▼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

Taltz is indicated for the treatment of moderate to severe plaque psoriasis in adults.

### 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 psoriasis.

Posology

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.

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 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.

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 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

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.

## 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 (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 4,204 patients were treated with Taltz in clinical development studies in plaque psoriasis. Of these, 2,190 psoriasis patients were exposed to Taltz for at least one year, representing 3,531 patient years of exposure.

Three placebo-controlled phase III studies in plaque psoriasis 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).

**Table 1. List of adverse reactions in clinical studies[a]**

| **System Organ Class** | | **Taltz** | | **Placebo** |
|---|---|---|---|---|
| | | **Q4W (N = 1161) n (%)** | **Q2W (N = 1167) n (%)** | **(N = 791) n (%)** |
| **Infections and infestations** | | | | |
| Very Common | Upper respiratory tract infection[b] | 155 (13.4) | 163 (14.0) | 101 (12.8) |
| Common | Tinea infection | 10 (0.9) | 17 (1.5) | 1 (0.1) |
| Uncommon | Influenza | 10 (0.9) | 8 (0.7) | 0 |
| | Rhinitis | 10 (0.9) | 9 (0.8) | 0 |
| | Oral candidiasis[c] | 2 (0.2) | 9 (0.8) | 0 |
| | Conjunctivitis | 1 (0.1) | 8 (0.7) | 3 (0.4) |
| | Cellulitis[d] | 10 (0.9) | 9 (0.8) | 2 (0.3) |
| **Blood and lymphatic system disorders** | | | | |
| Uncommon | Neutropenia [f] | 3 (0.3) | 6 (0.5) | 1 (0.1) |
| | Thrombocytopenia [f] | 2 (0.2) | 2 (0.2) | 0 |
| **Respiratory, thoracic, and mediastinal disorders** | | | | |
| Common | Oropharyngeal pain | 20 (1.7) | 16 (1.4) | 4 (0.5) |
| **Gastrointestinal disorders** | | | | |
| Common | Nausea | 15 (1.3) | 23 (2.0) | 5 (0.6) |
| **Skin and subcutaneous tissue disorders** | | | | |
| Uncommon | Urticaria | 6 (0.5) | 10 (0.9) | 0 |
| **General disorders and administration site conditions** | | | | |
| Very Common | Injection site reactions [e] | 150 (12.9) | 196 (16.8) | 26 (3.3) |

[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

[b] Upper respiratory tract infection includes nasopharyngitis and upper respiratory tract infection

[c] Oral candidiasis defined as events with the preferred terms oral candidiasis and oral fungal infection

[d] Cellulitis includes staphylococcal and external ear cellulitis, and erysipelas

[e] 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)

f Based on reported adverse events

Description of selected adverse reactions

*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).

*Laboratory assessment of neutropenia and thrombocytopenia*
9% of patients receiving Taltz developed neutropenia. In most cases, the blood neutrophil count was $\geq$1,000 cells/mm$^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 $\geq$75,000 cells/mm$^3$. Thrombocytopenia may persist, fluctuate or be transient.

*Immunogenicity*
Approximately 9–17 % of 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. 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.

### 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. 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.

Clinical efficacy and safety

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**

| Endpoints | Number of patients (%) | | | Difference from Placebo in Response Rate (95% CI) | |
|---|---|---|---|---|---|
| | Placebo (N = 431) | Taltz 80 mg Q4W (N = 432) | Taltz 80 mg Q2W (N = 433) | Taltz 80 mg Q4W | Taltz 80 mg Q2W |
| sPGA of "0" (clear) or "1" (minimal) | 14 (3.2) | 330 (76.4)[a] | 354 (81.8)[a] | 73.1 (68.8, 77.5) | 78.5 (74.5, 82.5) |
| sPGA of "0" (clear) | 0 | 149 (34.5)[a] | 160 (37.0)[a] | 34.5 (30.0, 39.0) | 37.0 (32.4, 41.5) |
| PASI 75 | 17 (3.9) | 357 (82.6)[a] | 386 (89.1)[a] | 78.7 (74.7, 82.7) | 85.2 (81.7, 88.7) |
| PASI 90 | 2 (0.5) | 279 (64.6)[a] | 307 (70.9)[a] | 64.1 (59.6, 68.7) | 70.4 (66.1, 74.8) |
| PASI 100 | 0 | 145 (33.6)[a] | 153 (35.3)[a] | 33.6 (29.1, 38.0) | 35.3 (30.8, 39.8) |
| Itch NRS reduction $\geq 4$[b] | 58 (15.5) | 305 (80.5)[a] | 336 (85.9)[a] | 65.0 (59.5, 70.4) | 70.4 (65.4, 75.5) |

*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] *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**

| Endpoints | Number of patients (%) | | | | Difference from Placebo in Response Rate (95% CI) | |
|---|---|---|---|---|---|---|
| | Placebo (N = 168) | Taltz 80 mg Q4W (N = 347) | Taltz 80 mg Q2W (N = 351) | Etanercept 50 mg twice weekly (N = 358) | Taltz 80 mg Q4W | Taltz 80 mg Q2W |
| sPGA of "0" (clear) or "1" (minimal) | 4 (2.4) | 253 (72.9)[a] | 292 (83.2)[a] | 129 (36.0) | 70.5 (65.3, 75.7) | 80.8 (76.3, 85.4) |
| sPGA of "0" (clear) | 1 (0.6) | 112 (32.3)[a,b] | 147 (41.9)[a,b] | 21 (5.9)[c] | 31.7 (26.6, 36.7) | 41.3 (36.0, 46.6) |
| PASI 75 | 4 (2.4) | 269 (77.5)[a] | 315 (89.7)[a] | 149 (41.6)[a] | 75.1 (70.2, 80.1) | 87.4 (83.4, 91.3) |
| PASI 90 | 1 (0.6) | 207 (59.7)[a,b] | 248 (70.7)[a,b] | 67 (18.7)[a] | 59.1 (53.8, 64.4) | 70.1 (65.2, 75.0) |
| PASI 100 | 1 (0.6) | 107 (30.8)[a,b] | 142 (40.5)[a,b] | 19 (5.3)[c] | 30.2 (25.2, 35.2) | 39.9 (34.6, 45.1) |
| Itch NRS reduction $\geq 4$[d] | 19 (14.1) | 225 (76.8)[a,b] | 258 (85.1)[a,b] | 177 (57.8)[a] | 62.7 (55.1, 70.3) | 71.1 (64.0, 78.2) |

*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.

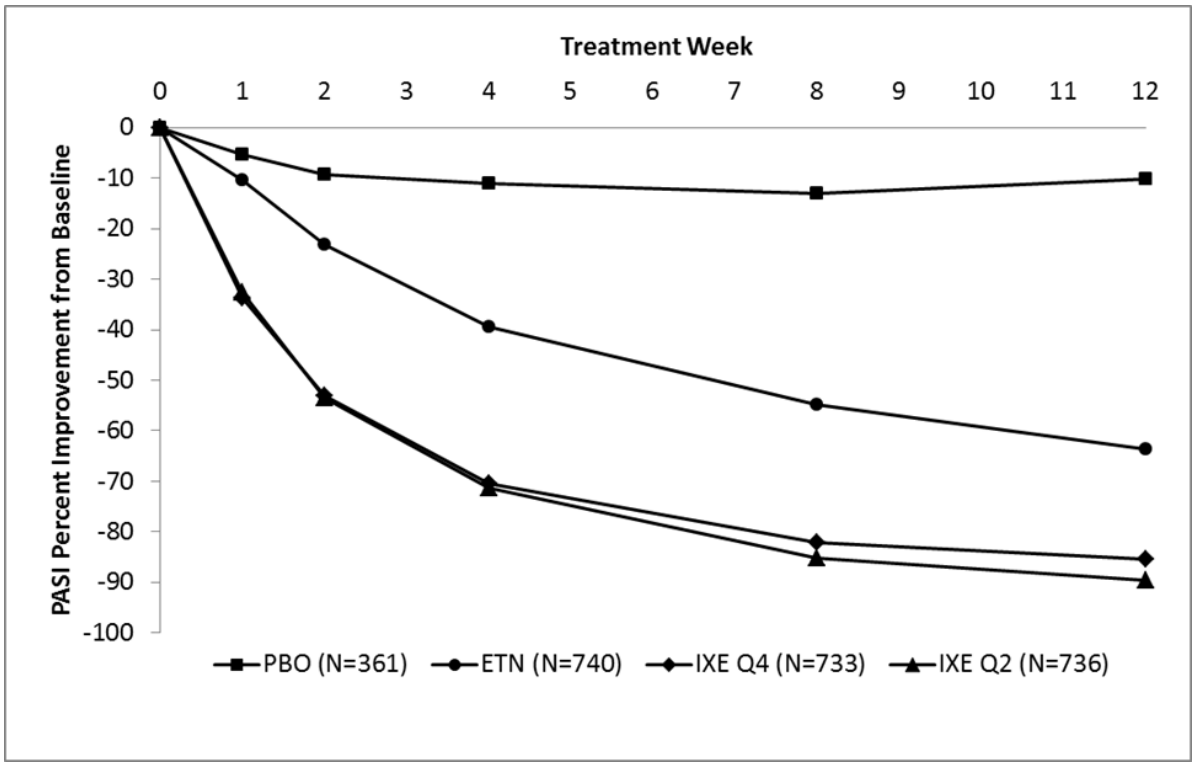
**Table 4. Efficacy results at Week 12 in UNCOVER-3**

| Endpoints | Number of patients (%) | | | | Difference from Placebo in Response Rate (95% CI) | |
|---|---|---|---|---|---|---|
| | Placebo (N = 193) | Taltz 80 mg Q4W (N = 386) | Taltz 80 mg Q2W (N = 385) | Etanercept 50 mg twice weekly (N = 382) | Taltz 80 mg Q4W | Taltz 80 mg Q2W |
| sPGA of "0" (clear) or "1" (minimal) | 13 (6.7) | 291 (75.4)[a,b] | 310 (80.5)[a,b] | 159 (41.6)[a] | 68.7 (63.1, 74.2) | 73.8 (68.5, 79.1) |
| sPGA of "0" (clear) | 0 | 139 (36.0)[a,b] | 155 (40.3)[a,b] | 33 (8.6)[a] | 36.0 (31.2, 40.8) | 40.3 (35.4, 45.2) |
| PASI 75 | 14 (7.3) | 325 (84.2)[a,b] | 336 (87.3)[a,b] | 204 (53.4)[a] | 76.9 (71.8, 82.1) | 80.0 (75.1, 85.0) |
| PASI 90 | 6 (3.1) | 252 (65.3)[a,b] | 262 (68.1)[a,b] | 98 (25.7)[a] | 62.2 (56.8, 67.5) | 64.9 (59.7, 70.2) |
| PASI 100 | 0 | 135 (35.0)[a,b] | 145 (37.7)[a,b] | 28 (7.3)[a] | 35 (30.2, 39.7) | 37.7 (32.8, 42.5) |
| Itch NRS reduction $\geq 4$[c] | 33 (20.9) | 250 (79.9)[a,b] | 264 (82.5)[a,b] | 200 (64.1)[a] | 59.0 (51.2, 66.7) | 61.6 (54.0, 69.2) |

*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] *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.

**Figure 1. PASI score, percent improvement at each post baseline visit (mBOCF)) in the Intent-to-Treat Population during the Induction Dosing Period - UNCOVER-2 and UNCOVER-3**




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)**

| Endpoints | Number of patients (%) | | | | Difference from Placebo in Response Rate (95% CI) | |
|---|---|---|---|---|---|---|
| | 80 mg Q4W (induction) / Placebo (maintenance) (N = 191) | 80 mg Q2W (induction) / Placebo (maintenance) (N = 211) | 80 mg Q4W (induction) / 80 mg Q4W (maintenance) (N = 195) | 80 mg Q2W (induction) / 80 mg Q4W (maintenance) (N = 221) | 80 mg Q4W (induction) / 80 mg Q4W (maintenance) | 80 mg Q2W (induction) / 80 mg Q4W (maintenance) |
| Maintained sPGA of "0" (clear) or "1" (minimal) | 12 (6.3) | 16 (7.6) | 134 (68.7)[a] | 173 (78.3)[a] | 62.4 (55.1, 69.8) | 70.7 (64.2, 77.2) |
| Maintained or Achieved sPGA 0 (clear) | 3 (1.6) | 6 (2.8) | 96 (49.2)[a] | 130 (58.8)[a] | 47.7 (40.4, 54.9) | 56.0 (49.1, 62.8) |
| Maintained or Achieved PASI 75 | 15 (7.9) | 19 (9.0) | 145 (74.4)[a] | 184 (83.3)[a] | 66.5 (59.3, 73.7) | 74.3 (68.0, 80.5) |
| Maintained or Achieved PASI 90 | 9 (4.7) | 10 (4.7) | 130 (66.7)[a] | 169 (76.5)[a] | 62.0 (54.7, 69.2) | 71.7 (65.4, 78.0) |
| Maintained or Achieved PASI 100 | 3 (1.6) | 6 (2.8) | 97 (49.7)[a] | 127 (57.5)[a] | 48.2 (40.9, 55.4) | 54.6 (47.7, 61.5) |

*Abbreviations: N = number of patients in the analysis population*
*Note: patients with missing data were counted as non-responders*
[a] *$p < 0.001$ 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 $\geq 3$) 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 $\geq 4$ 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.

*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 (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 ($C_{max}$) 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) $C_{max,ss,}$ 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.

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. 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.

## 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 Asia, Inc. Bangkok, Thailand

# 8. MARKETING AUTHORISATION NUMBER(S)

1C xx/xx (NBC)

# 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

DD-MMM-YYYY

# 10. DATE OF REVISION OF THE TEXT

19-Aug-2016