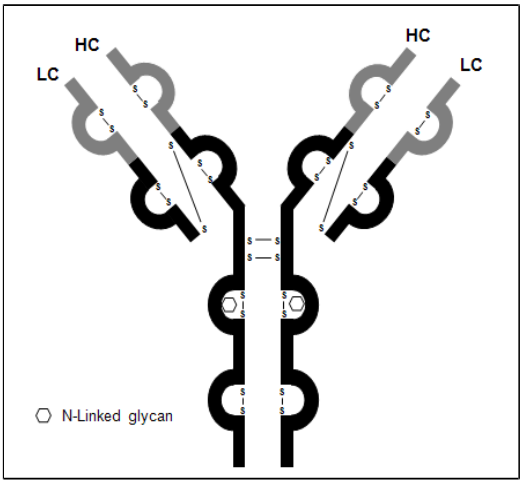
TALTZ®
(ixekizumab (rch))

NAME OF THE MEDICINE

TALTZ *(ixekizumab (rch))*



CAS registry number 1143503-69-8.

DESCRIPTION

TALTZ (ixekizumab (rch)) is a humanised immunoglobulin G subclass 4 (IgG4) monoclonal antibody (mAb) with neutralising activity against interleukin-17A (IL-17A). TALTZ is produced by recombinant DNA technology in a recombinant mammalian cell line and purified using standard technology for bioprocessing. Ixekizumab is comprised of two identical light chain polypeptides of 219 amino acids each and two identical heavy chain polypeptides of 445 amino acids each, and has a molecular weight of 146,158 Daltons for the protein backbone of the molecule.

TALTZ is available as a 1 mL single-dose prefilled pen (autoinjector) or a 1 mL single-dose prefilled syringe. The autoinjector and prefilled syringe each contain a 1 mL glass syringe with a fixed needle. The TALTZ autoinjector and prefilled syringe are manufactured to deliver 80 mg of ixekizumab. TALTZ is latex-free.

Each autoinjector or prefilled syringe is composed of ixekizumab (80 mg/mL) and the inactive ingredients sodium chloride 11.69 mg/mL; sodium citrate dihydrate 5.11 mg/mL; citric acid 0.51 mg/mL; polysorbate 80 0.30 mg/mL and water for injections. TALTZ contains less than 1 mmoL sodium (23 mg) per 80 mg dose.

TALTZ is for single use, therefore contains no antimicrobial preservative. The TALTZ solution is sterile, preservative free, clear and colourless to slightly yellow. The TALTZ solution has a pH of 5.3 to 6.1. TALTZ is administered as a subcutaneous (SC) injection.

PHARMACOLOGY

Mechanism of Action

Ixekizumab is an IgG4 monoclonal antibody that binds with high affinity (<3 pM) to IL-17A, a proinflammatory cytokine. Ixekizumab does not bind to ligands IL-17B, IL-17C, IL-17D, IL-17E or IL-17F. Elevated levels of IL-17A have been implicated in the pathogenesis of a variety of autoimmune diseases. In psoriasis, the IL-17A ligand plays a major role in driving excess keratinocyte proliferation and activation. Neutralisation of IL-17A by ixekizumab inhibits these actions.

In vitro binding assays showed that ixekizumab does not bind to human Fcγ receptors I, IIa and IIIa or to complement component C1q and is therefore not expected to elicit Fc-receptor mediated effects (e.g., antibody-dependent cell-mediated cytotoxicity, complement system activation).

Pharmacodynamics

Ixekizumab modulates biological responses that are induced or regulated by IL-17A.

Pharmacokinetics

Absorption

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

After the 160 mg starting dose, steady state was achieved by Week 8 with the ixekizumab 80 mg every 2 weeks (Q2W) dosing regimen. Mean (SD) $C_{max,ss}$ and $C_{trough,ss}$ estimates are 21.5 (9.16) microgram/mL and 5.23 (3.19) microgram/mL, respectively. After switching from the ixekizumab 80 mg Q2W dosing regimen to the ixekizumab 80 mg every 4 weeks (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) microgram/mL and 1.87 (1.30) microgram/mL, respectively.

The average SC bioavailability of ixekizumab was estimated in the range of 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 IgGs.

Elimination

In the population pharmacokinetic analysis, mean serum clearance was 0.0161 L/hour. Clearance is independent of dose. The mean elimination half-life is 13 days in plaque psoriasis patients. Ixekizumab clearance increases as body weight increases.

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

Special Populations
Elderly Patients (≥65 years)
Based on population pharmacokinetic analysis with limited number of elderly patients (N=82 for ≥65 years and N=7 for ≥75 years), clearance of ixekizumab in elderly patients was similar to patients aged less than 65 years.

Renal Impairment or Hepatic Impairment
Specific clinical pharmacology studies to evaluate the effects of renal impairment and hepatic impairment on the pharmacokinetics of ixekizumab have not been conducted.

CLINICAL TRIALS

The efficacy and safety of TALTZ were assessed in three randomised, double-blind, placebo-controlled phase III clinical trials in adult patients with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy (UNCOVER-1 [RHAZ], UNCOVER-2 [RHBA] and UNCOVER-3 [RHBC]). Patients were ≥18 years of age with plaque psoriasis who had a minimum body surface area involvement of 10%, a static Physician Global Assessment (sPGA) score of ≥3 and Psoriasis Area and Severity Index (PASI) score ≥12. Patients with guttate, erythrodermic or pustular psoriasis were excluded from clinical trials.

The efficacy and safety of TALTZ were also evaluated compared to etanercept (UNCOVER-2 and UNCOVER-3). Patients randomised to TALTZ who were responders (sPGA 0 (clear) or 1 (minimal) at Week 12) were re-randomised to receive TALTZ or placebo for an additional 48 weeks (UNCOVER-1 and UNCOVER-2). Patients randomised to placebo, etanercept or TALTZ who were non-responders (sPGA ≥1 at Week 12) received TALTZ for up to 48 weeks.

Of the 3866 patients enrolled in the placebo-controlled trials, 64% had received prior systemic therapy (biologic, conventional systemic or 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. A total of 23.4% of patients had a history of psoriatic arthritis.

In all three clinical trials, the primary endpoints were the proportion of patients who achieved at least a 75% reduction in PASI score (PASI 75) from baseline to Week 12 and an sPGA (0,1) with at least a 2-point improvement from baseline. The sPGA is a 6 category scale ranging from 0 (clear) to 5 (very severe) that indicates the physician's overall assessment of psoriasis based on plaque thickness/induration, erythema and scaling.

Other evaluated outcomes included the proportion of patients with a sPGA 0, a reduction of at least 90% in PASI (PASI 90), a reduction of 100% in PASI (PASI 100) and an improvement of itch severity as measured by an Itch Numeric Rating Scale (Itch NRS).

Patients in all treatment groups had a median baseline PASI score ranging from approximately 17.4 to 18.3. Baseline sPGA score was severe or very severe in 51.2% of patients in UNCOVER-1, 49.7% in UNCOVER-2 and 48.3% in UNCOVER-3.

Clinical Response at Week 12

UNCOVER-1 enrolled 1296 patients, randomised to receive either TALTZ (80 mg every two or four weeks [Q2W or Q4W]) following a 160 mg starting dose (two injections) at Week 0, or placebo for 12 weeks (see Table 1).

Table 1: Efficacy Results at Week 12 in UNCOVER-1

	UNCOVER-1 – Number of Patients (%), NRI		
	TALTZ		Placebo
	80 mg Q2W (N=433)	80 mg Q4W (N=432)	(N=431)
sPGA of (0,1)	354 (81.8%)[a]	330 (76.4%)[a]	14 (3.2%)
PASI 75	386 (89.1%)[a]	357 (82.6%)[a]	17 (3.9%)
sPGA 0	160 (37.0%)[a]	149 (34.5%)[a]	0
PASI 90	307 (70.9%)[a]	279 (64.6%)[a]	2 (0.5%)
PASI 100	153 (35.3%)[a]	145 (33.6%)	0
Itch NRS Reduction ≥4[b]	336 (85.9%)[a]	305 (80.5 %)[a]	58 (15.5%)

Abbreviations: N=number of patients in the intent-to-treat population; NRI=Non-Responder Imputation
[a] p<0.001 compared with placebo
[b] Patients with Itch NRS ≥4 at baseline: TALTZ 80 mg Q2W N=391, TALTZ 80 mg Q4W N=379, placebo N=374.

In the UNCOVER-2 and UNCOVER-3 trials, 1224 patients and 1346 patients were enrolled, respectively. Patients were randomised to receive either TALTZ (80 mg Q2W or Q4W) following a 160 mg starting dose at Week 0, placebo or etanercept 50 mg twice weekly for 12 weeks (see Table 2).

Table 2: Efficacy Results at Week 12 in UNCOVER-2 and UNCOVER-3

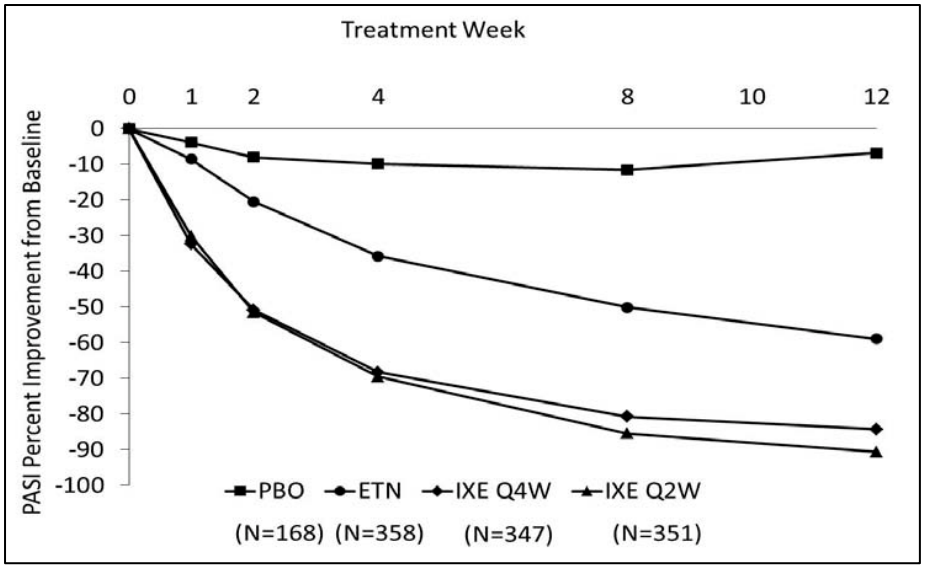
	UNCOVER-2 Number of Patients (%), NRI				UNCOVER-3 Number of Patients (%), NRI			
	TALTZ		Etanercept	Placebo	TALTZ		Etanercept	Placebo
	80 mg Q2W (N=351)	80 mg Q4W (N=347)	50 mg twice/week (N=358)	(N=168)	80 mg Q2W (N=385)	80 mg Q4W (N=386)	50 mg twice/week (N=382)	(N=193)
sPGA (0,1)	292 (83.2%)[a,b]	253 (72.9%)[a,b]	129 (36.0%)	4 (2.4%)	310 (80.5%)[a,b]	291 (75.4%)[a,b]	159 (41.6%)[a]	13 (6.7%)
PASI 75	315 (89.7%)[a,b]	269 (77.5%)[a,b]	149 (41.6%)[a]	4 (2.4%)	336 (87.3%)[a,b]	325 (84.2%)[a,b]	204 (53.4%)[a]	14 (7.3%)
sPGA 0	147 (41.9%)[a,c]	112 (32.3%)[a,c]	21 (5.9%)[d]	1 (0.6%)	155 (40.3%)[a,c]	139 (36.0%)[a,c]	33 (8.6%)[a]	0
PASI 90	248 (70.7%)[a,c]	207 (59.7%)[a,c]	67 (18.7%)[a]	1 (0.6%)	262 (68.1%)[a,c]	252 (65.3%)[a,c]	98 (25.7%)[a]	6 (3.1%)
PASI 100	142 (40.5%)[a,c]	107 (30.8%)[a,c]	19 (5.3%)[d]	1 (0.6%)	145 (37.7%)[a,c]	135 (35.0%)[a,c]	28 (7.3%)[a]	0
Itch NRS Reduction ≥4[e]	258 (85.1%)[f,c]	225 (76.8%)[f,c]	177 (57.8%)[f]	19 (14.1%)	264 (82.5%)[a,c]	250 (79.9%)[a,c]	200 (64.1%)[a]	33 (20.9%)

Abbreviations: N=number of patients in the intent-to-treat population; NRI=Non-Responder Imputation.
[a] p<0.001 compared with placebo, adjusted for multiplicity.
[b] Superior to etanercept using retention rate approach.
[c] p<0.001 compared with etanercept.
[d] p<0.01 compared with placebo.
[e] Patients with Itch NRS ≥ 4 at baseline: TALTZ 80 mg Q2W N=303, TALTZ 80 mg Q4W N=293, etanercept N=306, placebo N=135.
[f] p<0.001 compared with placebo.

The TALTZ 80 mg Q2W dose regimen provided superior efficacy (p<0.001) at Week 12 across all endpoints for all three clinical trials. Further, all TALTZ treatment groups consistently demonstrated superiority to placebo and to etanercept in achieving high rates of response (PASI 90) and complete resolution of psoriatic plaque (PASI 100). Further, TALTZ treatment groups had significantly greater improvements in itch severity, as early as Week 1 compared to placebo and to etanercept (p<0.001). The percentage of patients achieving a sPGA 0 (clear) or 1 (minimal) was statistically significant compared to placebo as early as Week 1 in all three clinical trials.

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).

Figure 1: PASI Score (Mean), Percent Improvement at Each Post Baseline Visit (LOCF) in the Intent-to-Treat Population During the Induction Dosing Period – UNCOVER-2



Note: Comparisons between each group were statistically significant (p<0.001) at each visit.

The efficacy and safety of TALTZ was demonstrated regardless of age, gender, race, body weight, PASI baseline severity and previous treatment with a biologic. Responses to TALTZ were consistent among patients who had nail psoriasis, facial psoriasis or scalp psoriasis at baseline.

TALTZ was efficacious in systemic treatment-naïve, biologic-naïve, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients. Improvements in sPGA and PASI endpoints in patients with concurrent psoriatic arthritis at baseline were similar to those in the overall moderate to severe plaque psoriasis population. Approximately 45% of patients had baseline facial psoriasis. Of these patients, 80.4% of patients treated with TALTZ had complete resolution of their facial psoriasis at Week 12.

Maintenance of Response

To evaluate the maintenance of response, patients originally randomised to TALTZ and who were responders at Week 12 (sPGA 0,1) in UNCOVER-1 and UNCOVER-2 trials, were re-randomised to an additional 48 weeks of one of the following treatment regimens: TALTZ 80 mg Q4W, TALTZ 80 mg Q12W or placebo. Patients who were non-responders (sPGA >1) at Week 12 and who relapsed (sPGA ≥3) during the maintenance period were placed on TALTZ 80 mg Q4W.

For responders at Week 12, the percentage of patients who maintained this response at Week 60 was higher for patients treated with TALTZ 80 mg Q4W (71%) compared to those treated with TALTZ 80 mg Q12W (35.5%) or placebo (7%). Further, of the responders at Week 12 who were treated with maintenance Q4W dosing, the proportion who maintained or achieved complete resolution of psoriatic plaques at Week 60 as measured by a sPGA (0) or PASI 100 was 52.0% and 51.4%, respectively. Additionally, 76.4% of patients achieved or maintained a PASI <5 at Week 60.

The response rates for those patients re-randomised to the recommended maintenance dose of TALTZ 80 mg Q4W based on induction dose are provided in Table 3.

Table 3: Maintenance of Response and Efficacy at Week 60 (Studies UNCOVER-1 and UNCOVER-2) for Patients Treated with 80 mg Q4W Maintenance Dosing Regimen Based on Induction Dosing Regimen; NRI

Endpoints at Week 60	80 mg Q4W (induction) / Placebo (maintenance) (N=181)	80 mg Q2W (induction) / Placebo (maintenance) (N=203)	80 mg Q4W (induction) / 80 mg Q4W (maintenance) (N=167)	80 mg Q2W (induction) / 80 mg Q4W (maintenance) (N=181)
Maintained sPGA (0,1)	6.1%	7.4%	67.1%	74.6%
Maintained or Achieved sPGA 0	1.1%	3.0%	48.5%	55.2%
Maintained or Achieved PASI 75	6.6%	7.9%	73.1%	80.1%
Maintained or Achieved PASI 90	3.3%	4.4%	65.9%	72.9%
Maintained or Achieved PASI 100	1.1%	3.0%	49.1%	53.6%

Abbreviations: N=number of patients in the integrated analysis population; NRI=Non-Responder Imputation

The improvements in itch severity were sustained up to Week 60 in patients treated with TALTZ who were responders at Week 12. TALTZ was efficacious in the maintenance of response in systemic treatment-naïve, biologic-naïve, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients.

For responders at Week 12 re-randomised to treatment withdrawal (i.e. placebo), the median time to relapse (sPGA ≥3) was 148 days in integrated UNCOVER-1 and UNCOVER-2 trials. Among these patients, 69.6% regained at least a 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]), in facial psoriasis (as measured by proportion who had complete resolution) 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 responders at Week 12.

Efficacy in Non-Responders to Etanercept

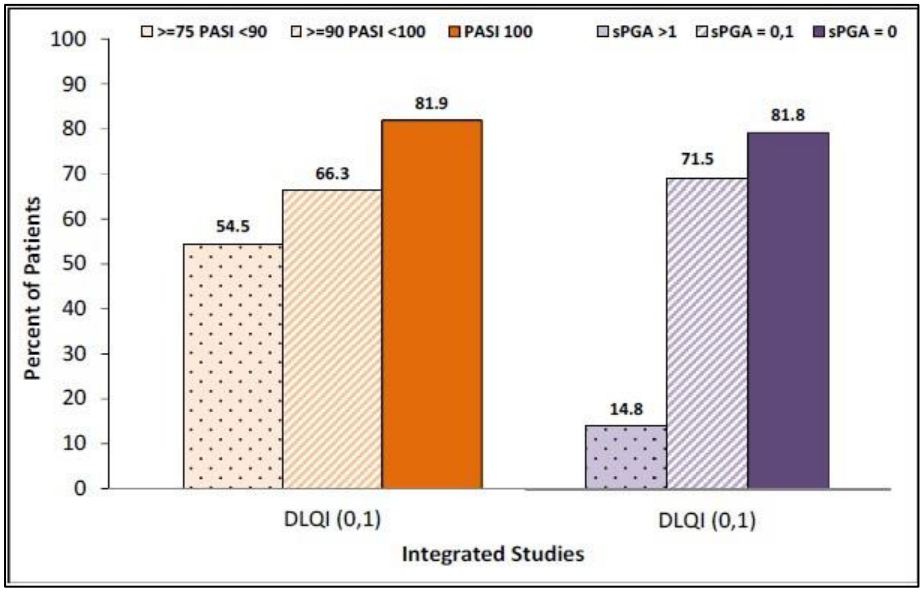
In the UNCOVER-2 clinical trial, patients identified as non-responder to etanercept (sPGA >1 at Week 12) were switched to TALTZ 80 mg Q4W after a 4 week washout period (N=200). Of these, 73% and 83.5% of patients were able to achieve sPGA (0,1) and PASI 75, respectively, after 12 weeks treatment with TALTZ. In the subset of etanercept non-responders who were biologic-naïve at baseline (N=154), the sPGA (0,1) and PASI 75 after 12 weeks of treatment with TALTZ were consistent (72.7% and 83.8%, respectively) with the overall etanercept non-responder population.

Quality of Life

Across all clinical trials at Week 12, TALTZ was associated with statistically significant improvement in Health-Related Quality of Life (HRQoL) as measured by the Dermatology Life Quality Index (DLQI). A DLQI (0,1) indicates no impact of psoriasis on quality of life. A significantly greater proportion of patients treated with TALTZ achieved a DLQI (0,1) compared with patients treated with placebo or etanercept, with higher response rates for the TALTZ Q2W group than for the Q4W group.

Across all treatments, patients who achieved sPGA (0) at Week 12 reported higher rates of DLQI (0,1) than patients who achieved sPGA (0,1), who likewise had higher DLQI (0,1) response rates than patients who achieved sPGA (>1). Similarly, each incremental increase in PASI was associated with greater responses of DLQI (0,1). For patients who achieved complete resolution of their psoriasis at 12 weeks, 82% reported that their psoriasis no longer had impact on their HRQoL (see Figure 2).

Figure 2: DLQI (0,1) Status at Week 12 by Level of Clinical Response (PASI or sPGA) at Week 12 (NRI), Intent-to-Treat Population, Integrated Analysis (UNCOVER-1, UNCOVER-2 and UNCOVER-3)



Abbreviations: NRI=Non-Responder Imputation
Note: For PASI and sPGA categories, comparisons between each group were statistically significant (p<0.001).

The statistically significant superior benefit of TALTZ over placebo and etanercept was seen as early as Week 2, increased over time to Week 12 and was sustained up to

Week 60 in patients treated with TALTZ who were responders (sPGA 0,1) at Week 12. At Week 12 and in comparison with etanercept and placebo, TALTZ was associated with a significantly greater decrease in skin pain (measured by the Skin Pain Visual Analogue Scale), greater improvements in the physical and mental component summary scores of the SF-36; patients treated with TALTZ also reported feeling significantly less bothered by redness/discolouration, thickness and scaling/flaking of skin as measured by the PSAB (Psoriasis Skin Appearance and Bothersomeness).

In patients treated with TALTZ who were responders at Week 12, these additional benefits were maintained up to Week 60. At Week 12 and in comparison with etanercept and placebo, TALTZ was associated with statistically significant improvement in depression as measured by the QIDS-SR16 and productivity as measured by the Work Productivity and Activity Impairment (WPAI).

Some patients who did not respond to the initial 12 weeks of treatment with TALTZ showed improvement in psoriasis with continued treatment up to 20 weeks. Patients not responding to TALTZ within 20 weeks of initial treatment are unlikely to respond to continued treatment.

INDICATIONS

TALTZ is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

CONTRAINDICATIONS

TALTZ is contraindicated in patients with known serious hypersensitivity to ixekizumab or any of the excipients.

PRECAUTIONS

Infections

TALTZ may increase the risk of infections. In clinical trials, a higher rate of infection such as upper respiratory tract infection, oral candidiasis, conjunctivitis and tinea infections were observed in TALTZ treated patients compared to placebo (see Adverse Effects).

TALTZ should be used with caution in patients with clinically important chronic or active infection. Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection or is not responding to standard therapy the patient should be closely monitored. TALTZ should be discontinued until the infection resolves.

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with TALTZ. Do not administer TALTZ to patients with active TB infection. Initiate treatment of latent TB prior to administering TALTZ. Consider anti-TB therapy prior to initiation of TALTZ in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving TALTZ should be monitored closely for signs and symptoms of active TB during and after treatment.

Hypersensitivity
Serious hypersensitivity reactions, including some cases of anaphylaxis, angioedema and urticaria, have been reported. If a serious hypersensitivity reaction occurs, administration of TALTZ should be discontinued immediately and appropriate therapy initiated.

Inflammatory Bowel Disease
Crohn's disease and ulcerative colitis, including exacerbations, occurred at a greater frequency in the TALTZ group (Crohn's disease 0.1%, ulcerative colitis 0.2%) than the placebo group (0%) during the 12-week, placebo-controlled period.

Exercise caution when prescribing TALTZ to patients with inflammatory bowel disease, including Crohn's disease and ulcerative colitis, as new cases or exacerbations have been reported. Patients treated with TALTZ and have inflammatory bowel disease should be monitored closely.

Immunisations
TALTZ should not be used with live vaccines. No data are available on the response to live or inactive vaccines.

Effects on Fertility
The effects of ixekizumab on human fertility have not been evaluated. In animal studies, ixekizumab did not indicate harmful effects with respect to fertility as assessed by a lack of effects on reproductive organs, menstrual cycles or sperm in sexually mature cynomolgus monkeys that received ixekizumab for 13 weeks at a weekly SC dose of 50 mg/kg (at least 50 times the human exposure at 80 mg every 2 weeks based on AUC). The monkeys were not mated to evaluate fertility.

Use in Pregnancy – Category C
There are no adequate and well controlled studies of TALTZ in pregnant women to establish the safety of TALTZ during pregnancy. The mechanism of action of ixekizumab suggests a theoretical risk that its use during pregnancy may affect neonatal immunity.

In developmental toxicity studies, SC administration of ixekizumab at doses up to 50 mg/kg once weekly to cynomolgus monkeys from the beginning of organogenesis through either near term pregnancy or until delivery of offspring, produced no embryotoxicity or teratogenicity, and no effects on offspring delivery, or on morphological, functional or immunological development of offspring from birth to 6 months of age. Ixekizumab was shown to cross the placenta and was present in the blood of offspring for up to 6 months of age.

TALTZ should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation
It is not known whether ixekizumab is excreted in human milk or absorbed systemically after ingestion. In a pre-/postnatal development study, ixekizumab was excreted at low levels in the milk of cynomolgus monkeys that had been dosed with ixekizumab during pregnancy until delivery of offspring. Ixekizumab was present in the blood of

offspring, due primarily to placental transfer. 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.

Paediatric Use
Safety and effectiveness of TALTZ in paediatric patients (<18 years of age) have not been evaluated.

Use in Elderly
Of the 4204 psoriasis patients exposed to TALTZ in clinical trials, a total of 265 patients were aged ≥65 years and 34 patients were aged ≥75 years. Although no differences in safety or efficacy were observed between older and younger patients, the number of patients aged ≥65 years is not sufficient to determine whether they respond differently from younger patients. (See Clinical Pharmacology).

Genotoxicity
The genotoxic potential of ixekizumab has not been studied.

Carcinogenicity
Nonclinical studies have not been conducted to evaluate the carcinogenic potential of ixekizumab.

Effect on Laboratory Tests
No information on the effect of ixekizumab on laboratory tests is available.

Effects on Ability to Drive and Use Machines
There are no known effects on the ability to drive or use machines associated with the use of TALTZ.

INTERACTIONS WITH OTHER MEDICINES

No interaction studies have been conducted with TALTZ.

The safety of ixekizumab in combination with other immunomodulatory agents or phototherapy has not been evaluated.

ADVERSE EFFECTS

Clinical Trials Experience
A total of 4204 plaque psoriasis patients were treated with TALTZ in clinical trials. Of these, 2190 patients were exposed to treatment with TALTZ for at least one year.
Three placebo-controlled phase III trials (UNCOVER-1, UNCOVER-2 and UNCOVER-3) in plaque psoriasis patients were integrated to evaluate the safety of TALTZ in comparison to placebo up to 12 weeks. In two of the clinical trials (UNCOVER-2 and UNCOVER-3), the safety of TALTZ included a comparison to an active comparator, etanercept, up to 12 weeks after treatment initiation (see Clinical Trials). In total, 3858 patients were evaluated (1167 to TALTZ 80 mg every 2 weeks [Q2W], 1161 to TALTZ 80 mg every 4 weeks [Q4W], 739 to etanercept 50 mg twice weekly group and 791 to placebo group).

The most frequently reported adverse reactions were injection site reactions and upper respiratory tract infections (most frequently nasopharyngitis). Most of the reactions were mild or moderate in severity.

Adverse reactions that occurred at a rate of at least 1% and at a higher rate in the TALTZ groups compared to the placebo group during the placebo-controlled 12 week period of UNCOVER-1, UNCOVER-2 and UNCOVER-3 are summarised in Table 4.

Table 4: Adverse Drug Reactions Reported by ≥1% of Patients with Plaque Psoriasis through Week 12 in Phase III Clinical Trials

Adverse Reactions	TALTZ		Etanercept[b]	Placebo
	80 mg Q2W (N=1167) (n%)	80 mg Q4W (N=1161) (n%)	50 mg twice weekly (N=739) (n%)	(N=791) (n%)
Injection site reactions	196 (16.8%)	150 (12.9%)	121 (16.4%)	26 (3.3%)
Upper respiratory tract infection[a]	163 (14.0%)	155 (13.4%)	92 (12.4%)	101 (12.8%)
Nausea	23 (2.0%)	15 (1.3%)	3 (0.4%)	5 (0.6%)
Oropharyngeal pain	16 (1.4%)	20 (1.7%)	7 (0.9%)	4 (0.5%)
Tinea infections	17 (1.5%)	10 (0.9%)	1 (0.1%)	1 (0.1%)

N=number of patients in the integrated analysis population; n=number of patients.

[a] Upper respiratory tract infection includes: nasopharyngitis and upper respiratory tract infection

[b] Etanercept data from UNCOVER-2 and UNCOVER-3 only.

Adverse reactions that occurred at rates less than 1% in the placebo-controlled clinical trials UNCOVER-1, UNCOVER-2 and UNCOVER-3 through to week 12 included: influenza, rhinitis, conjunctivitis, urticaria and oral candidiasis.

In the two clinical trials that included etanercept (UNCOVER-2 and UNCOVER-3), the rate of serious adverse events was 1.9% for both etanercept and 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 events being mild to moderate in severity. The rate of serious infections was 0.4% for etanercept and 0.5% for TALTZ.

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

The majority of infections consisted of non-serious and mild to moderate adverse reactions such as nasopharyngitis and upper respiratory tract infection, which did not necessitate treatment discontinuation.

In the placebo-controlled period of the phase III clinical trials in plaque psoriasis, infections were reported in 27.2% of patients treated with TALTZ compared with 22.9% of patients treated with placebo.

Serious infections occurred in 13 (0.6%) patients treated with TALTZ and in 3 (0.4%) patients treated with placebo (see Precautions). Infection-related serious adverse events (SAEs) reported by more than 1 patient in the TALTZ treated group were

cellulitis (n=3), appendicitis (n=2) and erysipelas (n=2). The proportion of patients who discontinued due to an infection related adverse reaction was similar in the total TALTZ treated group (n=8 [0.3%]) and the placebo group (n=2 [0.3%]).

Consistent with the mechanism of action, there was an increase in oral candidiasis. All, except one case, were mild or moderate in severity. No SAEs or discontinuations from treatment due to candidiasis were reported.

Overall, infections were reported in 52.8% of patients treated with TALTZ (46.9 per 100 patient years) and serious infections were reported in 1.6% of patients treated with TALTZ (1.5 per 100 patient years).

Laboratory Assessment of Neutropenia
Neutropenia was observed in clinical trials. In general, neutropenia was transient and did not require discontinuation of TALTZ, and was not associated with an increased rate of infections. In the placebo-controlled period of clinical trials, neutropenia ≥ Grade 3 (<1,000 cells/mm^3) was observed infrequently (0.1%) in patients receiving TALTZ compared to etanercept (0.5%) and placebo (0.1%). The remaining cases of neutropenia were low grade, either Grade 2 (2.0% for TALTZ, 3.3% for etanercept and 0.3% for placebo; ≥1,000 to <1,500 cells/mm^3) or Grade 1 (5.7% for TALTZ, 9.0% for etanercept and 2.3% for placebo; ≥1,500 cells/mm^3 up to normal).

Immunogenicity
Approximately 9% to 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 established.

Postmarketing Data
The following undesirable effect (adverse drug reaction) is based on postmarketing spontaneous reports:

Immune system disorders:
Anaphylaxis: Rare (≥ 0.01%, <0.1%)

DOSAGE AND ADMINISTRATION

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

Elderly Patients (≥65 years)
No dose adjustment is required for elderly patients.

Renal Impairment or Hepatic Impairment
TALTZ has not been studied in these patient populations. No dosage recommendations can be made.

Method of Administration
TALTZ is for SC injection. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

TALTZ is for single-use in one patient only. Discard any residue product.

Special Precautions for Handling and Disposal
The *Instructions for Use* included as a pack insert must be followed carefully.

Do not use TALTZ if it has been frozen.

TALTZ contains no antimicrobial preservative therefore discard any unused portion in accordance with local requirements.

OVERDOSAGE

Doses up to 180 mg have been administered subcutaneously in clinical trials without dose-limiting toxicity. Overdoses up to 240 mg 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.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26.

PRESENTATION AND STORAGE CONDITIONS

TALTZ is available as a 1 mL single-dose prefilled pen (autoinjector) or prefilled syringe* containing 80 mg ixekizumab solution. The solution is contained in a clear glass syringe barrel with bromobutyl plunger.

TALTZ is available in pack sizes of 1, 2 or 3** single-dose antoinjector or prefilled syringe*. Not all pack sizes may be marketed.

* prefilled syringe not marketed
** prefilled pen pack size of 3 not marketed

Storage Conditions
TALTZ single use autoinjector and prefilled syringe are to be stored at 2°C to 8°C. Refrigerate. Do not freeze. Protect from light. Do not shake.

If needed, for example while travelling or transporting the pens/syringes from the pharmacy, TALTZ may be exposed to temperatures not exceeding 30ºC for up to 5 days in total. After 5 days at temperatures not exceeding 30ºC the product must be used within these 5 days or discarded.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription Medicine – Schedule 4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

6 September 2016

DATE OF MOST RECENT AMENDMENT

05 April 2017

TALTZ® is a registered trademark of Eli Lilly and Company