Brand Name: Taltz

Generic Name: Ixekizumab

Manufacturer [1]: Eli Lilly and Company

Drug Class [1]: Humanized monoclonal antibody; interleukin-17A antagonist

Uses [1]:

Labeled: Treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy

Unlabeled: N/A

Mechanism of Action [1]: Interleukin 17A (IL-17A) is a naturally occurring inflammatory cytokine which mediates a number of immune responses by binding to the IL-17 receptor. Ixekizumab is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody which selectively binds to IL-17A and prevents interaction with its receptor. This reduces inflammation and blocks its downstream effects, including the release of proinflammatory cytokines and chemokines.

Pharmacokinetics [1]:

T_{max}	4 days
V_d	7.11 liters
$t_{1/2}$	13 days
Mean Systemic Clearance	0.39 liters/day
Protein Binding	N/A
Bioavailability	60-81% following subcutaneous injection

Absorption: Steady-state concentrations were achieved by week 8 following the every 2 weeks regimen. Steady-state concentrations were achieved 10 weeks after switching to the every 4 weeks regimen. Administration via injection into the thigh achieved a higher bioavailability relative to other injection sites, including the arm and abdomen.

Distribution: Ixekizumab clearance and volume of distribution increase as body weight increases.

Metabolism & Excretion: The metabolic pathway of ixekizumab has not been determined, but ixekizumab is expected to be degraded into small peptides in the same manner as endogenous IgG.

Efficacy:

Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, Braun D, Banerjee S. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. N Engl J Med. 2012 Mar 29;366(13):1190-9. doi: 10.1056/NEJMoa1109997.

Study Design: Phase 2, double-blind, multicenter, randomized, placebo-controlled, dose-ranging study

Description of Study: Inclusion criteria were an age of at least 18 years, chronic moderate-to-severe plaque psoriasis ≥ 6 months, scores ≥ 12 on the psoriasis area-and-severity index (PASI) and ≥ 3 on the static physician's global assessment, and psoriasis involving at least 10% of body-surface area. Exclusion criteria were the presence of non-plaque psoriasis, a clinically significant flare of psoriasis during the preceding 12 weeks, an active infection within 5 days of study drug administration, a recent serious infection, conventional systemic psoriasis therapy or phototherapy within 4 weeks, topical psoriasis treatment within 2 weeks, or use of any biologic agent recently or concurrently with the study drug. 142 patients were randomly assigned to receive subcutaneous injections of placebo or 10 mg, 25 mg, 75 mg, or 150 mg of ixekizumab at 0, 2, 4, 8, 12, and 16 weeks. Patients were allowed to use various topical preparations for skin conditions during the study. Other medications could be used as medically necessary. Weak topical steroids were permitted for limited uses. The primary end point was the proportion of patients with reduction in the PASI score by at least 75% at 12 weeks. Secondary end points included the proportion of patients with reduction in the PASI score by at least 90% or by 100%. At 12 weeks, patients achieving the primary outcome were significantly higher with ixekizumab (except with the lowest, 10-mg dose)--150 mg (82.1%), 75 mg (82.8%), and 25 mg (76.7%)--than with placebo (7.7%, P<0.001 for each comparison). The percentage of patients with a reduction in the PASI score by at least 90% was also greater with ixekizumab--150 mg (71.4%), 75 mg (58.6%), and 25 mg (50.0%)--versus placebo (0%, P<0.001 for each comparison). Similarly, a 100% reduction in the PASI score was achieved in significantly more patients in the 150-mg group (39.3%) and the 75-mg group (37.9%) than in the placebo group (0%) (P<0.001 for both comparisons). Significant differences occurred as early as 1 week and were sustained through 20 weeks. No serious adverse events or major cardiovascular events were observed. A total of 3 patients discontinued ixekizumab because of the following adverse events: peripheral edema, hypersensitivity, and urticaria.

Limitations: This study was sponsored by Eli Lilly, the manufacturer of ixekizumab. This trial was not large enough or long enough to detect rare adverse events, and it did not precisely control the usage of topical steroids or adjunctive medications. Usage in patients with infections is unlikely to be studied.

Conclusions: The data suggest that inhibition of interleukin-17 with ixekizumab may be an effective therapy for psoriasis. Patients with chronic moderate-to-severe plaque psoriasis treated with ixekizumab had significant improvement in clinical measures during the 12-week treatment period that were rapid and sustained through 20 weeks with continued treatment. Further studies are needed to establish the long-term safety and efficacy of ixekizumab in the treatment of psoriasis.

Gordon KB, Leonardi CL, Lebwohl M, Blauvelt A, Cameron GS, Braun D, Erickson J, Heffernan M. A 52-week, open-label study of the efficacy and safety of ixekizumab, an anti-interleukin-17A monoclonal antibody, in patients with chronic plaque psoriasis. J Am Acad Dermatol. 2014 Dec;71(6):1176-82. doi: 10.1016/j.jaad.2014.07.048. Epub 2014 Sep 19.

Study Design: Open-label, multicenter, single arm extension study of a phase 2 randomized controlled trial

Description of Study: Patients who completed 20 weeks of the previously described randomized controlled trial (RCT) and who had not experienced a treatment-related adverse event (AE) or a serious AE (SAE) deemed to be detrimental with continued treatment were eligible to participate in this open-label extension (OLE) study. At week 20 of the RCT, patients without 75% improvement from baseline on the Psoriasis Area and Severity Index (PASI75; n = 51) were eligible to enter the OLE and initiate monthly ixekizumab treatment. All other patients (n = 69) entered a treatment-free period from weeks 20 to 32 and became eligible to enter the OLE at the study visit where they fell below PASI75 (n = 24) or at week 32 if PASI75 or higher was maintained throughout the treatment-free period (n = 45). All patients were administered 120 mg of ixekizumab subcutaneously every 4 weeks once they entered the OLE. Of the 129 patients who completed the RCT, 120 (93%) entered the OLE and received at least 1 dose of study drug and 103 (86%) completed at least 52 weeks of treatment. Of the patients who entered the OLE, 92 of 120 (77%) had a PASI75, 81 (68%) had a PASI90, and 58 (48%) had a PASI100 response after 52 weeks of open-label ixekizumab treatment. For patients who met PASI75 (n = 69) response criteria by week 20 of the RCT, a PASI75 response was observed in 95% (57 of 60) at week 52. PASI90 and PASI100 response rates were similarly maintained during the OLE. Of the 69 patients who were PASI75 responders at week 20 of the RCT, 24 lost response during the treatment-free period and all but 2 regained the PASI75 response during the OLE. None of the patients initially assigned to placebo (n = 22) achieved PASI75 during the RCT. After 52 weeks of ixekizumab treatment in the OLE, a PASI75 response was observed in 95% (18 of 19), a PASI90 response was observed in 95% (18 of 19), and a PASI100 response was observed in 63% (12 of 19) of these patients. A total of 235 AEs were reported during the open-label period in 80 (67%) patients. No squamous cell carcinomas or melanomas were reported. One patient with a history of vasculitis was reported to have had a thalamic infarction based on clinical signs and symptoms. A total of 15 SAEs were reported in 10 (8%) patients during the open-label period. The SAEs were rectal cancer; exacerbation of hidradenitis suppurativa (3 events in 1 patient); depression, suicide attempt, and atherosclerosis (all in 1 patient); congestive heart failure and urinary tract obstruction (both in 1 patient); cellulitis; pyelonephritis; acute coronary syndrome; nephrolithiasis; wrist fracture; and laceration of the left arm. None of these SAEs were major cardiac events.

Limitations: Interpretation of the 52-week efficacy and safety of ixekizumab based on this OLE is limited by the absence of a control group and small sample sizes. In addition, there may be a bias toward retention in the OLE for patients who experienced disease improvement without safety concerns. This study was also sponsored by Eli Lilly.

Conclusions: A high proportion of patients responded to ixekizumab therapy and maintained clinical responses over 1 year of treatment. Similar to the RCT, nasopharyngitis and upper respiratory tract infections remained the most frequently reported events. These findings are consistent with no increase in the rate of AEs over the first year of therapy with ixekizumab. In the RCT, no SAEs were reported, whereas 10 patients in the OLE experienced an SAE, which is not unexpected with longer drug exposure.

Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, Cameron GS, Erickson J, Zhang L, Secrest RJ, Ball S, Braun DK, Osuntokun OO, Heffernan MP, Nickoloff BJ, Papp K; UNCOVER-2 and UNCOVER-3 investigators. Comparison of ixekizumab with etanercept or placebo in moderate-to-

severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet. 2015 Aug 8;386(9993):541-51. doi: 10.1016/S0140-6736(15)60125-8. Epub 2015 Jun 10.

Study Design: Two prospective, double-blind, double-dummy, randomized (1:2:2:2), multicenter, phase 3 studies (UNCOVER-2 and UNCOVER-3)

Description of Study: In these two prospective, double-blind, multicenter, phase 3 studies (UNCOVER-2 and UNCOVER-3), eligible participants were aged 18 years or older, had a confirmed diagnosis of chronic plaque psoriasis ≥ 6 months, 10% or greater body-surface area involvement, a score of ≥ 3 on the sPGA, a (PASI) score ≥ 12, and were candidates for phototherapy, systemic therapy, or both. During the 12-week placebo-controlled and active-controlled period in each trial, patients were randomly assigned (2:2:2:1) and stratified by center to receive either of two regimens of ixekizumab, etanercept, or placebo. A double-dummy design was used. Patients received ixekizumab 160 mg starting dose followed by either 80 mg every 2 weeks or every 4 weeks, etanercept 50 mg twice weekly, or placebo. 1224 and 1346 patients were randomized in UNCOVER-2 and UNCOVER-3, respectively. In both studies, primary objectives were met with regards to PASI 75 and sPGA 0/1, with both dose regimens of ixekizumab showing greater efficacy than placebo and etanercept at week 12 ($p<0.0001$ for each ixekizumab dose vs placebo and etanercept). Greater proportions of patients achieved PASI 75 as early as week 1 for both ixekizumab groups compared with etanercept (UNCOVER-2: $p=0.0001$ [ixekizumab every 4 weeks] and $p=0.022$ [ixekizumab every 2 weeks] and UNCOVER-3: $p=0.035$ [ixekizumab every 4 weeks] and $p=0.0003$ [ixekizumab every 2 weeks]) and by week 2 for both ixekizumab groups compared with placebo and etanercept ($p<0.0001$). By week 4 of both studies, about 50% of all patients given ixekizumab achieved PASI 75. Greater proportions of patients given ixekizumab achieved PASI 90 by week 2 compared with etanercept in both studies. At week 12, PASI 90 achievement was significantly higher with ixekizumab than placebo or etanercept. Greater proportions of patients given ixekizumab compared with etanercept achieved complete resolution of psoriatic plaques (PASI 100) by week 4. In both studies combined, the percentages of patients with adverse events were higher in both ixekizumab dose groups and etanercept groups than for placebo. Rates of treatment emergent adverse events were higher in both ixekizumab groups when compared to etanercept (58% and 58% vs 54%). The most common (≥2% of all patients given ixekizumab) adverse events in patients given ixekizumab in both studies combined were nasopharyngitis, upper respiratory tract infection, injection-site reaction, injection-site erythema, injection-site pain, pruritus, headache, and arthralgia. Most treatment-emergent adverse events were mild or moderate in severity. Serious adverse events were reported by 2% or fewer of patients in each treatment group across both studies. Rates of serious adverse events and discontinuations due to adverse events were comparable across study groups in both studies.

Limitations: This study was also sponsored by Eli Lilly. The main limitation of these studies was the fairly short duration. Hence, full assessment of the maximum potential to attain and sustain high-level responses and safety signals (detection of infrequent adverse events) require longer-term studies, which are currently ongoing (UNCOVER-1 [NCT01474512], UNCOVER-2, and UNCOVER-3). Additionally, the study population was mainly white; therefore, further evaluation in a larger population of non-white participants might be necessary to fully understand the efficacy and safety in a more genetically diverse population. Because patients previously on

etanercept were excluded, this may have led to a population that was overall more naive to biological drugs.

Conclusions: In these two double-blind, multicenter, phase 3 studies, both dose regimens of ixekizumab showed greater efficacy than did placebo and etanercept in treatment of moderate-to-severe psoriasis at 12 weeks. The overall recorded safety profile and common adverse events at week 12 for these phase 3 studies were comparable to those noted in previous phase 2 trials and comparable with etanercept. Overall rates of treatment-emergent adverse events and infections were more frequent in patients given ixekizumab than in those given etanercept or placebo.

Contraindications [1]:

Hypersensitivity: Ixekizumab is contraindicated in patients with a previous serious hypersensitivity reaction (such as anaphylaxis) to ixekizumab or any of its excipients.

Precautions [1]:

Infections: Ixekizumab may increase the risk of infection. In clinical trials, the ixekizumab group had a higher rate of infections than the placebo group (27% vs. 23%). Upper respiratory tract infections, oral candidiasis, conjunctivitis and tinea infections occurred more frequently in the ixekizumab group than in the placebo group. Instruct patients to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a serious infection or is not responding to standard therapy, monitor the patient closely and discontinue ixekizumab until the infection resolves.

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

Hypersensitivity: Serious hypersensitivity reactions, including angioedema and urticaria (each ≤0.1%), occurred in the ixekizumab group in clinical trials. If a serious hypersensitivity reaction occurs, discontinue immediately and initiate appropriate therapy.

Inflammatory Bowel Disease: Crohn's disease and ulcerative colitis, including exacerbations, occurred at a greater frequency in the ixekizumab group (Crohn's disease 0.1%, ulcerative colitis 0.2%) than the placebo group (0%) during the 12-week, placebo-controlled period. During treatment, monitor for onset or exacerbation of inflammatory bowel disease.

Immunizations: Prior to initiating therapy with ixekizumab, consider completion of all age appropriate immunizations according to current immunization guidelines. Avoid use of live vaccines in patients treated with ixekizumab. No data are available on the response to live or inactive vaccines.

Adverse Effects [2]:

Common (> 10%):

Antibody formation (10%)

Neutralizing antibody formation (2%)

Infection (27%)

Injection site reaction (14%)

Neutropenia (11%)

Infrequent (1-10%):

Nausea (2%)

Rare (< 1%):

Angioedema

Candidiasis

Inflammatory bowel disease

Influenza

Rhinitis

Urticaria

Unknown:

Anaphylactoid reactions

Ocular infection

Pharyngitis

Thrombocytopenia

Drug Interactions [1]:

Live Vaccinations: Avoid use of live vaccines in patients treated with ixekizumab.

Cytochrome P450 Substrates: The formation of CYP450 enzymes can be altered by increased levels of certain cytokines during chronic inflammation. Thus, ixekizumab, an antagonist of IL-17A, could affect the formation of CYP450 enzymes. Therefore, upon initiation or discontinuation of ixekizumab in patients who are receiving concomitant drugs which are CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and consider dosage modification of the CYP450 substrate.

Dosing/Administration [1]:

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

Tuberculosis Assessment Prior to Initiation of ixekizumab: Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with ixekizumab.

Important Administration Instructions: Ixekizumab is intended for use under the guidance and supervision of a physician. Patients may self-inject after training in subcutaneous injection technique using the autoinjector or prefilled syringe. Administer each injection at a different anatomic location (such as upper arms, thighs or any quadrant of abdomen) than the previous injection, and not into areas where the skin is tender, bruised, erythematous, indurated or affected by psoriasis. Administration of ixekizumab in the upper, outer arm may be performed by a caregiver or healthcare provider. There are two formulations for ixekizumab (i.e., autoinjector and prefilled syringe). If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

Preparation for Use of TALTZ Autoinjector and Prefilled Syringe: Before injection, remove TALTZ autoinjector or TALTZ prefilled syringe from the refrigerator and allow TALTZ to reach room temperature (30 minutes) without removing the needle cap. Inspect TALTZ visually for particulate matter and discoloration prior to administration. TALTZ is a clear and colorless to slightly yellow solution. Do not use if the liquid contains visible particles, is discolored or cloudy (other than clear and colorless to slightly yellow). TALTZ does not contain preservatives, therefore discard any unused product remaining in the autoinjector or prefilled syringe. Instruct patients using the autoinjector or prefilled syringe to inject the full amount (1 mL), which provides 80 mg of TALTZ.

Use in Special Circumstances [1, 2]:

Pregnancy: There are no available data on ixekizumab use in pregnant women to inform any drug associated risks. Human IgG is known to cross the placental barrier; therefore, ixekizumab may be transmitted from the mother to the developing fetus. An embryofetal development study conducted in pregnant monkeys at doses up to 19 times the maximum recommended human dose (MRHD) revealed no evidence of harm to the developing fetus. When dosing was continued until parturition, neonatal deaths were observed at 1.9 times the MRHD. The clinical significance of these nonclinical findings is unknown. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Lactation: There are no data on the presence of ixekizumab in human milk, the effects on the breastfed infant, or the effects on milk production. Ixekizumab was detected in the milk of lactating cynomolgus monkeys. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ixekizumab and any potential adverse effects on the breastfed infant from ixekizumab or from the underlying maternal condition.

Pediatric Use: The safety and effectiveness of ixekizumab in pediatric patients (<18 years of age) have not been evaluated.

Geriatric Use: Of the 4204 psoriasis subjects exposed to ixekizumab, a total of 301 were 65 years or older, and 36 subjects were 75 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects.

Hepatic and Renal Impairment: Specific guidelines for dosage adjustments in hepatic or renal impairment are not available; it appears no dosage adjustments are needed.

Conclusion: Ixekizumab appears to be an effective, durable agent (at least 52 weeks) in the management of moderate-to-severe plaque psoriasis. When compared to both placebo and etanercept, ixekizumab produces clinically significant reductions in disease severity, with an increased risk of certain adverse events including hypersensitivity reactions (angioedema, urticaria) and infections. In two separate 12 week trials comparing etanercept to ixekizumab, treatment with ixekizumab led to faster and higher rates of response (PASI 75, 90, and 100) throughout the 12 week periods, with a small increase in treatment-emergent adverse events (58% vs 54%; most were mild or moderate infections). However, ixekizumab is not the first approved IL-17A antibody. Secukinumab is another IL-17A monoclonal antibody shown to be more effective than etanercept [6]. Secukinumab has also been shown to be more effective than ustekinumab (an IL-12 and IL-23 antibody) in treating patients with moderate-to-severe plaque psoriasis who have failed at least one therapy [7], so the role of ixekizumab is unclear. Ixekizumab represents another treatment option in the management of plaque psoriasis but does not offer clear advantages compared to certain other biologic agents. In the event of treatment failure with secukinumab, use of ixekizumab is unlikely to be of benefit after consideration of their mechanisms.

Recommended References:

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