.9% with ustekinumab versus 11% with etanercept), rhinopharyngitis (9.9% versus 8.4%), upper respiratory tract infections (6.3% versus 5.8%), back pain (5.2% versus 2.0%), pruritus (5.0% versus 4.0%), fatigue (4.9% versus 3.7%) and arthralgia (3.8% versus 2%). Reactions at the injection site were more common with etanercept (skin erythema, 14.7% versus 0.7% and swelling, 7.2% versus 0.5%).

Serious adverse event rates were 1.9 and 1.2% with ustekinumab 45 mg and 90 mg and 1.2% with etanercept.

Adverse event rates leading to discontinuation of treatment were 1.9 and 1.2% with ustekinumab 45 mg and 90 mg and 2.3% with etanercept.

The only adverse event leading to discontinuation of treatment in more than one patient receiving ustekinumab was basal cell carcinoma, which affected one patient in the ustekinumab 45 mg group and one patient in the 90 mg ustekinumab group. The protocol specified that treatment must be discontinued if this should occur.

A rise in hepatic transaminase levels (ALAT) and aggravation of psoriasis led to discontinuation of treatment with etanercept 50 mg in four patients (two in each case).

Malignant tumours were observed in four patients being treated with ustekinumab (none were observed in patients being treated with etanercept). Three of these four patients had a history of cancer. The patient with no history of cancer contracted basal cell carcinoma, discovered 83 days after inclusion.
3.3. Conclusion

Ustekinumab was compared with placebo in two randomised double-blind studies (PHOENIX 1 and 2) conducted on patients suffering from moderate to severe psoriasis suitable for phototherapy or systemic treatment (either having had no previous treatment of this kind or having a history of prior treatments). Although the history of phototherapy or systemic treatments was not part of the inclusion criteria, 65 to 67% of patients included had undergone phototherapy and 55% had had conventional systemic treatment. Ustekinumab was administered at doses of 45 mg or 90 mg in the form of subcutaneous (SC) injections at an interval of four weeks and subsequently every 12 weeks.

After the first 12 weeks of treatment, ustekinumab was superior to placebo in terms of the percentage of patients with an improvement of at least 75% in their baseline PASI score (66.4 to 75.7% in the ustekinumab groups versus 3.1 and 3.7% of patients receiving placebo, p<0.001). Similarly, ustekinumab was superior to placebo in terms of the percentage of patients with a PGA response (patients with a score of 0 or 1 on a scale of 0 to 5) and experiencing a clinically relevant improvement in their DLQI quality of life score (secondary endpoints).

In a single-blind randomised study (ACCEPT), ustekinumab 45 or 90 mg administered in the form of two SC injections at a four-week interval and subsequently every 12 weeks was compared to etanercept 50 mg administered in the form of two SC injections per week in a patient population similar to that taking part in the PHOENIX 1 and 2 studies. After the first 12 weeks of treatment, ustekinumab 45 mg or 90 mg was found to be superior to etanercept 50 mg in terms of the percentage of patients with a PASI 75 response (56.8% with etanercept versus 67.5% with ustekinumab 45 mg, p = 0.012, and 73.8% with ustekinumab 90 mg, p < 0.001). Ustekinumab 45 mg or 90 mg was also superior to etanercept in terms of the percentage of patients with a PGA response (score of 0 or 1) and the percentage of patients with a PASI 90 response (secondary endpoints).

The adverse events most frequently observed were upper respiratory tract infections, arthralgia and headache. The tolerance profile of ustekinumab was similar to that of etanercept, except for reactions at the injection site which were more common with etanercept (skin erythema and swelling). The serious adverse events were serious infections and cutaneous and non-cutaneous malignant tumours; there was no difference compared to placebo. However, long-term data is needed to allow assessment of the carcinogenic risk that may be associated with ustekinumab.
4.1. Actual benefit

Psoriasis is a chronic inflammatory dermatosis, usually benign, which can in moderate to severe forms have a major impact on quality of life.

This proprietary product suspends the symptoms.

Public health benefit:

Psoriasis constitutes a significant public health burden. It is moderate in the small population likely to benefit from treatment.

In view of the rare but serious situations of psoriasis for which no other systemic treatment is possible, and the cumulative toxicity of these systemic treatments which restricts their use, it can be concluded that an unmet therapeutic need exists which can be regarded as significant from the point of view of public health as a consequence of the severe condition of the patients who could benefit.

In the light of the trial data available (especially the increased short-term efficacy compared to ENBREL), STELARA can be expected to have a small impact on morbidity and quality of life. However, neither this proprietary product nor other biotherapies/anti-TNF therapies are likely to have any long-term impact because of:

- tolerance concerns, especially the risk of patients developing cancer,
- uncertainty as to the transposability of the results of studies carried out over relatively short periods with very little data in the small population of patients who have actually failed therapy.

Accordingly, in the current state of knowledge, STELARA is not expected to have an impact on public health, as it is also the case for the other biotherapies which are available.

The efficacy/adverse effects ratio is high.

This proprietary product is a fallback treatment in the case of patients suffering from severe plaque psoriasis in whom at least two other systemic treatments from among phototherapy, methotrexate and ciclosporin have failed, are contraindicated or are not tolerated.

There are alternative treatments (anti-TNFα).

The opinion’s Committee is of the actual benefit provided by STELARA 45 mg solution for injection is substantial in adult patients suffering from serious chronic plaque psoriasis who have failed at least two systemic treatments, including phototherapy, methotrexate and ciclosporin (i.e. have not responded or cannot receive these treatments because of contraindication or intolerance).

The actual benefit for other patients who do not meet these criteria for receiving this treatment is insufficient.

4.2. Improvement in actual benefit (IAB)

STELARA 45 mg provides a minor improvement in actual benefit (IAB IV) in terms of efficacy compared to ENBREL among patients suffering from serious chronic plaque psoriasis who have failed at least two systemic treatments from among phototherapy, methotrexate and ciclosporin.
4.3. Therapeutic use

4.3.1. Treatment strategy

Current treatments of psoriasis do not produce a definitive cure for the disorder, but result in the temporary disappearance of the lesions to a greater or lesser extent. The therapeutic arsenal comprises local and general treatments. Local treatments can be used alone or in combination with other local treatments or general treatments.

Cutaneous hydration by means of emollients is often associated with topical treatments, which are the first-line treatment for limited psoriasis.

Several types of topical treatments exist: dermocorticosteroids, vitamin D3 analogues, retinoids (vitamin A derivatives) and, used to a lesser extent, tars, anthralin and keratolytics.

Systemic treatments are administered for severe forms of psoriasis. These are phototherapy, retinoids (sometimes administered in combination with phototherapy), methotrexate, ciclosporin and biological agents (etanercept, infliximab, adalimumab).

Patients generally respond well to phototherapy (UVA or PUVA and narrow-spectrum UVB), but the conditions under which this treatment is given (frequency of sessions, equipment needed) and the cumulative toxicity of this technique, especially in the case of PUVA, impose restrictions on access to this form of treatment and its long-term use (risk of skin cancer).

Experts believe that methotrexate is still the benchmark treatment for extensive or severe forms of psoriasis despite its severe hepatic adverse effects.

Retinoids alone are less effective, but they have a stronger synergic efficacy when administered in combination with phototherapy. This combination is used particularly in diffuse forms of psoriasis.

Biotherapies (etanercept, infliximab, adalimumab) must be reserved for severe forms of plaque psoriasis when at least two systemic treatments from among ciclosporin, methotrexate and PUVA therapy have failed, are contraindicated or are not tolerated.

The current treatment strategy is to rotate patients between the various alternatives, with the choice of treatment being based on the patient’s characteristics and the features of his or her pathology (concomitant pathology, extent of lesions, treatment history) and of the proprietary product (adverse effects, cumulative dose).

4.3.2. Role of STELARA 45 mg

Like other biotherapies indicated for use in psoriasis, STELARA 45 mg is a fallback treatment for adult patients suffering from chronic severe plaque psoriasis who have failed at least two systemic treatments from among phototherapy, methotrexate and ciclosporin (i.e. they have not responded to or tolerated these treatments, or the treatments are contraindicated).

Consideration should be given to discontinued the treatment in patients who have not responded after 28 weeks of treatment.

4.4. Target population

The target population for STELARA 45 mg is made up of adult patients suffering from chronic severe plaque psoriasis who have failed at least two systemic treatments from among phototherapy, methotrexate and ciclosporin.
Epidemiological data allows the prevalence of severe plaque psoriasis to be estimated, but the literature contains no data on the proportion of patients for whom the available systemic treatments have failed (lack of response, intolerance or contraindication).

However, the size of this population can be estimated by applying the average response rates to current systemic treatments to prevalence data for the condition (1.5 to 3%) derived from the literature\textsuperscript{4, 5}. This puts the number of patients likely to benefit from treatment with STELARA 45 mg at less than 10,000 a year.

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 hospital use and various public services.

The Committee would like to reassess the actual benefit of STELARA 45 mg in a year’s time, taking particular account of the latest clinical data, especially with regard to tolerance.

4.5.1. Scope of reimbursement

The Committee proposes that:
- STELARA 45 mg be reserved for the treatment of severe chronic plaque psoriasis in adults who have failed at least two systemic treatments from among phototherapy, methotrexate and ciclosporin, or who do not tolerate such treatments or where such treatments are contraindicated, and that it be administered at the doses specified in the marketing authorisation;
- STELARA be initially prescribed, and prescriptions renewal issued, only by dermatologists.

4.5.2. Exception drug status

The committee recommends awarding STELARA 45 mg exception drug status. A prescription guide will specify the scope of reimbursement and the relevant dosage, along with the conditions for initiating treatment, monitoring patients and discontinuing treatment with STELARA.

4.5.3. Request for a study

The Committee asks that a representative cohort of patients undergoing treatment in France be set up to investigate:
- the exact profile of populations who will receive treatment: history of the condition, prior treatments, reasons and aims of prescriptions, practical details taken into consideration to define (1) severe psoriasis and (2) treatment failure under observation.
- assessment of benefits over time: monitoring the cohort for at least five years should provide a better idea of the patient’s progress and the benefit of treatments in “real life” with regard to the following four aspects:
  - maintenance of benefits after several courses and the occurrence of a rebound effect
  - treatment strategy
  - long-term toxicity (especially relating to cancer, including skin cancer, and risks of infection)

\textsuperscript{4} CPMP guideline on clinical investigation of medicinal product indicated for the treatment of psoriasis (2004)
changes in quality of life perceived by the subject using multidimensional indicators (a summary index is not appropriate as individual patients may find that the consequences of treatment affect various areas of their quality of life differently).

If scheduled or ongoing studies, in particular within the scope of the European Risk Management plan, do not answer all the questions raised by the Transparency Committee, a specific study must be conducted.

The Committee requests:
- that this study be conducted jointly for ENBREL, REMICADE, HUMIRA and STELARA, according to similar methodologies and protocols;
- that the initial findings be submitted after one year of follow up and once a year thereafter.

4.5.4. Packaging
Appropriate for the prescription conditions.

4.5.5. Reimbursement rate
65%