PDL DRUG REVIEW

Proprietary Name: Taltz®
Common Name: ixekizumab
PDL Category: Anti-Inflammatories, Non-NSAID

Comparable Products	Preferred Drug List Status
Cosentyx	Preferred with Conditions

Summary

Pharmacology/Usage: Ixekizumab, the active ingredient of Taltz®, is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody (mAb); it selectively binds with the interleukin 17a (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in the normal inflammatory and immune responses, thus ixekizumab inhibits the release of pro-inflammatory cytokines and chemokines.

Indications: For the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

There is no pregnancy category with this product; however, the risk summary indicates that there are no studies of use in pregnant women to inform any drug-associated risks. Human IgG is known to cross the placental barrier; thus, Taltz® may be transmitted from the mother to the developing fetus. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Clear and colorless solution in a single-dose prefilled autoinjector AND single-dose prefilled syringe: 80mg/ml. Injections should be stored in the refrigerator.

Recommended Dosage: Inject 160mg subcutaneously (SC) at week 0, followed by 80mg SC at weeks 2, 4, 6, 8, 10, and 12, and then 80mg every 4 weeks. It is recommended to assess for TB infection prior to starting treatment with Taltz®, and not to administer to patients with active TB. Injections should be administered at a different location than the previous injection (such as upper arms, thighs, or any quadrant of the abdomen); however, treatment should not be injected into areas where the skin is tender, bruised, erythematous, indurated, or affected by psoriasis. The injection should be removed from the refrigerator and allowed to reach room temperature (30 minutes) without removing the needle cap.

There have been no formal studies of the effect of hepatic or renal impairment on the pharmacokinetics of ixekizumab.

Drug Interactions: It is recommended to complete all age appropriate immunizations prior to starting treatment with Taltz®. In addition, it is recommended to avoid the use of live vaccines in patients treated with Taltz®.

It is recommended, upon starting or discontinuing Taltz® in patients who are receiving concomitant drugs that are CYP450 substrates (especially those with a narrow therapeutic index), to monitor for effects (e.g. warfarin) or drug levels (e.g. cyclosporine) and to consider dose modification of the CYP450 substrate.

Common Adverse Drug Reactions: *The listed % incidence for adverse drug reactions= reported % incidence for drug (Taltz®) minus placebo.* The most frequently reported adverse events included injection site reactions (14%), upper respiratory tract infections (1%), nausea (1%), tinea infections (<1%), rhinitis (<1%), oral candidiasis (<1%), urticaria (<1%), influenza (<1%), conjunctivitis (<1%), inflammatory bowel disease (<1%), and angioedema (<1%). Neutropenia (8%) and Grade 1 thrombocytopenia (2%) were also reported.

There were reports of Crohn's disease (0.1%) and ulcerative colitis (0.2%), including exacerbations, during clinical trials with Taltz® vs placebo. It is therefore recommended to monitor for onset of exacerbation of inflammatory bowel disease.

Contraindications: In patients with a previous hypersensitivity reaction to ixekizumab or any component of the compound

Manufacturer: Eli Lilly & Company

Analysis: There were 3 randomized, double-blind, placebo-controlled trials (Trials 1, 2 and 3) to assess for the efficacy of ixekizumab in adult patients with plaque psoriasis who had a minimum body surface area involvement of 10%, a static Physician Global Assessment (sPGA) score of ≥3 on the overall assessment of psoriasis (on a scale of 0 to 5), a Psoriasis Area and Severity Index (PASI) score ≥12, and were candidates for phototherapy or systemic therapy. Patients were randomized to either placebo or Taltz® for 12 weeks, and there was an active comparator arm that included etanercept (50mg BIW) in Trials 2 and 3.

The co-primary endpoints were the same in each trial and included: (1.) the PASI 75, the proportion of subjects who achieved at least a 75% reduction in the PASI composite score that takes into consideration both the % of body surface area (BSA) affected and the nature and severity of psoriatic changes (induration, erythema, and scaling) within the affected regions AND (2.) sPGA of '0' (clear) or '1' (minimal), the proportion of subjects with an sPGA 0 or 1 and at least a 2-point improvement. Results of the Taltz® 80mg and placebo arms are illustrated in the table below, which was adapted from the prescribing information.

	Trial 1		Trial 2		Trial 3	
Endpoints	Taltz® Q2W (N=433)	Placebo (N=431)	Taltz® Q2W (N=351)	Placebo (N=168)	Taltz® Q2W (N=385)	Placebo (N=193)
sPGA of '0' or '1'	82% (N=354)	3% (N=14)	83% (N=292)	2% (N=4)	81% (N=310)	7% (N=13)
sPGA of '0'	37% (N=160)	0	42% (N=147)	1% (N=1)	40% (N=155)	0
PASI 75	89% (N=386)	4% (N=17)	90% (N=315)	2% (N=4)	87% (N=336)	7% (N=14)
PASI 90	71% (N=307)	1% (N=2)	71% (N=248)	1% (N=1)	68% (N=262)	3% (N=6)
PASI 100	35% (N=153)	0	40% (N=142)	1% (N=1)	38% (N=145)	0

Per an integrated analysis of the two active comparator studies with etanercept, Taltz® demonstrated superiority to etanercept 50mcg BIW on sPGA and PASI scores during the 12 weeks. The respective response rates for Taltz® 80mg Q2W and etanercept were: sPGA of 0 or 1 (73% and 27%); PASI 75 (87% and 41%); sPGA of 0 (34% and 5%); PASI 90 (64% and 18%); and PASI 100 (34% and 4%).

The following contains results for the Taltz® Q4W arm and the etanercept arm from Trial 2 and Trial 3 from the full-text study by Griffiths et al[2]. All comparisons between Taltz® Q4W and etanercept in both studies were statistically significant, in favor of Taltz® ($p<0.0001$ for all comparison). The authors also indicated that the differences between Taltz® Q2W and etanercept were also statistically significant, in favor of Taltz® ($p<0.0001$ for all comparisons).

	Trial 2		Trial 3	
Endpoints	Taltz® Q4W (N=347)	Etanercept (N=358)	Taltz® Q4W (N=386)	Etanercept (N=382)
sPGA of '0' or '1'	72.9% (N=253)	36% (N=129)	75.4% (N=291)	41.6% (N=159)
sPGA of '0'	32.3% (N=112)	5.9% (N=21)	36% (N=139)	8.6% (N=33)
PASI 75	77.5% (N=269)	41.6% (N=149)	84.2% (N=325)	53.4% (N=204)
PASI 90	59.7% (N=207)	18.7% (N=67)	65.3% (N=252)	25.7% (N=98)
PASI 100	30.8% (N=107)	5.3% (N=19)	35% (N=135)	7.3% (N=28)

To assess maintenance of response, subjects originally randomized to Taltz® and who were responders at week 12 in Trial 1 and 2 were then re-randomized to an additional 48 weeks of maintenance dose of Taltz® 80mg Q4W or placebo. Non-responders at week 12 and subjects who relapsed during the maintenance period were placed on Taltz® 80mg Q4W. Results suggested that for responders at week 12, the % who maintained this response at week 60 (sPGA 0 or 1) in the integrated trials (Trials 1 and 2) was higher for those treated with Taltz® vs placebo (75% vs 7%). For responders at week 12 who were re-randomized to treatment withdrawal (i.e. placebo), the median time to relapse (sPGA ≥3) was 164 days in the integrated trials. Of these, 66% regained a response of at least 0 or 1 on the sPGA within 12 weeks of restarting treatment with Taltz®.

Place in Therapy: Taltz® is a subcutaneous injectable indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. In the UNCOVER-2 and UNCOVER-3 phase 3 studies, Taltz® Q2W and Taltz® Q4W were found to be superior to placebo and etanercept for several outcomes assessed, including the PASI 75 and the sPGA.[2]

There is some evidence at this time to support that Taltz® is more effective than etanercept for several assessed outcomes in two phase 3 studies. Long-term efficacy of Taltz® up to 60 months was assessed and maintained. Currently, there is no evidence of direct comparisons of Taltz® to drugs other than etanercept. It is recommended that Taltz® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Taltz [package insert]. Indianapolis, IN: Eli Lilly and Company; 2016.

[2] Griffiths CE, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomized trials. *Lancet.* 2015; 386(9993): 541-51.