ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Taltz 80 mg solution for injection in pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 80 mg ixekizumab in 1 ml.

Ixekizumab is a recombinant humanised monoclonal antibody produced in CHO cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe (injection).

The solution is clear and colourless to slightly yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plaque psoriasis

Taltz is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Psoriatic arthritis

Taltz, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drug (DMARD) therapies (see section 5.1).

4.2 Posology and method of administration

Taltz is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Taltz is indicated.

Posology

Plaque psoriasis

The recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks.

Psoriatic arthritis

The recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) every 4 weeks thereafter. For psoriatic arthritis patients with
concomitant moderate to severe plaque psoriasis, the recommended dosing regimen is the same as for plaque psoriasis.

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks.

_Elderly (≥ 65 years)_

No dose adjustment is required (see section 5.2).

There is limited information in subjects aged ≥ 75 years.

_Renal or hepatic impairment_

Taltz has not been studied in these patient populations. No dose recommendations can be made.

_Paediatric population_

The safety and efficacy of Taltz in children and adolescents aged 6 to 18 years in the treatment of moderate to severe plaque psoriasis have not yet been established. No data are available. There is no relevant use of Taltz in children below the age of 6 years in the treatment of moderate to severe plaque psoriasis.

The safety and efficacy of Taltz in children and adolescents aged 2 to less than 18 years in the treatment of psoriatic arthritis (a category of juvenile idiopathic arthritis) have not yet been established. No data are available. There is no relevant use of Taltz in children below 2 years for the indication of psoriatic arthritis.

_Method of administration_

Subcutaneous use.

Taltz is for subcutaneous injection. Injection sites may be alternated. If possible, areas of the skin that show psoriasis should be avoided as injection sites. The solution/the syringe must not be shaken.

After proper training in subcutaneous injection technique, patients may self-inject Taltz if a healthcare professional determines that it is appropriate. However, the physician should ensure appropriate follow-up of patients. Comprehensive instructions for administration are given in the package leaflet.

4.3 **Contraindications**

Serious hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically important active infections (e.g. active tuberculosis, see section 4.4).

4.4 **Special warnings and precautions for use**

_Infections_

Treatment with Taltz is associated with an increased rate of infections such as upper respiratory tract infection, oral candidiasis, conjunctivitis, and tinea infections (see section 4.8).

Taltz should be used with caution in patients with clinically important chronic infection. If such an infection develops, monitor carefully and discontinue Taltz if the patient is not responding to standard therapy or the infection becomes serious. Taltz should not be resumed until the infection resolves.

Taltz must not be given to patients with active tuberculosis (TB). Consider anti-TB therapy prior to initiation of Taltz in patients with latent TB.
Hypersensitivity

Serious hypersensitivity reactions, including some cases of anaphylaxis, angioedema, urticaria and, rarely, late (10-14 days following injection) serious hypersensitivity reactions including widespread urticaria, dyspnea and high antibody titres have been reported. If a serious hypersensitivity reaction occurs, administration of Taltz should be discontinued immediately and appropriate therapy initiated.

Inflammatory Bowel Disease

Cases of new or exacerbations of Crohn’s disease and ulcerative colitis have been reported. Caution should be exercised when prescribing Taltz to patients with inflammatory bowel disease, including Crohn’s disease and ulcerative colitis, and patients should be monitored closely.

Immunisations

Taltz should not be used with live vaccines. No data are available on the response to live vaccines; there are insufficient data on response to inactive vaccines (see section 5.1).

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per 80 mg dose, i.e., essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

In plaque psoriasis studies, the safety of Taltz in combination with other immunomodulatory agents or phototherapy has not been evaluated.

No formal in vivo drug-drug interaction studies have been conducted. A role for IL-17 in the regulation of CYP450 enzymes has not been reported. The formation of some CYP450 enzymes is, however, suppressed by increased levels of cytokines during chronic inflammation. Thus, anti-inflammatory treatments, such as with the IL-17A inhibitor ixekizumab, may result in normalisation of CYP450 levels with accompanying lower exposure of CYP450-metabolised co-medications. Therefore, a clinically relevant effect on CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g. warfarin), cannot be excluded. On initiation of ixekizumab therapy in patients being treated with these types of medicinal products, therapeutic monitoring should be considered.

No interaction was seen when Taltz was administered concomitantly with methotrexate (MTX) and/or corticosteroids in patients with psoriatic arthritis.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use an effective method of contraception during treatment and for at least 10 weeks after treatment.

Pregnancy

There is a limited amount of data from the use of ixekizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or post-natal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Taltz during pregnancy.
Breast-feeding

It is not known whether ixekizumab is excreted in human milk or absorbed systemically after ingestion. However, ixekizumab is excreted at low levels in the milk of cynomolgus monkeys. A decision should be made whether to discontinue breast-feeding or to discontinue Taltz taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of ixekizumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Taltz has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions (ADRs) were injection site reactions and upper respiratory tract infections (most frequently nasopharyngitis).

Tabulated list of adverse reactions

ADRs from clinical studies and postmarketing reports (Table 1) are listed by MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each ADR is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

A total of 7,339 patients have been treated with Taltz in blinded and open-label clinical studies in plaque psoriasis, psoriatic arthritis, and other autoimmune conditions. Of these, 4,500 patients were exposed to Taltz for at least one year, cumulatively representing 13,645.6 patient years of exposure.

In plaque psoriasis, three placebo-controlled phase III studies were integrated to evaluate the safety of Taltz in comparison to placebo up to 12 weeks after treatment initiation. A total of 3,119 patients were evaluated (1,161 patients on 80 mg every 4 weeks (Q4W), 1,167 patients on 80 mg every 2 weeks (Q2W) and 791 patients on placebo).

In psoriatic arthritis, two placebo-controlled phase III studies were integrated to evaluate the safety of Taltz in comparison to placebo up to 24 weeks after treatment initiation. A total of 678 patients were evaluated (229 patients on 80 mg every 4 weeks (Q4W), 225 patients on 80 mg every 2 weeks (Q2W) and 224 patients on placebo). The safety profile observed in patients with psoriatic arthritis treated with Taltz is consistent with the safety profile in plaque psoriasis with the exception of the frequencies of the adverse reactions of influenza and conjunctivitis which were common in patients with psoriatic arthritis.
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Very Common</td>
<td>Upper respiratory tract infection&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Tinea infection, Herpes simplex (mucocutaneous)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Influenza&lt;sup&gt;i&lt;/sup&gt;, Rhinitis, Oral candidiasis&lt;sup&gt;d&lt;/sup&gt;, Conjunctivitis&lt;sup&gt;i&lt;/sup&gt;, Cellulitis&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Uncommon</td>
<td>Neutropenia, Thrombocytopenia&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Uncommon</td>
<td>Angioedema</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Anaphylaxis&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Common</td>
<td>Oropharyngeal pain</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Nausea</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td>Uncommon</td>
<td>Urticaria, Rash, Eczema</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common</td>
<td>Injection site reactions&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Placebo-controlled clinical studies (phase III) in moderate to severe plaque psoriasis patients exposed to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W or placebo for up to 12 weeks of treatment duration, or in active psoriatic arthritis patients exposed to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W or placebo for up to 24 weeks of treatment duration.

<sup>b</sup> Upper respiratory tract infection includes nasopharyngitis and upper respiratory tract infection.

<sup>c</sup> Herpes simplex (mucocutaneous) is defined as events with the preferred terms Oral herpes, Herpes simplex, Genital herpes, Herpes dermatitis, and Genital herpes simplex.

<sup>d</sup> Oral candidiasis defined as events with the preferred terms oral candidiasis and oral fungal infection.

<sup>e</sup> Cellulitis includes staphylococcal and external ear cellulitis, and erysipelas.

<sup>f</sup> In the plaque psoriasis studies, injection site reactions were more common in subjects with a body weight < 60 kg compared with the group with a body weight ≥ 60 kg (25 % vs. 14 % for the combined Q2W and Q4W groups). In the psoriatic arthritis studies, injection site reactions were more common in subjects with a body weight < 100 kg compared with the group with a body weight ≥ 100 kg (24 % vs. 13 % for the combined Q2W and Q4W groups). The increased frequency of injection site reactions in the combined Q2W and Q4W groups did not result in an increase in discontinuations in either the plaque psoriasis or the psoriatic arthritis studies.

<sup>g</sup> Based on reported adverse events.

<sup>h</sup> Based on postmarketing reports.

<sup>i</sup> Adverse drug reactions in patients treated with ixekizumab in the plaque psoriasis and psoriatic arthritis clinical trials were similar with the exception of the frequencies of influenza (common) and conjunctivitis (common) in the psoriatic arthritis clinical trials.

Description of selected adverse reactions

(Based on adverse reactions data from 4,204 patients with moderate to severe plaque psoriasis [4,729.7 patient years] and 1,117 patients with active psoriatic arthritis [1,050.6 patient years] who have received at least 1 dose of ixekizumab.)

Injection site reactions

The most frequent injection site reactions observed were erythema and pain. These reactions were predominantly mild to moderate in severity and did not lead to discontinuation of Taltz.
**Infections**
In the placebo-controlled period of the phase III clinical studies in plaque psoriasis, infections were reported in 27.2% of patients treated with Taltz for up to 12 weeks compared with 22.9% of patients treated with placebo.

The majority of infections were non-serious and mild to moderate in severity, most of which did not necessitate treatment discontinuation. Serious infections occurred in 13 (0.6%) of patients treated with Taltz and in 3 (0.4%) of patients treated with placebo (see section 4.4). Over the entire treatment period infections were reported in 52.8% of patients treated with Taltz (46.9 per 100 patient years). Serious infections were reported in 1.6% of patients treated with Taltz (1.5 per 100 patient years).

Infection rates observed in psoriatic arthritis clinical studies were similar to those observed in the plaque psoriasis studies with the exception of the frequencies of the adverse reactions of influenza and conjunctivitis which were common in patients with psoriatic arthritis.

**Laboratory assessment of neutropenia and thrombocytopenia**
In plaque psoriasis studies, 9% of patients receiving Taltz developed neutropenia. In most cases, the blood neutrophil count was ≥1,000 cells/mm³. Such levels of neutropenia may persist, fluctuate or be transient. 0.1% of patients receiving Taltz developed a neutrophil count <1000 cells/mm³. In general, neutropenia did not require discontinuation of Taltz. 3% of patients exposed to Taltz had a shift from a normal baseline platelet value to <150,000 platelet cells/mm³ to ≥75,000 cells/mm³. Thrombocytopenia may persist, fluctuate or be transient.

The frequency of neutropenia and thrombocytopenia in psoriatic arthritis clinical studies is similar to that observed in the plaque psoriasis studies.

**Immunogenicity**
Approximately 9–17% of plaque psoriasis patients treated with Taltz at the recommended dosing regimen developed anti-drug antibodies, the majority of which were low titres and not associated with reduced clinical response up to 60 weeks of treatment. However, approximately 1% of patients treated with Taltz had confirmed neutralising antibodies associated with low drug concentrations and reduced clinical response.

In psoriatic arthritis patients treated with Taltz at the recommended dosing regimen up to 52 weeks, approximately 11% developed anti-drug antibodies, the majority of which were low titre, and approximately 8% had confirmed neutralising antibodies. No apparent association between the presence of neutralising antibodies and impact on drug concentration or efficacy was observed.

An association between immunogenicity and treatment emergent adverse events has not been clearly established.

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

**4.9 Overdose**
Doses up to 180 mg have been administered subcutaneously in clinical trials without dose-limiting toxicity. Overdoses up to 240 mg, subcutaneously, as a single administration in clinical trials, have been reported without any serious adverse events. In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC13

Mechanism of action

Ixekizumab is an IgG4 monoclonal antibody that binds with high affinity (< 3 pM) and specificity to interleukin 17A (both IL-17A and IL-17A/F). Elevated concentrations of IL-17A have been implicated in the pathogenesis of psoriasis by promoting keratinocyte proliferation and activation, as well as in the pathogenesis of psoriatic arthritis. Neutralisation of IL-17A by ixekizumab inhibits these actions. Ixekizumab does not bind to ligands IL-17B, IL-17C, IL-17D, IL-17E or IL-17F.

In vitro binding assays confirmed that ixekizumab does not bind to human Fcγ receptors I, IIa, and IIIa or to complement component C1q.

Pharmacodynamic effects

Ixekizumab modulates biological responses that are induced or regulated by IL-17A. Based on psoriatic skin biopsy data from a phase I study, there was a dose-related trend towards decreased epidermal thickness, number of proliferating keratinocytes, T cells, and dendritic cells, as well as reductions in local inflammatory markers from baseline to day 43. As a direct consequence treatment with ixekizumab reduces erythema, induration and desquamation present in plaque psoriasis lesions.

Taltz has been shown to lower (within 1 week of treatment) levels of C-reactive protein, which is a marker of inflammation.

Clinical efficacy and safety

Plaque psoriasis

The efficacy and safety of Taltz were assessed in three randomised, double-blind, placebo-controlled phase III studies in adult patients with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy (UNCOVER-1, UNCOVER-2, and UNCOVER-3). The efficacy and safety of Taltz were also evaluated versus etanercept (UNCOVER-2 and UNCOVER-3). Patients randomised to Taltz who were sPGA (0,1) responders at Week 12 were re-randomised to receive placebo or Taltz for an additional 48 weeks (UNCOVER-1 and UNCOVER-2); patients randomised to placebo, etanercept or Taltz who were sPGA (0,1) non-responders received Taltz for up to 48 weeks.

Of the 3,866 patients enrolled in these placebo-controlled studies, 64 % had received prior systemic therapy (biologic, conventional systemic or psoralen and ultraviolet A (PUVA)), 43.5 % had received prior phototherapy, 49.3 % had received prior conventional systemic therapy, and 26.4 % had received prior biologic therapy for the treatment of psoriasis. Of all patients, 14.9 % had received at least one anti-TNF alpha agent, and 8.7 % had received an anti-IL-12/IL-23. 23.4 % of patients had a history of psoriatic arthritis at baseline.

In all three studies, the co-primary endpoints were the proportion of patients who achieved a PASI 75 response and an sPGA of 0 (“clear”) or 1 (“minimal”) response at Week 12 versus placebo. Patients in all treatment groups had a median baseline PASI score ranging from 17.4 to 18.3; 48.3 % to 51.2 % of patients had a baseline sPGA score of severe or very severe, and mean baseline itch Numeric Rating Scale (itch NRS) ranging from 6.3 to 7.1.

Clinical response at 12 weeks

UNCOVER-1 enrolled 1,296 patients. Patients were randomised (1:1:1) to receive either placebo or Taltz (80 mg every two or four weeks [Q2W or Q4W] following a 160 mg starting dose) for 12 weeks.
Table 2. **Efficacy results at Week 12 in UNCOVER-1**

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Number of patients (%)</th>
<th>Difference from Placebo in Response Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 431)</td>
<td>Taltz 80 mg Q4W (N = 432)</td>
</tr>
<tr>
<td>sPGA of “0” (clear) or “1” (minimal)</td>
<td>14 (3.2)</td>
<td>330 (76.4)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>sPGA of “0” (clear)</td>
<td>0</td>
<td>149 (34.5)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>PASI 75</td>
<td>17 (3.9)</td>
<td>357 (82.6)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>PASI 90</td>
<td>2 (0.5)</td>
<td>279 (64.6)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>PASI 100</td>
<td>0</td>
<td>145 (33.6)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Itch NRS reduction ≥ 4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>58 (15.5)</td>
<td>305 (80.5)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Abbreviations:** N = number of patients in the intent-to-treat population

**Note:** patients with missing data were counted as non-responders

<sup>a</sup> p < 0.001 compared with placebo

<sup>b</sup> Patients with Itch NRS ≥ 4 at baseline: placebo N = 374, Taltz 80 mg Q4W N = 379, Taltz 80 mg Q2W N = 391

UNCOVER-2 enrolled 1,224 patients. Patients were randomised (1:2:2:2) to receive either placebo, or Taltz (80 mg every two or four weeks [Q2W or Q4W] following a 160 mg starting dose) or etanercept 50 mg twice weekly for 12 weeks.
Table 3. Efficacy results at Week 12 in UNCOVER-2

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Number of patients (%)</th>
<th>Difference from Placebo in Response Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 168)</td>
<td>Taltz 80 mg Q4W (N = 347)</td>
</tr>
<tr>
<td>sPGA of “0” (clear) or “1” (minimal)</td>
<td>4 (2.4)</td>
<td>253 (72.9)a</td>
</tr>
<tr>
<td>sPGA of “0” (clear)</td>
<td>1 (0.6)</td>
<td>112 (32.3)ab</td>
</tr>
<tr>
<td>PASI 75</td>
<td>4 (2.4)</td>
<td>269 (77.5)ab</td>
</tr>
<tr>
<td>PASI 90</td>
<td>1 (0.6)</td>
<td>207 (59.7)ab</td>
</tr>
<tr>
<td>PASI 100</td>
<td>1 (0.6)</td>
<td>107 (30.8)ab</td>
</tr>
<tr>
<td>Itch NRS reduction ≥ 4</td>
<td>19 (14.1)</td>
<td>225 (76.8)ab</td>
</tr>
</tbody>
</table>

Abbreviations: N = number of patients in the intent-to-treat population
Note: patients with missing data were counted as non-responders.

\textsuperscript{a} p < 0.001 compared with placebo
\textsuperscript{b} p < 0.001 compared with etanercept
\textsuperscript{c} p < 0.01 compared with placebo
\textsuperscript{d} Patients with Itch NRS ≥ 4 at baseline: placebo N = 135, Taltz 80 mg Q4W N = 293, Taltz 80 mg Q2W N = 303, Etanercept N = 306

UNCOVER-3 enrolled 1,346 patients. Patients were randomised (1:2:2:2) to receive either placebo, or Taltz (80 mg every two or four weeks [Q2W or Q4W] following a 160 mg starting dose) or etanercept 50 mg twice weekly for 12 weeks.
Table 4. Efficacy results at Week 12 in UNCOVER-3

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Placebo (N = 193)</th>
<th>Taltz 80 mg Q4W (N = 386)</th>
<th>Taltz 80 mg Q2W (N = 385)</th>
<th>Etanercept 50 mg twice weekly (N = 382)</th>
<th>Taltz 80 mg Q4W</th>
<th>Taltz 80 mg Q2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>sPGA of “0” (clear) or “1” (minimal)</td>
<td>13 (6.7)</td>
<td>291 (75.4)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>310 (80.5)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>159 (41.6)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>68.7 (63.1, 74.2)</td>
<td>73.8 (68.5, 79.1)</td>
</tr>
<tr>
<td>sPGA of “0” (clear)</td>
<td>0</td>
<td>139 (36.0)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>155 (40.3)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>33 (8.6)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>36.0 (31.2, 40.8)</td>
<td>40.3 (35.4, 45.2)</td>
</tr>
<tr>
<td>PASI 75</td>
<td>14 (7.3)</td>
<td>325 (84.2)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>336 (87.3)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>204 (53.4)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>76.9 (71.8, 82.1)</td>
<td>80.0 (75.1, 85.0)</td>
</tr>
<tr>
<td>PASI 90</td>
<td>6 (3.1)</td>
<td>252 (65.3)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>262 (68.1)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>98 (25.7)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>62.2 (56.8, 67.5)</td>
<td>64.9 (59.7, 70.2)</td>
</tr>
<tr>
<td>PASI 100</td>
<td>0</td>
<td>135 (35.0)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>145 (37.7)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>28 (7.3)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>35 (30.2, 39.7)</td>
<td>37.7 (32.8, 42.5)</td>
</tr>
<tr>
<td>Itch NRS reduction ≥ 4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>33 (20.9)</td>
<td>250 (79.9)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>264 (82.5)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>200 (64.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>59.0 (51.2, 66.7)</td>
<td>61.6 (54.0, 69.2)</td>
</tr>
</tbody>
</table>

Abbreviations: N = number of patients in the intent-to-treat population
Note: patients with missing data were counted as non-responders
<sup>a</sup> p < 0.001 compared with placebo
<sup>b</sup> p < 0.001 compared with etanercept
<sup>c</sup> Patients with Itch NRS ≥ 4 at baseline: placebo N = 158, Taltz 80 mg Q4W N = 313, Taltz 80 mg Q2W N = 320, Etanercept N = 312

Taltz was associated with a fast onset of efficacy with > 50 % reduction in mean PASI by Week 2 (Figure 1). The percentage of patients achieving PASI 75 was significantly greater for Taltz compared with placebo and etanercept as early as Week 1. Approximately 25 % of patients treated with Taltz achieved a PASI score < 5 by Week 2, more than 55 % achieved the PASI score < 5 by Week 4, and increased to 85 % by Week 12 (compared to 3 %, 14 % and 50 % for etanercept). Significant improvements in itch severity were seen at Week 1 in patients treated with Taltz.
The efficacy and safety of Taltz was demonstrated regardless of age, gender, race, body weight, PASI baseline severity, plaques location, concurrent psoriatic arthritis, and previous treatment with a biologic. Taltz was efficacious in systemic treatment-naive, biologic-naive, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients.

Efficacy in Non-Responders to Etanercept: For patients identified as an sPGA (0,1) non-responder to etanercept at Week 12 in UNCOVER-2 (N = 200) and who were switched to Taltz 80 mg Q4W after a 4 week washout period, 73 % and 83.5 % of patients were able to achieve sPGA (0,1) and PASI 75, respectively, after 12 weeks of being treated with Taltz.

In the 2 clinical studies that included an active comparator (UNCOVER-2 and UNCOVER-3), the rate of serious adverse events was 1.9 % for both etanercept and for Taltz, and the rate of discontinuation due to adverse events was 1.2 % for etanercept and 2.0 % for Taltz. The rate of infections was 21.5 % for etanercept and 26.0 % for Taltz, with the majority of the events mild to moderate in severity. The rate of serious infections was 0.4 % for etanercept and 0.5 % for Taltz.

**Maintenance of Response at Week 60**

Patients originally randomised to Taltz and who were responders at Week 12 (i.e., sPGA score of 0,1) in UNCOVER-1 and UNCOVER-2 were re-randomised to an additional 48 weeks of one of the following treatment regimens: placebo, or Taltz (80 mg every four or twelve weeks [Q4W or Q12W]).
Table 5. Maintenance of Response and Efficacy at Week 60 (Studies UNCOVER-1 and UNCOVER-2)

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Number of patients (%)</th>
<th>Difference from Placebo in Response Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg Q4W (induction) / Placebo (maintenance) (N = 191)</td>
<td>80 mg Q2W (induction) / Placebo (maintenance) (N = 211)</td>
<td>80 mg Q4W (induction) / 80 mg Q4W (maintenance) (N = 195)</td>
</tr>
<tr>
<td>Maintained sPGA of “0” (clear) or “1” (minimal)</td>
<td>12 (6.3)</td>
<td>16 (7.6)</td>
</tr>
<tr>
<td>Maintained or Achieved sPGA 0 (clear)</td>
<td>3 (1.6)</td>
<td>6 (2.8)</td>
</tr>
<tr>
<td>Maintained or Achieved PASI 75</td>
<td>15 (7.9)</td>
<td>19 (9.0)</td>
</tr>
<tr>
<td>Maintained or Achieved PASI 90</td>
<td>9 (4.7)</td>
<td>10 (4.7)</td>
</tr>
<tr>
<td>Maintained or Achieved PASI 100</td>
<td>3 (1.6)</td>
<td>6 (2.8)</td>
</tr>
</tbody>
</table>

Abbreviations: N = number of patients in the analysis population
Note: patients with missing data were counted as non-responders
*p < 0.001 compared with placebo

Taltz was efficacious in the maintenance of response in systemic treatment-naive, biologic-naive, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients.

For sPGA (0,1) responders at Week 12 re-randomised to treatment withdrawal (i.e., placebo), the median time to relapse (sPGA ≥ 3) was 164 days in integrated UNCOVER-1 and UNCOVER-2 studies. Among these patients, 71.5 % regained at least an sPGA (0,1) response within 12 weeks of restarting treatment with Taltz 80 mg Q4W.

Significantly greater improvements at Week 12 from baseline compared to placebo and etanercept were demonstrated in nail psoriasis (as measured by the Nail Psoriasis Severity Index [NAPSI]), in scalp psoriasis (as measured by Psoriasis Scalp Severity Index [PSSI]) and in palmoplantar psoriasis (as measured by Psoriasis Palmoplantar Severity Index [PPASI]). These improvements in nail, scalp and palmoplantar psoriasis were maintained at Week 60 in patients treated with Taltz who were sPGA (0,1) responders at Week 12.

Quality of Life/Patient-Reported Outcomes
At Week 12 and across studies, Taltz was associated with statistically significant improvement in Health-related Quality of Life as assessed by mean decrease ranges from baseline in the Dermatology Life Quality Index (DLQI) (Taltz 80 mg Q2W from -10.2 to -11.1, Taltz 80 mg Q4W from -9.4 to -10.7, etanercept from -7.7 to -8.0 and placebo -1.0 to -2.0). A significantly greater proportion of patients treated with Taltz achieved a DLQI 0 or 1. Across studies, Taltz was associated with statistically significant improvement of itching severity assessed by the Itch NRS score. A significantly greater proportion of patients treated with Taltz achieved a reduction of Itch NRS ≥ 4 points at week 12 (84.6% for Taltz Q2W, 79.2% for Taltz Q4W and 16.5% for placebo) and the benefit was sustained over time up to Week 60 in patients treated with Taltz who were sPGA (0 or 1)
responders at Week 12. There was not any evidence of worsening of depression up to 60 weeks treatment with Taltz as assessed by the Quick Inventory of Depressive Symptomatology Self Report.

**Psoriatic arthritis**

The safety and efficacy of Taltz were assessed in two randomised, double-blind, placebo-controlled phase III studies in 780 patients with active psoriatic arthritis (≥3 swollen and ≥3 tender joints). Patients in these studies had a diagnosis of psoriatic arthritis (Classification Criteria for Psoriatic Arthritis [CASPAR] criteria) for a median of 5.33 years. Randomised patients also had current plaque psoriasis skin lesions (94.0%) or a documented history of plaque psoriasis, with 12.1% of patients with moderate to severe plaque psoriasis at baseline. Over 58.9% and 22.3% of the psoriatic arthritis patients had enthesitis and dactylitis at baseline, respectively. For both studies, the primary endpoint was American College of Rheumatology (ACR) 20 response at Week 24.

In Psoriatic Arthritis Study 1 (SPIRIT-P1), patients naive to biologic therapy with active psoriatic arthritis were randomised to subcutaneous injections of placebo, adalimumab 40 mg once every 2 weeks (active control reference arm), Taltz 80 mg once every 2 weeks (Q2W), or 80 mg once every 4 weeks (Q4W). Both Taltz regimens included a 160 mg starting dose. 85.3% of patients in this study had received prior treatment with ≥1 cDMARD. 53% of patients had concomitant use of MTX at a mean weekly dose of 15.8 mg. 67% of patients who had concomitant use of MTX had a dose of 15 mg or greater. Patients in all treatment groups with an inadequate response at week 16 received rescue therapy (modification to background therapy). Patients on Taltz Q2W or Q4W remained on their originally assigned dose of Taltz. Patients receiving adalimumab or placebo were re-randomised 1:1 to Taltz Q2W or Q4W at week 16 or 24 based on responder status.

Psoriatic Arthritis Study 2 (SPIRIT-P2) enrolled patients who were previously treated with an anti-TNF agent and discontinued the anti-TNF agent for either lack of efficacy or intolerance (anti-TNF-IR patients). Patients were randomised to subcutaneous injections of placebo, Taltz 80 mg once every 2 weeks (Q2W), or 80 mg once every 4 weeks (Q4W). Both Taltz regimens included a 160 mg starting dose. 56% and 35% of patients were inadequate responders to 1 anti-TNF or 2 anti-TNF, respectively. SPIRIT-P2 evaluated 363 patients, of whom 41% had concomitant use of MTX at a mean weekly dose of 16.1 mg. 73.2% of patients who had concomitant use of MTX had a dose of 15 mg or greater. Patients in all treatment groups with an inadequate response at week 16 received rescue therapy (modification to background therapy). Patients in Taltz Q2W or Q4W remained on their originally assigned dose of Taltz. Patients receiving placebo were re-randomised 1:1 to Taltz Q2W or Q4W at week 16 or 24 based on responder status.

**Signs and symptoms**

Treatment with Taltz resulted in significant improvement in measures of disease activity compared to placebo at Week 24 (see Table 6).

## Table 6. Efficacy results in SPIRIT-P1 and SPIRIT-P2 at week 24

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>SPIRIT-P1</th>
<th>SPIRIT-P2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference from Placebo in Response Rate (95% CI)</td>
<td>Difference from Placebo in Response Rate (95% CI)</td>
</tr>
<tr>
<td>PBO (N = 106)</td>
<td>Taltz Q4W (N = 107)</td>
<td>Taltz Q2W (N = 103)</td>
</tr>
<tr>
<td>ACR 20 response, n (%)</td>
<td>Week 24</td>
<td>32 (30.2)</td>
</tr>
<tr>
<td>Endpoints</td>
<td>SPIRIT-P1</td>
<td>SPIRIT-P2</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Difference from Placebo in Response Rate (95% CI)</td>
<td>Difference from Placebo in Response Rate (95% CI)</td>
</tr>
<tr>
<td></td>
<td>PBO (N = 106) Taltz Q4W (N = 107) Taltz Q2W (N = 103) ADA (N = 101) Taltz Q4W Taltz Q2W</td>
<td>PBO (N = 118) Taltz Q4W (N = 122) Taltz Q2W (N = 123) Taltz Q4W Taltz Q2W</td>
</tr>
<tr>
<td>ACR 50 response, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>16 (15.1) 43 (40.2) 48 (46.6) 39 (38.6) 25.1 (13.6, 36.6) 31.5 (19.7, 43.3) 6 (5.1) 43 (35.2) 41 (33.3) 30.2 (20.8, 39.5) 28.3 (19.0, 37.5)</td>
<td></td>
</tr>
<tr>
<td>ACR 70 response, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>6 (5.7) 25 (23.4) 35 (34.0) 26 (25.7) 17.7 (8.6, 26.8) 28.3 (18.2, 38.5) 0 27 (22.1) 15 (12.2) 22.1 (14.8, 29.5) 12.2 (6.4, 18.0)</td>
<td></td>
</tr>
<tr>
<td>Minimal Disease Activity n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>16 (15.1) 32 (29.9) 42 (40.8) 32 (31.7) 14.8 (3.8, 25.8) 25.7 (14.0, 37.4) 4 (3.4) 34 (27.9) 29 (23.6) 24.5 (15.9, 33.1) 20.2 (12.0, 28.4)</td>
<td></td>
</tr>
<tr>
<td>ACR 50 and PASI 100 in patients with ≥3% BSA psoriasis skin involvement at baseline, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>1 (1.5) 21 (28.8) 19 (32.2) 9 (13.2) 27.3 (16.5, 38.1) 30.7 (18.4, 43.0) 0 (0.0) 12 (17.6) 10 (14.7) 17.6 (8.6, 26.7) 14.7 (6.3, 23.1)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations**: ACR 20/50/70 = American College of Rheumatology 20%/50%/70% response rate; ADA = adalimumab; BSA = body surface area; CI = confidence interval; Q4W = Taltz 80 mg every 4 weeks; Q2W = Taltz 80 mg every 2 weeks; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = non-responder imputation; PASI 100 = psoriasis area and severity index 100% improvement; PBO = placebo. 
**Note**: patients who were rescued at week 16 or discontinued or with missing data were imputed as non-responders for week 24 analyses. 
Concomitant cDMARDs included MTX, leflunomide and sulfasalazine. 

- **p <0.05**; b **p <0.01**; c **p <0.001 compared with placebo**.

In patients with pre-existing dactylitis or enthesitis, treatment with Taltz Q4W resulted in improvement in dactylitis and enthesitis at Week 24 compared to placebo (resolution: 78% vs. 24%; p<0.001, and 39% vs. 21%; p<0.01, respectively).

In patients with ≥3% BSA, the improvement in skin clearance at Week 12 as measured by 75% improvement in Psoriasis Area Severity Index (PASI 75), was 67% (94/141) for those treated with the Q4W dosing regimen, and 9% (12/134) for those treated with placebo (p<0.001). The proportion of patients achieving a PASI 75, PASI 90, and PASI 100 response at Week 24 was greater with Taltz Q4W compared to placebo (p<0.001). In patients with concomitant moderate to severe psoriasis and psoriatic arthritis, Taltz Q2W dose regimen showed significantly higher response rate for PASI75, PASI 90 and PASI 100 compared to placebo (p<0.001) and demonstrated clinically meaningful benefit over the Q4W dose regimen.

The treatment responses on Taltz were significantly greater than those on placebo as early as week 1 for ACR 20, week 4 for ACR 50 and week 8 for ACR 70 and persisted through week 24.
Figure 2. ACR 20 response in SPIRIT-P1 over time up to Week 24

For both Taltz Q2W and Q4W: \( b \) \( p<0.01 \) and \( c \) \( p<0.001 \) compared with placebo.

In SPIRIT-P1 and SPIRIT-P2, similar responses for ACR 20/50/70 were seen in patients with psoriatic arthritis regardless of whether they were on concomitant cDMARDs, including MTX treatment, or not.

In SPIRIT-P1 and SPIRIT-P2, improvements were shown in all components of the ACR scores including patient assessment of pain. At Week 24 the proportion of patients achieving a modified Psoriatic Arthritis Response Criteria (PsARC) response was greater in the Taltz-treated patients compared to placebo.

In SPIRIT-P1, efficacy was maintained up to Week 52 as assessed by ACR 20/50/70, MDA, enthesitis resolution, dactylitis resolution, and PASI 75/90/100 response rates.

The efficacy and safety of Taltz was demonstrated regardless of age, gender, race, disease duration, baseline body weight, baseline psoriasis involvement, baseline CRP, baseline DAS28-CRP, concomitant corticosteroid use, and previous treatment with a biologic. Taltz was efficacious in biologic-naïve, biologic-exposed and biologic-failure patients.

Radiographic response
In SPIRIT-P1, inhibition of progression of structural damage was assessed radiographically and expressed as the change in modified total Sharp Score (mTSS) and its components, the Erosion Score (ES) and the Joint Space Narrowing score (JSN) at Weeks 24 and 52, compared to baseline. Week 24 data are presented in Table 7.
Table 7. Change in modified Total Sharp Score in SPIRIT-P1

<table>
<thead>
<tr>
<th></th>
<th>PBO (N = 106)</th>
<th>Taltz Q4W (N = 107)</th>
<th>Taltz Q2W (N = 103)</th>
<th>ADA (N = 101)</th>
<th>Difference from Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline score, mean (SD)</td>
<td>17.6 (28.62)</td>
<td>19.2 (32.68)</td>
<td>15.2 (28.86)</td>
<td>15.9 (27.37)</td>
<td>NA</td>
</tr>
<tr>
<td>Change from baseline at Week 24, LSM (SE)</td>
<td>0.51 (0.092)</td>
<td>0.18 (0.090)</td>
<td>0.09 (0.091)</td>
<td>0.13 (0.093)</td>
<td>-0.33 (-0.57, -0.09) ** b</td>
</tr>
<tr>
<td></td>
<td>Taltz Q4W</td>
<td>Taltz Q2W</td>
<td></td>
<td></td>
<td>-0.42 (-0.66, -0.19) ** c</td>
</tr>
</tbody>
</table>

Abbreviations: ADA = adalimumab; CI = confidence interval; Q4W = Taltz 80 mg every 4 weeks; Q2W = Taltz 80 mg every 2 weeks; LSM = least squares mean; N = number of patients in the analysis population; PBO = placebo; SE = standard error.

* p<0.01; ** p<0.001 compared with placebo.

Radiographic joint damage progression was inhibited by Taltz (Table 7) at Week 24, and the percentage of patients with no radiographic joint damage progression (defined as a change from baseline in mTSS of ≤0.5) from randomisation to Week 24 was 94.8% for Taltz Q2W (p<0.001), 89.0% for Taltz Q4W (p=0.026), 95.8% for adalimumab (p<0.001), all compared to 77.4% for placebo. At Week 52, the mean change from baseline in mTSS was 0.27 for placebo/Taltz Q4W, 0.54 for Taltz Q4W/Taltz Q4W, and 0.32 for adalimumab/Taltz Q4W. The percentage of patients with no radiographic joint damage progression from randomisation to Week 52 was 90.9% for placebo/Taltz Q4W, 85.6% for Taltz Q4W/Taltz Q4W, and 89.4% for adalimumab/Taltz Q4W.

Physical function and health-related quality of life

In both SPIRIT-P1 and SPIRIT-P2, patients treated with Taltz Q2W (p<.001) and Q4W (p<.001) showed significant improvement in physical function compared to patients treated with placebo as assessed by Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24, and maintained at Week 52 in SPIRIT-P1.

Taltz-treated patients reported improvements in health-related quality of life as measured by the Physical Component Summary of the Short Form-36 Health Survey (SF-36 PCS) score (p<.001). There were also improvements demonstrated in fatigue as assessed by Fatigue severity NRS scores (p<0.001).

Immunisations

In a study in healthy subjects, no safety concerns were identified of two inactivated vaccines (tetanus and pneumococcal), received after two doses of ixekizumab (160 mg followed by a second dose of 80 mg two weeks later). However, the data concerning immunisation were insufficient to conclude on an adequate immune response to these vaccines following administration of Taltz.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Taltz in one or more subsets of the paediatric population in the treatment of plaque psoriasis and psoriatic arthritis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following a single subcutaneous dose of ixekizumab in patients with psoriasis, mean peak concentrations were achieved within 4 to 7 days, across a dose range of 5 to 160 mg. The mean (SD) maximum plasma concentration (Cmax) of ixekizumab, after the 160 mg starting dose, was 19.9 (8.15) µg/ml.
After the 160 mg starting dose, steady state was achieved by Week 8 with the 80 mg Q2W dosing regimen. Mean (SD) C_{max,ss}, and C_{trough,ss} estimates are 21.5 (9.16) µg/ml, and 5.23 (3.19) µg/ml.

After switching from the 80 mg Q2W dosing regimen to the 80 mg Q4W dosing regimen at Week 12, steady state would be achieved after approximately 10 weeks. Mean (SD) C_{max,ss}, and C_{trough,ss} estimates are 14.6 (6.04) µg/ml, and 1.87 (1.30) µg/ml.

The average bioavailability of ixekizumab after subcutaneous administration was 54 % to 90 % across analyses.

Distribution

From population pharmacokinetic analyses, the mean total volume of distribution at steady state was 7.11 L.

Biotransformation

Ixekizumab is a monoclonal antibody and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous immunoglobulins.

Elimination

In the population PK analysis, mean serum clearance was 0.0161 L/hr. Clearance is independent of dose. The mean elimination half-life, as estimated from population pharmacokinetic analysis, is 13 days in patients with plaque psoriasis.

Linearity/non-linearity

Exposure (AUC) increased proportionally over a dose range of 5 to 160 mg given as a subcutaneous injection.

Psoriatic arthritis

The pharmacokinetic properties of Taltz observed in psoriatic arthritis patients were similar to those displayed in plaque psoriasis patients. The bioavailability of Taltz in psoriatic arthritis patients was in the range of 61-84% on the basis of the population pharmacokinetic model.

Elderly

Of the 4,204 plaque psoriasis patients exposed to Taltz in clinical studies, a total of 301 were 65 years of age or older and 36 patients were 75 years of age or older. Of the 1,118 psoriatic arthritis patients exposed to Taltz in clinical studies, a total of 122 patients were 65 years of age or older and 6 patients were 75 years of age or older.

Based on population pharmacokinetic analysis with a limited number of elderly patients (n = 94 for age ≥ 65 years and n = 12 for age ≥ 75 years), clearance in elderly patients and patients less than 65 years of age was similar.

Renal or hepatic impairment

Specific clinical pharmacology studies to evaluate the effects of renal impairment and hepatic impairment on the PK of ixekizumab have not been conducted. Renal elimination of intact ixekizumab, an IgG MAb, is expected to be low and of minor importance; similarly, IgG MAbs are mainly eliminated via intracellular catabolism and hepatic impairment is not expected to influence clearance of ixekizumab.
5.3 Preclinical safety data

Non-clinical data from cynomolgus monkeys revealed no special hazards for humans based on repeat-dose toxicity studies, safety pharmacology evaluations, and reproductive and developmental toxicity studies.

Ixekizumab administration to cynomolgus monkeys for 39 weeks at subcutaneous doses up to 50 mg/kg weekly produced no organ toxicity or undesirable effects on immune function (e.g. T-cell dependent antibody response and NK cell activity). A weekly subcutaneous dose of 50 mg/kg to monkeys is approximately 19 times the 160 mg starting dose of Taltz and in monkeys results in exposure (AUC) that is at least 61-fold higher than the predicted mean steady-state exposure in humans administered the recommended dose regimen.

Non-clinical studies have not been conducted to evaluate the carcinogenic or mutagenic potential of ixekizumab.

No effects on reproductive organs, menstrual cycles or sperm were observed in sexually mature cynomolgus monkeys that received ixekizumab for 13 weeks at a weekly subcutaneous dose of 50 mg/kg.

In developmental toxicity studies, ixekizumab was shown to cross the placenta and was present in the blood of offspring for up to 6 months of age. A higher incidence of postnatal mortality occurred in the offspring of monkeys given ixekizumab compared to concurrent controls. This was related primarily to early delivery or maternal neglect of offspring, common findings in nonhuman primate studies, and considered clinically irrelevant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Sodium citrate
- Citric acid, anhydrous
- Sodium chloride
- Polysorbate 80
- Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in a refrigerator (2 ºC – 8 ºC).
Do not freeze.
Store in the original package in order to protect from light.

Taltz may be stored unrefrigerated for up to 5 days at a temperature not above 30 ºC.
6.5 Nature and contents of container

1 ml solution in a type I clear glass syringe. Pack sizes of 1, 2, or 3 pre-filled syringes. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use
The instructions for using the syringe, included with the package leaflet, must be followed carefully.

The pre-filled syringe is for single use only.

Taltz should not be used if particles appear or if the solution is cloudy and/or distinctly brown.

Taltz that has been frozen must not be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands.

8. MARKETING AUTHORIZATIATION NUMBER(S)

EU/1/15/1085/004
EU/1/15/1085/005
EU/1/15/1085/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

Date of first authorisation: 25 April 2016

10. DATE OF REVISION OF THE TEXT

1. **NAME OF THE MEDICINAL PRODUCT**

Taltz 80 mg solution for injection in pre-filled pen.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each pre-filled pen contains 80 mg ixekizumab in 1 ml.

Ixekizumab is a recombinant humanised monoclonal antibody produced in CHO cells.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Solution for injection in pre-filled pen.

The solution is clear and colourless to slightly yellow.

4. **CLINICAL PARTICULARS**

4.1 Therapeutic indications

Plaque psoriasis

Taltz is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Psoriatic arthritis

Taltz, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drug (DMARD) therapies (see section 5.1).

4.2 Posology and method of administration

Taltz is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Taltz is indicated.

**Posology**

*Plaque psoriasis*

The recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks.

*Psoriatic arthritis*

The recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) every 4 weeks thereafter. For psoriatic arthritis patients with
concomitant moderate to severe plaque psoriasis, the recommended dosing regimen is the same as for plaque psoriasis.

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks.

Elderly (≥ 65 years)
No dose adjustment is required (see section 5.2).

There is limited information in subjects aged ≥ 75 years.

Renal or hepatic impairment
Taltz has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population
The safety and efficacy of Taltz in children and adolescents aged 6 to 18 years in the treatment of moderate to severe plaque psoriasis have not yet been established. No data are available.
There is no relevant use of Taltz in children below the age of 6 years in the treatment of moderate to severe plaque psoriasis.

The safety and efficacy of Taltz in children and adolescents aged 2 to less than 18 years in the treatment of psoriatic arthritis (a category of juvenile idiopathic arthritis) have not yet been established. No data are available. There is no relevant use of Taltz in children below 2 years for the indication of psoriatic arthritis.

Method of administration
Subcutaneous use.
Taltz is for subcutaneous injection. Injection sites may be alternated. If possible, areas of the skin that show psoriasis should be avoided as injection sites. The solution/the syringe must not be shaken.

After proper training in subcutaneous injection technique, patients may self-inject Taltz if a healthcare professional determines that it is appropriate. However, the physician should ensure appropriate follow-up of patients. Comprehensive instructions for administration are given in the package leaflet.

4.3 Contraindications
Serious hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically important active infections (e.g. active tuberculosis, see section 4.4).

4.4 Special warnings and precautions for use
Infections
Treatment with Taltz is associated with an increased rate of infections such as upper respiratory tract infection, oral candidiasis, conjunctivitis, and tinea infections (see section 4.8).

Taltz should be used with caution in patients with clinically important chronic infection. If such an infection develops, monitor carefully and discontinue Taltz if the patient is not responding to standard therapy or the infection becomes serious. Taltz should not be resumed until the infection resolves.

Taltz must not be given to patients with active tuberculosis (TB). Consider anti-TB therapy prior to initiation of Taltz in patients with latent TB.
Hypersensitivity

Serious hypersensitivity reactions, including some cases of anaphylaxis, angioedema, urticaria and, rarely, late (10-14 days following injection) serious hypersensitivity reactions including widespread urticaria, dyspnea and high antibody titres have been reported. If a serious hypersensitivity reaction occurs, administration of Taltz should be discontinued immediately and appropriate therapy initiated.

Inflammatory Bowel Disease

Cases of new or exacerbations of Crohn’s disease and ulcerative colitis have been reported. Caution should be exercised when prescribing Taltz to patients with inflammatory bowel disease, including Crohn’s disease and ulcerative colitis, and patients should be monitored closely.

Immunisations

Taltz should not be used with live vaccines. No data are available on the response to live vaccines; there are insufficient data on response to inactive vaccines (see section 5.1).

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per 80 mg dose, i.e., essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

In plaque psoriasis studies, the safety of Taltz in combination with other immunomodulatory agents or phototherapy has not been evaluated.

No formal in vivo drug-drug interaction studies have been conducted. A role for IL-17 in the regulation of CYP450 enzymes has not been reported. The formation of some CYP450 enzymes is, however, suppressed by increased levels of cytokines during chronic inflammation. Thus, anti-inflammatory treatments, such as with the IL-17A inhibitor ixekizumab, may result in normalisation of CYP450 levels with accompanying lower exposure of CYP450-metabolised co-medications. Therefore, a clinically relevant effect on CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g. warfarin), cannot be excluded. On initiation of ixekizumab therapy in patients being treated with these types of medicinal products, therapeutic monitoring should be considered.

No interaction was seen when Taltz was administered concomitantly with methotrexate (MTX) and/or corticosteroids in patients with psoriatic arthritis.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use an effective method of contraception during treatment and for at least 10 weeks after treatment.

Pregnancy

There is a limited amount of data from the use of ixekizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or post-natal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Taltz during pregnancy.
Breast-feeding

It is not known whether ixekizumab is excreted in human milk or absorbed systemically after ingestion. However, ixekizumab is excreted at low levels in the milk of cynomolgus monkeys. A decision should be made whether to discontinue breast-feeding or to discontinue Taltz taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of ixekizumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Taltz has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions (ADRs) were injection site reactions and upper respiratory tract infections (most frequently nasopharyngitis).

Tabulated list of adverse reactions

ADRs from clinical studies and postmarketing reports (Table 1) are listed by MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each ADR is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

A total of 7,339 patients have been treated with Taltz in blinded and open-label clinical studies in plaque psoriasis, psoriatic arthritis, and other autoimmune conditions. Of these, 4,500 patients were exposed to Taltz for at least one year, cumulatively representing 13,645.6 patient years of exposure.

In plaque psoriasis, three placebo-controlled phase III studies were integrated to evaluate the safety of Taltz in comparison to placebo up to 12 weeks after treatment initiation. A total of 3,119 patients were evaluated (1,161 patients on 80 mg every 4 weeks (Q4W), 1,167 patients on 80 mg every 2 weeks (Q2W) and 791 patients on placebo).

In psoriatic arthritis, two placebo-controlled phase III studies were integrated to evaluate the safety of Taltz in comparison to placebo up to 24 weeks after treatment initiation. A total of 678 patients were evaluated (229 patients on 80 mg every 4 weeks (Q4W), 225 patients on 80 mg every 2 weeks (Q2W) and 224 patients on placebo). The safety profile observed in patients with psoriatic arthritis treated with Taltz is consistent with the safety profile in plaque psoriasis with the exception of the frequencies of the adverse reactions of influenza and conjunctivitis which were common in patients with psoriatic arthritis.
Table 1. List of adverse reactions in clinical studies\textsuperscript{a} and postmarketing reports

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Very Common</td>
<td>Upper respiratory tract infection\textsuperscript{b}</td>
</tr>
<tr>
<td>Common</td>
<td>Tinea infection, Herpes simplex (mucocutaneous)\textsuperscript{c}</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Influenza\textsuperscript{i}, Rhinitis, Oral candidiasis\textsuperscript{d}, Conjunctivitis\textsuperscript{i}, Cellulitis\textsuperscript{e}</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Uncommon</td>
<td>Neutropenia, Thrombocytopenia\textsuperscript{g}</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Uncommon</td>
<td>Angioedema</td>
</tr>
<tr>
<td>Rare</td>
<td>Anaphylaxis\textsuperscript{h}</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Common</td>
<td>Oropharyngeal pain</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Nausea</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td>Uncommon</td>
<td>Urticaria, Rash, Eczema,</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common</td>
<td>Injection site reactions\textsuperscript{f}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Placebo-controlled clinical studies (phase III) in moderate to severe plaque psoriasis patients exposed to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W or placebo for up to 12 weeks of treatment duration, or in active psoriatic arthritis patients exposed to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W or placebo for up to 24 weeks of treatment duration.

\textsuperscript{b} Upper respiratory tract infection includes nasopharyngitis and upper respiratory tract infection.

\textsuperscript{c} Herpes simplex (mucocutaneous) is defined as events with the preferred terms Oral herpes, Herpes simplex, Genital herpes, Herpes dermatitis, and Genital herpes simplex.

\textsuperscript{d} Oral candidiasis defined as events with the preferred terms oral candidiasis and oral fungal infection.

\textsuperscript{e} Cellulitis includes staphylococcal and external ear cellulitis, and erysipelas.

\textsuperscript{f} In the plaque psoriasis studies, injection site reactions were more common in subjects with a body weight < 60 kg compared with the group with a body weight ≥ 60 kg (25 % vs. 14 % for the combined Q2W and Q4W groups). In the psoriatic arthritis studies, injection site reactions were more common in subjects with a body weight < 100 kg compared with the group with a body weight ≥ 100 kg (24 % vs. 13 % for the combined Q2W and Q4W groups). The increased frequency of injection site reactions in the combined Q2W and Q4W groups did not result in an increase in discontinuations in either the plaque psoriasis or the psoriatic arthritis studies.

\textsuperscript{g} Based on reported adverse events.

\textsuperscript{h} Based on postmarketing reports.

\textsuperscript{i} Adverse drug reactions in patients treated with ixekizumab in the plaque psoriasis and psoriatic arthritis clinical trials were similar with the exception of the frequencies of influenza (common) and conjunctivitis (common) in the psoriatic arthritis clinical trials.

Description of selected adverse reactions

(Based on adverse reactions data from 4,204 patients with moderate to severe plaque psoriasis [4,729.7 patient years] and 1,117 patients with active psoriatic arthritis [1,050.6 patient years] who have received at least 1 dose of ixekizumab.)

Injection site reactions
The most frequent injection site reactions observed were erythema and pain. These reactions were predominantly mild to moderate in severity and did not lead to discontinuation of Taltz.
Infections
In the placebo-controlled period of the phase III clinical studies in plaque psoriasis, infections were reported in 27.2% of patients treated with Taltz for up to 12 weeks compared with 22.9% of patients treated with placebo.

The majority of infections were non-serious and mild to moderate in severity, most of which did not necessitate treatment discontinuation. Serious infections occurred in 13 (0.6%) of patients treated with Taltz and in 3 (0.4%) of patients treated with placebo (see section 4.4). Over the entire treatment period infections were reported in 52.8% of patients treated with Taltz (46.9 per 100 patient years). Serious infections were reported in 1.6% of patients treated with Taltz (1.5 per 100 patient years).

Infection rates observed in psoriatic arthritis clinical studies were similar to those observed in the plaque psoriasis studies with the exception of the frequencies of the adverse reactions of influenza and conjunctivitis which were common in patients with psoriatic arthritis.

Laboratory assessment of neutropenia and thrombocytopenia
In plaque psoriasis studies, 9% of patients receiving Taltz developed neutropenia. In most cases, the blood neutrophil count was ≥1,000 cells/mm$^3$. Such levels of neutropenia may persist, fluctuate or be transient. 0.1% of patients receiving Taltz developed a neutrophil count <1000 cells/mm$^3$. In general, neutropenia did not require discontinuation of Taltz. 3% of patients exposed to Taltz had a shift from a normal baseline platelet value to <150,000 platelet cells/mm$^3$ to ≥75,000 cells/mm$^3$. Thrombocytopenia may persist, fluctuate or be transient.

The frequency of neutropenia and thrombocytopenia in psoriatic arthritis clinical studies is similar to that observed in the plaque psoriasis studies.

Immunogenicity
Approximately 9–17% of plaque psoriasis patients treated with Taltz at the recommended dosing regimen developed anti-drug antibodies, the majority of which were low titres and not associated with reduced clinical response up to 60 weeks of treatment. However, approximately 1% of patients treated with Taltz had confirmed neutralising antibodies associated with low drug concentrations and reduced clinical response.

In psoriatic arthritis patients treated with Taltz at the recommended dosing regimen up to 52 weeks, approximately 11% developed anti-drug antibodies, the majority of which were low titre, and approximately 8% had confirmed neutralising antibodies. No apparent association between the presence of neutralising antibodies and impact on drug concentration or efficacy was observed.

An association between immunogenicity and treatment emergent adverse events has not been clearly established.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose
Doses up to 180 mg have been administered subcutaneously in clinical trials without dose-limiting toxicity. Overdoses up to 240 mg, subcutaneously, as a single administration in clinical trials, have been reported without any serious adverse events. In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC13

Mechanism of action

Ixekizumab is an IgG4 monoclonal antibody that binds with high affinity (< 3 pM) and specificity to interleukin 17A (both IL-17A and IL-17A/F). Elevated concentrations of IL-17A have been implicated in the pathogenesis of psoriasis by promoting keratinocyte proliferation and activation, as well as in the pathogenesis of psoriatic arthritis. Neutralisation of IL-17A by ixekizumab inhibits these actions. Ixekizumab does not bind to ligands IL-17B, IL-17C, IL-17D, IL-17E or IL-17F.

In vitro binding assays confirmed that ixekizumab does not bind to human Fcγ receptors I, IIa, and IIIa or to complement component C1q.

Pharmacodynamic effects

Ixekizumab modulates biological responses that are induced or regulated by IL-17A. Based on psoriatic skin biopsy data from a phase I study, there was a dose-related trend towards decreased epidermal thickness, number of proliferating keratinocytes, T cells, and dendritic cells, as well as reductions in local inflammatory markers from baseline to day 43. As a direct consequence treatment with ixekizumab reduces erythema, induration and desquamation present in plaque psoriasis lesions.

Taltz has been shown to lower (within 1 week of treatment) levels of C-reactive protein, which is a marker of inflammation.

Clinical efficacy and safety

Plaque psoriasis

The efficacy and safety of Taltz were assessed in three randomised, double-blind, placebo-controlled phase III studies in adult patients with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy (UNCOVER-1, UNCOVER-2, and UNCOVER-3). The efficacy and safety of Taltz were also evaluated versus etanercept (UNCOVER-2 and UNCOVER-3). Patients randomised to Taltz who were sPGA (0,1) responders at Week 12 were re-randomised to receive placebo or Taltz for an additional 48 weeks (UNCOVER-1 and UNCOVER-2); patients randomised to placebo, etanercept or Taltz who were sPGA (0,1) non-responders received Taltz for up to 48 weeks.

Of the 3,866 patients enrolled in these placebo-controlled studies, 64 % had received prior systemic therapy (biologic, conventional systemic or psoralen and ultraviolet A (PUVA)), 43.5 % had received prior phototherapy, 49.3 % had received prior conventional systemic therapy, and 26.4 % had received prior biologic therapy for the treatment of psoriasis. Of all patients, 14.9 % had received at least one anti-TNF alpha agent, and 8.7 % had received an anti-IL-12/IL-23. 23.4 % of patients had a history of psoriatic arthritis at baseline.

In all three studies, the co-primary endpoints were the proportion of patients who achieved a PASI 75 response and an sPGA of 0 (“clear”) or 1 (“minimal”) response at Week 12 versus placebo. Patients in all treatment groups had a median baseline PASI score ranging from 17.4 to 18.3; 48.3 % to 51.2 % of patients had a baseline sPGA score of severe or very severe, and mean baseline itch Numeric Rating Scale (itch NRS) ranging from 6.3 to 7.1.

Clinical response at 12 weeks

UNCOVER-1 enrolled 1,296 patients. Patients were randomised (1:1:1) to receive either placebo or Taltz (80 mg every two or four weeks [Q2W or Q4W] following a 160 mg starting dose) for 12 weeks.
Table 2. Efficacy results at Week 12 in UNCOVER-1

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Number of patients (%)</th>
<th>Difference from Placebo in Response Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 431)</td>
<td>Taltz 80 mg Q4W (N = 432)</td>
</tr>
<tr>
<td>sPGA of “0” (clear) or “1” (minimal)</td>
<td>14 (3.2)</td>
<td>330 (76.4)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>sPGA of “0” (clear)</td>
<td>0</td>
<td>149 (34.5)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>PASI 75</td>
<td>17 (3.9)</td>
<td>357 (82.6)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>PASI 90</td>
<td>2 (0.5)</td>
<td>279 (64.6)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>PASI 100</td>
<td>0</td>
<td>145 (33.6)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Itch NRS reduction ≥ 4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>58 (15.5)</td>
<td>305 (80.5)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: N = number of patients in the intent-to-treat population
Note: patients with missing data were counted as non-responders
<sup>a</sup>p < 0.001 compared with placebo
<sup>b</sup>Patients with Itch NRS >= 4 at baseline: placebo N = 374, Taltz 80 mg Q4W N = 379, Taltz 80 mg Q2W N = 391

UNCOVER-2 enrolled 1,224 patients. Patients were randomised (1:2:2:2) to receive either placebo, or Taltz (80 mg every two or four weeks [Q2W or Q4W] following a 160 mg starting dose) or etanercept 50 mg twice weekly for 12 weeks.
Table 3. Efficacy results at Week 12 in UNCOVER-2

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Number of patients (%)</th>
<th>Difference from Placebo in Response Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 168)</td>
<td>Taltz 80 mg Q4W (N = 347)</td>
</tr>
<tr>
<td>sPGA of “0” (clear) or “1” (minimal)</td>
<td>4 (2.4)</td>
<td>253 (72.9)a</td>
</tr>
<tr>
<td>sPGA of “0” (clear)</td>
<td>1 (0.6)</td>
<td>112 (32.3)a,b</td>
</tr>
<tr>
<td>PASI 75</td>
<td>4 (2.4)</td>
<td>269 (77.5)a,b</td>
</tr>
<tr>
<td>PASI 90</td>
<td>1 (0.6)</td>
<td>207 (59.7)a,b</td>
</tr>
<tr>
<td>PASI 100</td>
<td>1 (0.6)</td>
<td>107 (30.8)a,b</td>
</tr>
<tr>
<td>Itch NRS reduction ≥ 4d</td>
<td>19 (14.1)</td>
<td>225 (76.8)a,b</td>
</tr>
</tbody>
</table>

Abbreviations: N = number of patients in the intent-to-treat population
Note: patients with missing data were counted as non-responders.
a p < 0.001 compared with placebo
b p < 0.001 compared with etanercept
c p < 0.01 compared with placebo
d Patients with Itch NRS ≥ 4 at baseline: placebo N = 135, Taltz 80 mg Q4W N = 293, Taltz 80 mg Q2W N = 303, Etanercept N = 306

UNCOVER-3 enrolled 1,346 patients. Patients were randomised (1:2:2:2) to receive either placebo, or Taltz (80 mg every two or four weeks [Q2W or Q4W] following a 160 mg starting dose) or etanercept 50 mg twice weekly for 12 weeks.
<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Number of patients (%)</th>
<th>Difference from Placebo in Response Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N = 193)</td>
<td>Taltz 80 mg Q4W (N = 386)</td>
<td>Taltz 80 mg Q2W (N = 385)</td>
</tr>
<tr>
<td>sPGA of “0” (clear)</td>
<td>13 (6.7)</td>
<td>291 (75.4)&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>sPGA of “0” (minimal)</td>
<td>0</td>
<td>139 (36.0)&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>sPGA of “0” (clear)</td>
<td>14 (7.3)</td>
<td>325 (84.2)&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>PASI 75</td>
<td>6 (3.1)</td>
<td>252 (65.3)&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>PASI 100</td>
<td>0</td>
<td>135 (35.0)&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Itch NRS reduction ≥ 4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>33 (20.9)</td>
<td>250 (79.9)&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Abbreviations:** N = number of patients in the intent-to-treat population

**Note:** patients with missing data were counted as non-responders

<sup>a</sup> p < 0.001 compared with placebo

<sup>b</sup> p < 0.001 compared with etanercept

<sup>c</sup> Patients with Itch NRS ≥ 4 at baseline: placebo N = 158, Taltz 80 mg Q4W N = 313, Taltz 80 mg Q2W N = 320, Etanercept N = 312

Taltz was associated with a fast onset of efficacy with > 50% reduction in mean PASI by Week 2 (Figure 1). The percentage of patients achieving PASI 75 was significantly greater for Taltz compared with placebo and etanercept as early as Week 1. Approximately 25% of patients treated with Taltz achieved a PASI score < 5 by Week 2, more than 55% achieved the PASI score < 5 by Week 4, and increased to 85% by Week 12 (compared to 3%, 14% and 50% for etanercept). Significant improvements in itch severity were seen at Week 1 in patients treated with Taltz.
The efficacy and safety of Taltz was demonstrated regardless of age, gender, race, body weight, PASI baseline severity, plaques location, concurrent psoriatic arthritis, and previous treatment with a biologic. Taltz was efficacious in systemic treatment-naive, biologic-naive, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients.

Efficacy in Non-Responders to Etanercept: For patients identified as an sPGA (0,1) non-responder to etanercept at Week 12 in UNCOVER-2 (N = 200) and who were switched to Taltz 80 mg Q4W after a 4 week washout period, 73 % and 83.5 % of patients were able to achieve sPGA (0,1) and PASI 75, respectively, after 12 weeks of being treated with Taltz.

In the 2 clinical studies that included an active comparator (UNCOVER-2 and UNCOVER-3), the rate of serious adverse events was 1.9 % for both etanercept and for Taltz, and the rate of discontinuation due to adverse events was 1.2 % for etanercept and 2.0 % for Taltz. The rate of infections was 21.5 % for etanercept and 26.0 % for Taltz, with the majority of the events mild to moderate in severity. The rate of serious infections was 0.4 % for etanercept and 0.5 % for Taltz.

Maintenance of Response at Week 60
Patients originally randomised to Taltz and who were responders at Week 12 (i.e., sPGA score of 0,1) in UNCOVER-1 and UNCOVER-2 were re-randomised to an additional 48 weeks of one of the following treatment regimens: placebo, or Taltz (80 mg every four or twelve weeks [Q4W or Q12W]).
Table 5. Maintenance of Response and Efficacy at Week 60 (Studies UNCOVER-1 and UNCOVER-2)

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Number of patients (%)</th>
<th>Difference from Placebo in Response Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg Q4W (induction) / Placebo (maintenance) (N = 191)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 mg Q2W (induction) / Placebo (maintenance) (N = 211)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 mg Q4W (induction) / 80 mg Q4W (maintenance) (N = 195)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 mg Q2W (induction) / 80 mg Q4W (maintenance) (N = 221)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Maintained sPGA of “0” (clear) or “1” (minimal)

<table>
<thead>
<tr>
<th></th>
<th>Number of patients (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg Q4W (induction) / Placebo (maintenance) (N = 191)</td>
<td>12 (6.3)</td>
<td>62.4 (55.1, 69.8)</td>
</tr>
<tr>
<td>80 mg Q2W (induction) / Placebo (maintenance) (N = 211)</td>
<td>16 (7.6)</td>
<td>70.7 (64.2, 77.2)</td>
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<tr>
<td>80 mg Q4W (induction) / 80 mg Q4W (maintenance) (N = 195)</td>
<td>134 (68.7)</td>
<td>6.3 (60.1, 69.8)</td>
</tr>
<tr>
<td>80 mg Q2W (induction) / 80 mg Q4W (maintenance) (N = 221)</td>
<td>173 (78.3)</td>
<td></td>
</tr>
</tbody>
</table>

Maintained or Achieved sPGA 0 (clear)

<table>
<thead>
<tr>
<th></th>
<th>Number of patients (%)</th>
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</thead>
<tbody>
<tr>
<td>80 mg Q4W (induction) / Placebo (maintenance) (N = 191)</td>
<td>3 (1.6)</td>
<td>47.7 (40.4, 54.9)</td>
</tr>
<tr>
<td>80 mg Q2W (induction) / Placebo (maintenance) (N = 211)</td>
<td>6 (2.8)</td>
<td>56.0 (49.1, 62.8)</td>
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<tr>
<td>80 mg Q4W (induction) / 80 mg Q4W (maintenance) (N = 195)</td>
<td>96 (49.2)</td>
<td></td>
</tr>
<tr>
<td>80 mg Q2W (induction) / 80 mg Q4W (maintenance) (N = 221)</td>
<td>130 (58.8)</td>
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</table>

Maintained or Achieved PASI 75

<table>
<thead>
<tr>
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<th>Number of patients (%)</th>
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<tbody>
<tr>
<td>80 mg Q4W (induction) / Placebo (maintenance) (N = 191)</td>
<td>15 (7.9)</td>
<td>66.5 (59.3, 73.7)</td>
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<tr>
<td>80 mg Q2W (induction) / Placebo (maintenance) (N = 211)</td>
<td>19 (9.0)</td>
<td>74.3 (68.0, 80.5)</td>
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<tr>
<td>80 mg Q4W (induction) / 80 mg Q4W (maintenance) (N = 195)</td>
<td>145 (74.4)</td>
<td></td>
</tr>
<tr>
<td>80 mg Q2W (induction) / 80 mg Q4W (maintenance) (N = 221)</td>
<td>184 (83.3)</td>
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Maintained or Achieved PASI 90

<table>
<thead>
<tr>
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<th>Number of patients (%)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>80 mg Q4W (induction) / Placebo (maintenance) (N = 191)</td>
<td>9 (4.7)</td>
<td>62.0 (54.7, 69.2)</td>
</tr>
<tr>
<td>80 mg Q2W (induction) / Placebo (maintenance) (N = 211)</td>
<td>10 (4.7)</td>
<td>71.7 (65.4, 78.0)</td>
</tr>
<tr>
<td>80 mg Q4W (induction) / 80 mg Q4W (maintenance) (N = 195)</td>
<td>130 (66.7)</td>
<td></td>
</tr>
<tr>
<td>80 mg Q2W (induction) / 80 mg Q4W (maintenance) (N = 221)</td>
<td>169 (76.5)</td>
<td></td>
</tr>
</tbody>
</table>

Maintained or Achieved PASI 100

<table>
<thead>
<tr>
<th></th>
<th>Number of patients (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg Q4W (induction) / Placebo (maintenance) (N = 191)</td>
<td>3 (1.6)</td>
<td>48.2 (40.9, 55.4)</td>
</tr>
<tr>
<td>80 mg Q2W (induction) / Placebo (maintenance) (N = 211)</td>
<td>6 (2.8)</td>
<td>54.6 (47.7, 61.5)</td>
</tr>
<tr>
<td>80 mg Q4W (induction) / 80 mg Q4W (maintenance) (N = 195)</td>
<td>97 (49.7)</td>
<td></td>
</tr>
<tr>
<td>80 mg Q2W (induction) / 80 mg Q4W (maintenance) (N = 221)</td>
<td>127 (57.5)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: N = number of patients in the analysis population
Note: patients with missing data were counted as non-responders

Significantly greater improvements at Week 12 from baseline compared to placebo and etanercept were demonstrated in nail psoriasis (as measured by the Nail Psoriasis Severity Index [NAPSI]), in scalp psoriasis (as measured by Psoriasis Scalp Severity Index [PSSI]) and in palmoplantar psoriasis (as measured by Psoriasis Palmoplantar Severity Index [PPASI]). These improvements in nail, scalp and palmoplantar psoriasis were maintained at Week 60 in patients treated with Taltz who were sPGA (0 or 1) responders at Week 12.

Quality of Life/Patient-Reported Outcomes

At Week 12 and across studies, Taltz was associated with statistically significant improvement in Health-related Quality of Life as assessed by mean decrease ranges from baseline in the Dermatology Life Quality Index (DLQI) (Taltz 80 mg Q2W from -10.2 to -11.1, Taltz 80 mg Q4W from -9.4 to -10.7, etanercept from -7.7 to -8.0 and placebo -1.0 to -2.0). A significantly greater proportion of patients treated with Taltz achieved a DLQI 0 or 1. Across studies, Taltz was associated with statistically significant improvement of itching severity assessed by the Itch NRS score. A significantly greater proportion of patients treated with Taltz achieved a reduction of Itch NRS ≥ 4 points at week 12 (84.6% for Taltz Q2W, 79.2% for Taltz Q4W and 16.5% for placebo) and the benefit was sustained over time up to Week 60 in patients treated with Taltz who were sPGA (0 or 1).
responders at Week 12. There was not any evidence of worsening of depression up to 60 weeks treatment with Taltz as assessed by the Quick Inventory of Depressive Symptomatology Self Report.

Psoriatic arthritis
The safety and efficacy of Taltz were assessed in two randomised, double-blind, placebo-controlled phase III studies in 780 patients with active psoriatic arthritis (≥3 swollen and ≥3 tender joints). Patients in these studies had a diagnosis of psoriatic arthritis (Classification Criteria for Psoriatic Arthritis [CASPAR] criteria) for a median of 5.33 years. Randomised patients also had current plaque psoriasis skin lesions (94.0%) or a documented history of plaque psoriasis, with 12.1% of patients with moderate to severe plaque psoriasis at baseline. Over 58.9% and 22.3% of the psoriatic arthritis patients had enthesitis and dactylitis at baseline, respectively. For both studies, the primary endpoint was American College of Rheumatology (ACR) 20 response at Week 24.

In Psoriatic Arthritis Study 1 (SPIRIT-P1), patients naive to biologic therapy with active psoriatic arthritis were randomised to subcutaneous injections of placebo, adalimumab 40 mg once every 2 weeks (active control reference arm), Taltz 80 mg once every 2 weeks (Q2W), or 80 mg once every 4 weeks (Q4W). Both Taltz regimens included a 160 mg starting dose. 85.3% of patients in this study had received prior treatment with ≥1 cDMARD. 53% of patients had concomitant use of MTX at a mean weekly dose of 15.8 mg. 67% of patients who had concomitant use of MTX had a dose of 15 mg or greater. Patients in all treatment groups with an inadequate response at week 16 received rescue therapy (modification to background therapy). Patients on Taltz Q2W or Q4W remained on their originally assigned dose of Taltz. Patients receiving adalimumab or placebo were re-randomised 1:1 to Taltz Q2W or Q4W at week 16 or 24 based on responder status.

Psoriatic Arthritis Study 2 (SPIRIT-P2) enrolled patients who were previously treated with an anti-TNF agent and discontinued the anti-TNF agent for either lack of efficacy or intolerance (anti-TNF-IR patients). Patients were randomised to subcutaneous injections of placebo, Taltz 80 mg once every 2 weeks (Q2W), or 80 mg once every 4 weeks (Q4W). Both Taltz regimens included a 160 mg starting dose. 56% and 35% of patients were inadequate responders to 1 anti-TNF or 2 anti-TNF, respectively. SPIRIT-P2 evaluated 363 patients, of whom 41% had concomitant use of MTX at a mean weekly dose of 16.1 mg. 73.2% of patients who had concomitant use of MTX had a dose of 15 mg or greater. Patients in all treatment groups with an inadequate response at week 16 received rescue therapy (modification to background therapy). Patients in Taltz Q2W or Q4W remained on their originally assigned dose of Taltz. Patients receiving placebo were re-randomised 1:1 to Taltz Q2W or Q4W at week 16 or 24 based on responder status.

Signs and symptoms
Treatment with Taltz resulted in significant improvement in measures of disease activity compared to placebo at Week 24 (see Table 6).

Table 6. Efficacy results in SPIRIT-P1 and SPIRIT-P2 at week 24

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>SPIRIT-P1</th>
<th>SPIRIT-P2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference from Placebo in Response Rate (95% CI)</td>
<td>Difference from Placebo in Response Rate (95% CI)</td>
</tr>
<tr>
<td></td>
<td>PBO (N = 106)</td>
<td>Taltz Q4W (N = 107)</td>
</tr>
<tr>
<td>ACR 20 response, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>32 (30.2)</td>
<td>62 (57.9)</td>
</tr>
<tr>
<td>Endpoints</td>
<td>SPIRIT-P1</td>
<td>SPIRIT-P2</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td>PBO (N = 106)</td>
<td>Taltz Q4W (N = 107)</td>
</tr>
<tr>
<td></td>
<td>Difference from Placebo in Response Rate (95% CI)</td>
<td>Difference from Placebo in Response Rate (95% CI)</td>
</tr>
<tr>
<td>ACR 50 response, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>16 (15.1)</td>
<td>43 (40.2)</td>
</tr>
<tr>
<td>ACR 70 response, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>6 (5.7)</td>
<td>25 (23.4)</td>
</tr>
<tr>
<td>Minimal Disease Activity n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>16 (15.1)</td>
<td>32 (29.9)</td>
</tr>
<tr>
<td>ACR 50 and PASI 100 in patients with ≥3% BSA psoriasis skin involvement at baseline, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>1 (1.5)</td>
<td>21 (28.8)</td>
</tr>
</tbody>
</table>

Abbreviations:  ACR 20/50/70 = American College of Rheumatology 20%/50%/70% response rate;  ADA = adalimumab;  BSA = body surface area;  CI = confidence interval;  Q4W = Taltz 80 mg every 4 weeks;  Q2W = Taltz 80 mg every 2 weeks;  N = number of patients in the analysis population;  n = number of patients in the specified category;  NRI = non-responder imputation;  PASI 100 = psoriasis area and severity index 100% improvement;  PBO = placebo.

Note: patients who were rescued at week 16 or discontinued or with missing data were imputed as non-responders for week 24 analyses.

Concomitant cDMARDs included MTX, leflunomide and sulfasalazine.

In patients with pre-existing dactylitis or enthesitis, treatment with Taltz Q4W resulted in improvement in dactylitis and enthesitis at Week 24 compared to placebo (resolution: 78% vs. 24%; p<0.001, and 39% vs. 21%; p<0.01, respectively).

In patients with ≥3% BSA, the improvement in skin clearance at Week 12 as measured by 75% improvement in Psoriasis Area Severity Index (PASI 75), was 67% (94/141) for those treated with the Q4W dosing regimen, and 9% (12/134) for those treated with placebo (p<0.001). The proportion of patients achieving a PASI 75, PASI 90, and PASI 100 response at Week 24 was greater with Taltz Q4W compared to placebo (p<0.001). In patients with concomitant moderate to severe psoriasis and psoriatic arthritis, Taltz Q2W dose regimen showed significantly higher response rate for PASI75, PASI 90 and PASI 100 compared to placebo (p<0.001) and demonstrated clinically meaningful benefit over the Q4W dose regimen.

The treatment responses on Taltz were significantly greater than those on placebo as early as week 1 for ACR 20, week 4 for ACR 50 and week 8 for ACR 70 and persisted through week 24.
In SPIRIT-P1 and SPIRIT-P2, similar responses for ACR 20/50/70 were seen in patients with psoriatic arthritis regardless of whether they were on concomitant cDMARDs, including MTX treatment, or not.

In SPIRIT-P1 and SPIRIT-P2, improvements were shown in all components of the ACR scores including patient assessment of pain. At Week 24 the proportion of patients achieving a modified Psoriatic Arthritis Response Criteria (PsARC) response was greater in the Taltz-treated patients compared to placebo.

In SPIRIT-P1, efficacy was maintained up to Week 52 as assessed by ACR 20/50/70, MDA, enthesitis resolution, dactylitis resolution, and PASI 75/90/100 response rates.

The efficacy and safety of Taltz was demonstrated regardless of age, gender, race, disease duration, baseline body weight, baseline psoriasis involvement, baseline CRP, baseline DAS28-CRP, concomitant corticosteroid use, and previous treatment with a biologic. Taltz was efficacious in biologic-naive, biologic-exposed and biologic-failure patients.

**Radiographic response**

In SPIRIT-P1, inhibition of progression of structural damage was assessed radiographically and expressed as the change in modified total Sharp Score (mTSS) and its components, the Erosion Score (ES) and the Joint Space Narrowing score (JSN) at Weeks 24 and 52, compared to baseline. Week 24 data are presented in Table 7.

**Table 7. Change in modified Total Sharp Score in SPIRIT-P1**

<table>
<thead>
<tr>
<th></th>
<th>PBO (N = 106)</th>
<th>Taltz Q4W (N = 107)</th>
<th>Taltz Q2W (N = 103)</th>
<th>ADA (N = 101)</th>
<th>Taltz Q4W</th>
<th>Taltz Q2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline score, mean (SD)</td>
<td>17.6 (28.62)</td>
<td>19.2 (32.68)</td>
<td>15.2 (28.86)</td>
<td>15.9 (27.37)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Change from baseline at Week 24, LSM (SE)</td>
<td>0.51 (0.092)</td>
<td>0.18 (0.090)</td>
<td>0.09 (0.091)</td>
<td>0.13 (0.093)</td>
<td>-0.33 (-0.57,-0.09)</td>
<td>-0.42 (-0.66,-0.19)</td>
</tr>
</tbody>
</table>

For both Taltz Q2W and Q4W: \( b \) \( p<0.01 \) and \( c \) \( p<0.001 \) compared with placebo.
Radiographic joint damage progression was inhibited by Taltz (Table 7) at Week 24, and the percentage of patients with no radiographic joint damage progression (defined as a change from baseline in mTSS of $\leq 0.5$) from randomisation to Week 24 was 94.8% for Taltz Q2W ($p<0.001$), 89.0% for Taltz Q4W ($p=0.026$), 95.8% for adalimumab ($p<0.001$), all compared to 77.4% for placebo. At Week 52, the mean change from baseline in mTSS was 0.27 for placebo/Taltz Q4W, 0.54 for Taltz Q4W/Taltz Q4W, and 0.32 for adalimumab/Taltz Q4W. The percentage of patients with no radiographic joint damage progression from randomisation to Week 52 was 90.9% for placebo/Taltz Q4W, 85.6% for Taltz Q4W/Taltz Q4W, and 89.4% for adalimumab/Taltz Q4W.

**Physical function and health-related quality of life**

In both SPIRIT-P1 and SPIRIT-P2, patients treated with Taltz Q2W ($p<.001$) and Q4W ($p<.001$) showed significant improvement in physical function compared to patients treated with placebo as assessed by Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24, and maintained at Week 52 in SPIRIT-P1.

Taltz-treated patients reported improvements in health-related quality of life as measured by the Physical Component Summary of the Short Form-36 Health Survey (SF-36 PCS) score ($p<.001$). There were also improvements demonstrated in fatigue as assessed by Fatigue severity NRS scores ($p<0.001$).

**Immunisations**

In a study in healthy subjects, no safety concerns were identified of two inactivated vaccines (tetanus and pneumococcal), received after two doses of ixekizumab (160 mg followed by a second dose of 80 mg two weeks later). However, the data concerning immunisation were insufficient to conclude on an adequate immune response to these vaccines following administration of Taltz.

**Paediatric population**

The European Medicines Agency has deferred the obligation to submit the results of studies with Taltz in one or more subsets of the paediatric population in the treatment of plaque psoriasis and psoriatic arthritis (see section 4.2 for information on paediatric use).

**5.2 Pharmacokinetic properties**

**Absorption**

Following a single subcutaneous dose of ixekizumab in patients with psoriasis, mean peak concentrations were achieved within 4 to 7 days, across a dose range of 5 to 160 mg. The mean (SD) maximum plasma concentration ($C_{\text{max}}$) of ixekizumab, after the 160 mg starting dose, was 19.9 (8.15) µg/ml.

After the 160 mg starting dose, steady state was achieved by Week 8 with the 80 mg Q2W dosing regimen. Mean (SD) $C_{\text{max,ss}}$, and $C_{\text{trough,ss}}$ estimates are 21.5 (9.16) µg/ml, and 5.23 (3.19) µg/ml.

After switching from the 80 mg Q2W dosing regimen to the 80 mg Q4W dosing regimen at Week 12, steady state would be achieved after approximately 10 weeks. Mean (SD) $C_{\text{max,ss}}$, and $C_{\text{trough,ss}}$ estimates are 14.6 (6.04) µg/ml, and 1.87 (1.30) µg/ml.

The average bioavailability of ixekizumab after subcutaneous administration was 54% to 90% across analyses.
Distribution

From population pharmacokinetic analyses, the mean total volume of distribution at steady state was 7.11 L.

Biotransformation

Ixekizumab is a monoclonal antibody and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous immunoglobulins.

Elimination

In the population PK analysis, mean serum clearance was 0.0161 L/hr. Clearance is independent of dose. The mean elimination half-life, as estimated from population pharmacokinetic analysis, is 13 days in patients with plaque psoriasis.

Linearity/non-linearity

Exposure (AUC) increased proportionally over a dose range of 5 to 160 mg given as a subcutaneous injection.

Psoriatic arthritis

The pharmacokinetic properties of Taltz observed in psoriatic arthritis patients were similar to those displayed in plaque psoriasis patients. The bioavailability of Taltz in psoriatic arthritis patients was in the range of 61-84% on the basis of the population pharmacokinetic model.

Elderly

Of the 4,204 plaque psoriasis patients exposed to Taltz in clinical studies, a total of 301 were 65 years of age or older and 36 patients were 75 years of age or older. Of the 1,118 psoriatic arthritis patients exposed to Taltz in clinical studies, a total of 122 patients were 65 years of age or older and 6 patients were 75 years of age or older.

Based on population pharmacokinetic analysis with a limited number of elderly patients (n = 94 for age ≥ 65 years and n = 12 for age ≥ 75 years), clearance in elderly patients and patients less than 65 years of age was similar.

Renal or hepatic impairment

Specific clinical pharmacology studies to evaluate the effects of renal impairment and hepatic impairment on the PK of ixekizumab have not been conducted. Renal elimination of intact ixekizumab, an IgG MAb, is expected to be low and of minor importance; similarly, IgG MAbs are mainly eliminated via intracellular catabolism and hepatic impairment is not expected to influence clearance of ixekizumab.

5.3 Preclinical safety data

Non-clinical data from cynomolgus monkeys revealed no special hazards for humans based on repeat-dose toxicity studies, safety pharmacology evaluations, and reproductive and developmental toxicity studies.

Ixekizumab administration to cynomolgus monkeys for 39 weeks at subcutaneous doses up to 50 mg/kg weekly produced no organ toxicity or undesirable effects on immune function (e.g. T-cell dependent antibody response and NK cell activity). A weekly subcutaneous dose of 50 mg/kg to monkeys is approximately 19 times the 160 mg starting dose of Taltz and in monkeys results in exposure (AUC) that is at least 61-fold higher than the predicted mean steady-state exposure in humans administered the recommended dose regimen.
Non-clinical studies have not been conducted to evaluate the carcinogenic or mutagenic potential of ixekizumab.

No effects on reproductive organs, menstrual cycles or sperm were observed in sexually mature cynomolgus monkeys that received ixekizumab for 13 weeks at a weekly subcutaneous dose of 50 mg/kg.

In developmental toxicity studies, ixekizumab was shown to cross the placenta and was present in the blood of offspring for up to 6 months of age. A higher incidence of postnatal mortality occurred in the offspring of monkeys given ixekizumab compared to concurrent controls. This was related primarily to early delivery or maternal neglect of offspring, common findings in nonhuman primate studies, and considered clinically irrelevant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Citric acid, anhydrous
Sodium chloride
Polysorbate 80
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Store in the original package in order to protect from light.

Taltz may be stored unrefrigerated for up to 5 days at a temperature not above 30 °C.

6.5 Nature and contents of container

1 ml solution in a type I clear glass syringe. The syringe is encased in a disposable, single-dose pen. Packs of 1, 2, or 3 pre-filled pens. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use
The instructions for using the pen, included with the leaflet, must be followed carefully.

The pre-filled pen is for single use only.

Taltz should not be used if particles appear or if the solution is cloudy and/or distinctly brown.

Taltz that has been frozen must not be used.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1085/001
EU/1/15/1085/002
EU/1/15/1085/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 April 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Eli Lilly S.A.
Dunderrow
Kinsale
Co. Cork
Ireland

Name and address of the manufacturer responsible for batch release

Eli Lilly Italia S.p.A.
Via Gramsci 731/733
50019 Sesto Fiorentino (FI)
Italy.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

   Taltz 80 mg solution for injection in pre-filled syringe
   ixekizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

   Each pre-filled syringe contains 80 mg of ixekizumab in 1 ml solution.

3. LIST OF EXCIPIENTS

   Excipients: sodium citrate; citric acid, anhydrous; sodium chloride; polysorbate 80; water for
   injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

   Solution for injection,
   1 pre-filled syringe of 1 ml solution
   2 pre-filled syringes of 1 ml solution
   3 pre-filled syringes of 1 ml solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

   For single use only.
   Read the package leaflet before use.
   Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
   OF THE SIGHT AND REACH OF CHILDREN

   Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

   If seal is broken, do not use.
   Do not shake.

8. EXPIRY DATE

   EXP
9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1085/004 1 pre-filled syringe
EU/1/15/1085/005 2 pre-filled syringes
EU/1/15/1085/006 3 pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Taltz

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Taltz 80 mg solution for injection in pre-filled pen
ixekizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 80 mg of ixekizumab in 1 ml solution.

3. LIST OF EXCIPIENTS

Excipients: sodium citrate; citric acid, anhydrous; sodium chloride; polysorbate 80; water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
1 pre-filled pen of 1 ml solution
2 pre-filled pens of 1 ml solution
3 pre-filled pens of 1 ml solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If seal is broken, do not use.
Do not shake.

8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1085/001 1 pre-filled pen
EU/1/15/1085/002 2 pre-filled pens
EU/1/15/1085/003 3 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Taltz

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

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<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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<tbody>
<tr>
<td>Taltz 80 mg injection</td>
</tr>
<tr>
<td>ixekizumab</td>
</tr>
<tr>
<td>Subcutaneous use</td>
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<table>
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<tr>
<th>2. METHOD OF ADMINISTRATION</th>
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</thead>
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<table>
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<tr>
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<td>---------------------------------------------------------------</td>
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<td>PRE-FILLED PEN LABEL</td>
</tr>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</td>
</tr>
<tr>
<td>Taltz 80 mg solution for injection</td>
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<tr>
<td>ixekizumab</td>
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<tr>
<td>Subcutaneous use</td>
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This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet
1. What Taltz is and what it is used for
2. What you need to know before you use Taltz
3. How to use Taltz
4. Possible side effects
5. How to store Taltz
6. Contents of the pack and other information

1. What Taltz is and what it is used for

Taltz contains the active substance ixekizumab.

Ixekizumab belongs to a group of medicines called interleukin (IL) inhibitors. This medicine works by neutralising the activity of a protein called IL-17A, which promotes psoriasis and psoriatic arthritis.

Plaque psoriasis
Taltz is used to treat a skin condition called “plaque psoriasis” in adults with moderate to severe disease. Taltz reduces the signs and symptoms of the disease.

Using Taltz will benefit you by improvements of skin clearance and reducing your symptoms such as scaling, itching and pain.

Psoriatic arthritis
Taltz is used to treat a condition called “psoriatic arthritis”, an inflammatory disease of the joints, often accompanied by psoriasis. If you have psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Taltz to reduce the signs and symptoms of the disease. Taltz can be used alone or with another medicine named methotrexate.

Using Taltz will benefit you by reducing the signs and symptoms of the disease, improving physical function (ability to do normal daily activities), and slowing down the damage to the joints.

2. What you need to know before you use Taltz

Do not use Taltz
- if you are allergic to ixekizumab or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice before using Taltz.
- if you have an infection which your doctor thinks is important (for example, active tuberculosis).

**Warnings and precautions**
Talk to your doctor, nurse or pharmacist before using Taltz:

- if you currently have an infection or if you have long-term or repeated infections.
- if you have Crohn’s disease.
- if you have ulcerative colitis.
- if you are receiving any other treatment for psoriasis (such as immunosuppressant or phototherapy with ultraviolet light) or for psoriatic arthritis.

If you are not sure if any of the above applies to you, talk to your doctor or nurse before using Taltz.

**Look out for infections and allergic reactions**
Taltz can potentially cause serious side effects, including infections and allergic reactions. You must look out for signs of these conditions while you are using Taltz.

Stop using Taltz and tell your doctor or seek medical help immediately if you notice any signs of a serious infection or an allergic reaction. Such signs are listed under “Serious side effects” in section 4.

**Children and adolescents**
Taltz is not recommended for children and adolescents under 18 years of age because it has not been studied in this age group.

**Other medicines and Taltz**
Tell your doctor, pharmacist or nurse
- if you are using, have recently used or might use any other medicine.
- if you have recently had or are due to have a vaccination. You should not be given certain types of vaccines while using Taltz.

**Pregnancy and breast-feeding**
If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before using this medicine. It is preferable to avoid the use of Taltz in pregnancy. The effects of this medicine in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Taltz and for at least 10 weeks after the last Taltz dose.

If you are breast-feeding or are planning to breast-feed, talk to your doctor before using this medicine. You and your doctor should decide if you will breast-feed or use Taltz. You should not do both.

**Driving and using machines**
Taltz is unlikely to influence your ability to drive and use machines.

**Taltz contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per 80 mg dose, i.e., essentially “sodium-free”.

3. **How to use Taltz**
Always use this medicine exactly as your doctor or nurse has told you. Check with your doctor, nurse or pharmacist if you are not sure how to use this medicine.

Taltz is given by injection under your skin (subcutaneous injection). You and your doctor or nurse should decide if you should inject Taltz yourself.
It is important not to try to inject yourself until you have been trained by your doctor or nurse. A caregiver may also give you your Taltz injection after proper training.

Each syringe contains one dose of Taltz (80 mg). Each syringe delivers only one dose. The syringe must not be shaken.

Read the “Instructions for Use” for the syringe carefully before using Taltz.

**How much Taltz is given and for how long**
Your doctor will decide how much Taltz you need and for how long.

**Plaque psoriasis**
- The first dose is 160 mg (two 80 mg injections) by subcutaneous injection. This may be given by your doctor or nurse.
- After the first dose, you will use an 80 mg dose (one injection) at Weeks 2, 4, 6, 8, 10, and 12. From Week 12, you will use an 80 mg dose (one injection) every 4 weeks.

**Psoriatic arthritis**
For psoriatic arthritis patients who also have moderate to severe plaque psoriasis:
- The first dose is 160 mg (two 80 mg injections) by subcutaneous injection. This may be given by your doctor or nurse.
- After the first dose, you will use an 80 mg dose (one injection) at Weeks 2, 4, 6, 8, 10, and 12. From Week 12, you will use an 80 mg dose (one injection) every 4 weeks.

For other psoriatic arthritis patients:
- The first dose is 160 mg (two 80 mg injections) by subcutaneous injection. This may be given by your doctor or nurse.
- After the first dose you will use an 80 mg dose (one injection) every 4 weeks.

Use a reminder method such as notes in a calendar or diary to help you remember your next dose so that you avoid missing or repeating doses.

Taltz is for long-term treatment. Your doctor or nurse will regularly monitor your condition to check that the treatment is having the desired effect.

**If you use more Taltz than you should**
If you have received more Taltz than you should or the dose has been given sooner than prescribed, inform your doctor.

**If you forget to use Taltz**
If you have forgotten to inject a dose of Taltz, talk to your doctor.

**If you stop using Taltz**
You should not stop using Taltz without speaking to your doctor first. If you stop treatment, symptoms of psoriasis or psoriatic arthritis may come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.
4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Serious side effects**
Stop using Taltz and tell your doctor or seek medical help immediately if you get any of the following side effects. Your doctor will decide if and when you may restart the treatment:

**Possible serious infection** (may affect up to 1 in 100 people) - the signs may include:
- fever, flu-like symptoms, night sweats
- feeling tired or short of breath, cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters

**Serious allergic reaction** (may affect up to 1 in 1,000 people) - the signs may include:
- difficulty breathing or swallowing
- low blood pressure, which can cause dizziness or light-headedness
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps

**Other side effects that have been reported**

**Some side effects are very common** (may affect more than 1 in 10 people):
- upper respiratory tract infections with symptoms such as sore throat and stuffy nose (nasopharyngitis).
- injection site reactions (e.g. red skin, pain).

**Some side effects are common** (may affect up to 1 in 10 people):
- nausea (feeling sick).
- tinea (fungal) infections such as athlete’s foot.
- pain in the back of the throat.
- Cold sores of mouth, skin and mucous membranes (herpes simplex, mucocutaneous)

**Some side effects are uncommon** (may affect up to 1 in 100 people):
- oral thrush (oral candidiasis).
- influenza.
- runny nose.
- bacterial skin infection.
- hives.
- discharge from the eye with itching, redness and swelling (conjunctivitis).
- signs of low levels of white blood cells, such as fever, sore throat or mouth ulcers due to infections (neutropenia).
- low blood platelet count (thrombocytopenia).
- Eczema
- Rash
- Rapid swelling of the tissues of the neck, face, mouth or throat (angioedema)

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.
5. **How to store Taltz**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the syringe label and on the outer carton after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze.

Store in the original packaging in order to protect from light.

Taltz can be left out of the fridge for up to 5 days at a temperature not above 30 ºC.

Do not use this medicine if you notice that the syringe is damaged, or the medicine is cloudy, distinctly brown, or has particles in it.

This medicine is for single use only.

Do not throw away any medicines via wastewater or household waste. Ask your doctor, nurse or pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. **Contents of the pack and other information**

**What Taltz contains**
- The active substance is ixekizumab.
  Each pre-filled syringe contains 80 mg of ixekizumab in 1 ml solution.
- The other ingredients are sodium citrate; citric acid, anhydrous; sodium chloride; polysorbate 80; water for injections.

**What Taltz looks like and contents of the pack**
Taltz is a solution in a clear glass syringe. Its colour may vary from colourless to slightly yellow.

Pack sizes of 1, 2, 3 pre-filled syringes. Not all pack sizes may be available in your country.

**Marketing Authorisation Holder**
Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands.

**Manufacturer**
Eli Lilly Italia S.p.A., Via Gramsci 731/733, 50019, Sesto Fiorentino (FI), Italy.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:

---------------------------------------------------------------------------------------------
Package leaflet: Information for the patient

Taltz 80 mg solution for injection in pre-filled pen
ixekizumab

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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2. What you need to know before you use Taltz

Do not use Taltz
- if you are allergic to ixekizumab or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice before using Taltz.
– if you have an infection which your doctor thinks is important (for example, active tuberculosis).

**Warnings and precautions**
Talk to your doctor, nurse or pharmacist before using Taltz:

– if you currently have an infection or if you have long-term or repeated infections.
– if you have Crohn’s disease.
– if you have ulcerative colitis.
– if you are receiving any other treatment for psoriasis (such as immunosuppressant or phototherapy with ultraviolet light) or for psoriatic arthritis.

If you are not sure if any of the above applies to you, talk to your doctor or nurse before using Taltz.

**Look out for infections and allergic reactions**
Taltz can potentially cause serious side effects, including infections and allergic reactions. You must look out for signs of these conditions while you are using Taltz.

Stop using Taltz and tell your doctor or seek medical help immediately if you notice any signs of a serious infection or an allergic reaction. Such signs are listed under “Serious side effects” in section 4.

**Children and adolescents**
Taltz is not recommended for children and adolescents under 18 years of age because it has not been studied in this age group.

**Other medicines and Taltz**
Tell your doctor, pharmacist or nurse
– if you are using, have recently used or might use any other medicine.
– if you have recently had or are due to have a vaccination. You should not be given certain types of vaccines while using Taltz.

**Pregnancy and breast-feeding**
If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before using this medicine. It is preferable to avoid the use of Taltz in pregnancy. The effects of this medicine in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Taltz and for at least 10 weeks after the last Taltz dose.

If you are breast-feeding or are planning to breast-feed, talk to your doctor before using this medicine. You and your doctor should decide if you will breast-feed or use Taltz. You should not do both.

**Driving and using machines**
Taltz is unlikely to influence your ability to drive and use machines.

**Taltz contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per 80 mg dose, i.e., essentially “sodium-free”.

3. **How to use Taltz**

Always use this medicine exactly as your doctor or nurse has told you. Check with your doctor, nurse or pharmacist if you are not sure how to use this medicine.

Taltz is given by injection under your skin (subcutaneous injection). You and your doctor or nurse should decide if you should inject Taltz yourself.
It is important not to try to inject yourself until you have been trained by your doctor or nurse. A caregiver may also give you your Taltz injection after proper training.

Each pen contains one dose of Taltz (80 mg). Each pen delivers only one dose. The pen must not be shaken.

Read the “Instructions for Use” for the pen carefully before using Taltz.

**How much Taltz is given and for how long**

Your doctor will decide how much Taltz you need and for how long.

**Plaque psoriasis**
- The first dose is 160 mg (two 80 mg injections) by subcutaneous injection. This may be given by your doctor or nurse.
- After the first dose, you will use an 80 mg dose (one injection) at Weeks 2, 4, 6, 8, 10, and 12. From Week 12, you will use an 80 mg dose (one injection) every 4 weeks.

**Psoriatic arthritis**
For psoriatic arthritis patients who also have moderate to severe plaque psoriasis:
- The first dose is 160 mg (two 80 mg injections) by subcutaneous injection. This may be given by your doctor or nurse.
- After the first dose, you will use an 80 mg dose (one injection) at Weeks 2, 4, 6, 8, 10, and 12. From Week 12, you will use an 80 mg dose (one injection) every 4 weeks.

For other psoriatic arthritis patients:
- The first dose is 160 mg (two 80 mg injections) by subcutaneous injection. This may be given by your doctor or nurse.
- After the first dose you will use an 80 mg dose (one injection) every 4 weeks.

Use a reminder method such as notes in a calendar or diary to help you remember your next dose so that you avoid missing or repeating doses.

Taltz is for long-term treatment. Your doctor or nurse will regularly monitor your condition to check that the treatment is having the desired effect.

**If you use more Taltz than you should**
If you have received more Taltz than you should or the dose has been given sooner than prescribed, inform your doctor.

**If you forget to use Taltz**
If you have forgotten to inject a dose of Taltz, talk to your doctor.

**If you stop using Taltz**
You should not stop using Taltz without speaking to your doctor first. If you stop treatment, symptoms of psoriasis or psoriatic arthritis may come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. **Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Serious side effects**
Stop using Taltz and tell your doctor or seek medical help immediately if you get any of the following side effects. Your doctor will decide if and when you may restart the treatment:
Possible serious infection (may affect up to 1 in 100 people) - the signs may include:
- fever, flu-like symptoms, night sweats
- feeling tired or short of breath, cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters

Serious allergic reaction (may affect up to 1 in 1,000 people) - the signs may include:
- difficulty breathing or swallowing
- low blood pressure, which can cause dizziness or light-headedness
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps

Other side effects that have been reported

Some side effects are very common (may affect more than 1 in 10 people):
- upper respiratory tract infections with symptoms such as sore throat and stuffy nose (nasopharyngitis).
- injection site reactions (e.g. red skin, pain).

Some side effects are common (may affect up to 1 in 10 people):
- nausea (feeling sick).
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- pain in the back of the throat.
- Cold sores of mouth, skin and mucous membranes (herpes simplex, mucocutaneous)

Some side effects are uncommon (may affect up to 1 in 100 people):
- oral thrush (oral candidiasis).
- influenza.
- runny nose.
- bacterial skin infection.
- hives.
- discharge from the eye with itching, redness and swelling (conjunctivitis).
- signs of low levels of white blood cells, such as fever, sore throat or mouth ulcers due to infections (neutropenia).
- low blood platelet count (thrombocytopenia).
- Eczema
- Rash
- Rapid swelling of the tissues of the neck, face, mouth or throat (angioedema)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Taltz

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pen label and on the outer carton after “EXP”. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze.

Store in the original packaging in order to protect from light.
Taltz can be left out of the fridge for up to 5 days at a temperature not above 30 ºC.

Do not use this medicine if you notice that the pen is damaged, or the medicine is cloudy, distinctly brown, or has particles in it.

This medicine is for single use only.

Do not throw away any medicines via wastewater or household waste. Ask your doctor, nurse or pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Taltz contains

- The active substance is ixekizumab.
  Each pre-filled pen contains 80 mg of ixekizumab in 1 ml solution.
- The other ingredients are sodium citrate; citric acid, anhydrous; sodium chloride; polysorbate 80; water for injections.

What Taltz looks like and contents of the pack

Taltz is a solution in a clear glass syringe. Its colour may vary from colourless to slightly yellow.

The syringe is encased in a disposable, single-dose pen.

Pack sizes of 1, 2, 3 pre-filled pens. Not all pack sizes may be available in your country.

Marketing Authorisation Holder

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands.

Manufacturer

Eli Lilly Italia S.p.A., Via Gramsci 731/733, 50019, Sesto Fiorentino (FI), Italy.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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<th>Address Details</th>
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<td>Belgique/België/Belgien</td>
<td>Eli Lilly Benelux S.A./N.V. Tél/Tel: + 32-(0)2 548 84 84</td>
</tr>
<tr>
<td>Lietuva</td>
<td>Eli Lilly Holdings Limited atstovybė Tel: +370 (5) 2649600</td>
</tr>
<tr>
<td>България</td>
<td>ТП &quot;Ели Лили Нидерланд&quot; Б.В. - България тел. + 359 2 491 41 40</td>
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<tr>
<td>Česká republika</td>
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<td>Magyarország</td>
<td>Lilly Hungária Kft. Tel: + 36 1 328 5100</td>
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<td>Malta</td>
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<tr>
<td>Deutschland</td>
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<tr>
<td>Nederland</td>
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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
Instructions for use

Taltz 80 mg solution for injection in pre-filled syringe

Ixekizumab

Before using your pre-filled syringe:

Important points to know

- Before you use the Taltz pre-filled syringe, read and carefully follow all the step-by-step instructions. Keep the Instructions for Use and refer to them as needed.
- The pre-filled syringe contains 1 dose of Taltz. The syringe is for ONE-TIME USE ONLY.
- The syringe must not be shaken.
- Your doctor, pharmacist or nurse may help you decide where on your body to inject your dose.
- Read the Taltz Package Leaflet inside this box to learn more about your medicine.

INSTRUCTIONS FOR USE

Before you use the TALTZ pre-filled syringe, read and carefully follow all the step-by-step instructions.
1 GET READY

1a Take the syringe from the refrigerator. Leave the needle cap on the syringe until you are ready to inject. Wait **30 minutes** to let the syringe warm to room temperature before you use it.

**DO NOT** use any heat sources to warm the medicine, for example: a microwave, hot water, or direct sunlight.

1b Gather the supplies for your injection:

- 1 alcohol wipe
- 1 cotton ball or piece of gauze
- 1 sharps container for disposal of syringes
1c Inspect the pre-filled syringe for damage to the outside. Leave the needle cap on the syringe until you are ready to inject. Check the label. Make sure the name Taltz appears on the label.

The medicine inside should be clear. Its colour may vary from colourless to slightly yellow.

If you see any of the following, **DO NOT USE** the syringe, and dispose of it as directed:

- It is past the expiry date.
- It looks damaged.
- The medicine is cloudy, is distinctly brown, or has small particles.

1d Wash your hands before you inject your medicine.

1e Choose your injection site.

You may inject in your abdomen (stomach area), in your thigh, or in the back of your arm. To inject in your arm, you will need someone to help you.

**DO NOT** inject into areas where the skin is tender, bruised, red, or hard or where you have scars or stretch marks. **DO NOT** inject within 2.5 centimetres of the navel (belly button).

**Alternate your injection sites.** **DO NOT** inject in the exact same spot every time. For example, if your last injection was in your left thigh, your next injection should be in your right thigh, your abdomen, or the back of either arm.

1f Prepare your skin. Clean your skin with an alcohol wipe. Let the injection site dry naturally before you inject your medicine.
2 INJECT

2a Pull the needle cap off and throw it away.
DO NOT put the needle cap back on—you could damage the needle or injure yourself by accident.
DO NOT touch the needle.

2b Gently pinch and hold a fold of skin where you will inject.

2c Insert the needle at a 45-degree angle. Then gently let go of your skin. Make sure to keep the needle in place.
Push in the plunger.

Slowly push the plunger all the way in until all the medicine is injected. The grey syringe plunger should be pushed all the way to the end of the syringe. Gently remove the needle from your skin.

Press a cotton ball or gauze over the injection site. **DO NOT** rub the injection site, as this may cause bruising. You may have slight bleeding. This is normal.

You should see the green plunger rod showing through the syringe body when the injection is complete.

3  **FINISH**

3a  Dispose of the pre-filled syringe.

**DO NOT** put the needle cap back on. Dispose of the syringe in a sharps container or as directed by your doctor, pharmacist or nurse.

When you dispose of syringes and the sharps container:

- Dispose of the syringe in a sharps container or as directed by your doctor, pharmacist or nurse.
- Do not recycle the filled sharps container.
- Ask your doctor, pharmacist or nurse about how to dispose of medicines you no longer use.
Safety tips

- If you have questions or need help with your pre-filled syringe, call your doctor, pharmacist or nurse.
- If you have vision problems, DO NOT use the pre-filled syringe without help from a person trained to use it.
- DO NOT share or reuse your Taltz pre-filled syringe. You may give or get an infection
- Keep the syringe out of the reach and sight of children.
- If you do not have a sharps container, ask your doctor, pharmacist or nurse about where you can get one.

Commonly asked questions

Q. What if I see air bubbles in my syringe?
A. It is normal to sometimes have air bubbles in the syringe. Taltz is injected under your skin (subcutaneous injection). Air bubbles are not a problem in this type of injection. They will not harm you or affect your dose.

Q. What if there is a drop of liquid on the tip of the needle when I remove the needle cap?
A. It is okay to see a drop of liquid on the tip of the needle. This will not harm you or affect your dose.

Q. What if I cannot push in the plunger?
A. If the plunger is stuck or damaged:
    - DO NOT continue to use the syringe.
    - Remove the needle from your skin.

Q. How can I tell if my injection is complete?
A. When your injection is complete:
    - The green plunger rod should show through the body of the syringe.
    - The grey syringe plunger should be pushed all the way to the end of the syringe.

Read the full Instructions for Use and the Patient Information Leaflet for Taltz inside this box to learn more about your medicine.
Instructions for use

Taltz 80 mg solution for injection in pre-filled pen

Ixekizumab

Before using your pre-filled pen:

Important points to know

- Before you use the Taltz pre-filled pen, read and carefully follow all the step-by-step instructions. Keep the Instructions for Use and refer to them as needed.
- The pre-filled pen contains 1 dose of Taltz. The pre-filled pen is for ONE-TIME USE ONLY.
- The pre-filled pen must not be shaken.
- The pre-filled pen contains glass parts. Handle it carefully. If you drop it on a hard surface, do not use it. Use a new pre-filled pen for your injection.
- Your doctor, pharmacist or nurse may help you decide where on your body to inject your dose.
- Read the Taltz Package Leaflet inside this box to learn more about your medicine.

INSTRUCTIONS FOR USE

Before you use the Taltz pre-filled pen, read and carefully follow all the step-by-step instructions.
1 GET READY

1a Take the pre-filled pen from the refrigerator. Leave the base cap on until you are ready to inject. Wait 30 minutes to let the pre-filled pen warm to room temperature before you use it.

**DO NOT** use any heat sources to warm the medicine, for example: a microwave, hot water, or direct sunlight.

1b Gather the supplies for your injection:

- 1 alcohol wipe
- 1 cotton ball or piece of gauze
- 1 sharps container for disposal of pre-filled pen
1c **Inspect the pre-filled pen.** Check the label. Make sure the name Taltz appears on the label.

The medicine inside should be clear. Its colour may vary from colourless to slightly yellow.

If you see any of the following, **DO NOT USE** the pre-filled pen, and dispose of it as directed:

- It is past the expiry date.
- It looks damaged.
- The medicine is cloudy, is distinctly brown, or has small particles.

1d **Wash your hands before you inject your medicine.**

1e **Choose your injection site.**

You may inject in your abdomen (stomach area), in your thigh, or in the back of your arm. To inject in your arm, you will need someone to help you.

**DO NOT** inject into areas where the skin is tender, bruised, red, or hard or where you have scars or stretch marks. **DO NOT** inject within 2.5 centimetres of the navel (belly button).

**Alternate your injection sites.** **DO NOT** inject in the exact same spot every time. For example, if your last injection was in your left thigh, your next injection should be in your right thigh, your abdomen, or the back of either arm.

1f **Prepare your skin.** Clean your skin with an alcohol wipe. Let the injection site dry naturally before you inject your medicine.
2 INJECT

2a Make sure the lock ring is in the lock position.

Leave the base cap on until you are ready to inject. **DO NOT** touch the needle.

**Twist off the base cap.**

Throw the base cap in the bin. You will not need to put the base cap back on—doing so could damage the needle or cause you to injure yourself by accident.

2b Place the clear base flat and firmly against your skin.

2c Keep the base on your skin, and then turn the lock ring to the unlock position. You are now ready to inject.
Press the green injection button. There will be a loud click.

Keep holding the clear base firmly against your skin. You will hear a second loud click in about 5 to 10 seconds after the first one. The second loud click tells you that your injection is complete.

You will also see the grey plunger at the top of the clear base.

Remove the pre-filled pen from your skin.

Press a cotton ball or gauze over the injection site. DO NOT rub the injection site, as this may cause bruising. You may have slight bleeding. This is normal.

3 FINISH

Dispose of the pre-filled pen.

DO NOT put the base cap back on. Dispose of the pre-filled pen in a sharps container or as directed by your doctor, pharmacist or nurse.

When you dispose of the pre-filled pen and the sharps container:

- Dispose of the pen in a sharps container or as directed by your doctor, pharmacist or nurse.
- Do not recycle the filled sharps container.
- Ask your doctor, pharmacist or nurse about how to dispose of medicines you no longer use.

Safety tips

- If you have questions or need help with your pre-filled pen, call your doctor, pharmacist or nurse.
- If you have vision problems, DO NOT use the pre-filled pen without help from a person trained to use it.
- Keep the pre-filled pen out of the reach and sight of children.
• If you do not have a sharps container, ask your doctor, pharmacist or nurse where you can get one.

Commonly asked questions

Q. What if I see air bubbles in the pre-filled pen?
A. It is normal to have air bubbles in the pre-filled pen. Taltz is injected under the skin (subcutaneous injection). Air bubbles are not a problem in this type of injection. They will not harm you or affect your dose.

Q. What if there is a drop of liquid on the tip of the needle when I remove the base cap?
A. It is okay to see a drop of liquid on the tip of the needle. This will not harm you or affect your dose.

Q. What if I unlocked the pre-filled pen and pressed the green injection button before I twisted off the base cap?
A. Do not remove the base cap. Contact your doctor, pharmacist or nurse.

Q. Do I need to hold the injection button down until the injection is complete?
A. This is not necessary, but it may help you keep the pre-filled pen steady and firm against your skin.

Q. What if the needle did not retract after my injection?
A. Do not touch the needle or replace the base cap. Dispose of the pre-filled pen in a closable, puncture-resistant sharps container. Contact your doctor, pharmacist or nurse.

Q. What if I heard more than 2 clicks during my injection—2 loud clicks and a soft one. Did I get my complete injection?
A. Some patients may hear a soft click right before the second loud click. That is normal. Do not remove the pre-filled pen from your skin until you hear the second loud click.

Q. How can I tell if my injection is complete?
A. After you press the green injection button, you will hear 2 loud clicks. The second click tells you that your injection is complete. You will also see the grey plunger at the top of the clear base.

Read the full Patient Information Leaflet for Taltz inside this box to learn more about your medicine.