CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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<u>OFFICE DIRECTOR MEMO</u>

Office Director Decisional Memorandum

Date	March 23, 2016
From	Julie Beitz, MD
Subject	Office Director Decisional Memo
BLA #	125521
Applicant Name	Eli Lilly and Company
Date of Submission	March 23, 2015
PDUFA Goal Date	March 23, 2016
Proprietary Name / Established (USAN) Name	Taltz (ixekizumab) injection
Dosage Forms / Strengths	80 mg / mL solution in a single dose prefilled autoinjector; 80 mg/mL solution in a single dose prefilled syringe
Proposed Indication	Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Recommended Action:	Approval

Materials Reviewed/Consulted OND Action Package, including reviews from:	**Discipline Reviewers**
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Cross Discipline Team Leader, DDDP	Jill Lindstrom, MD
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DDDP = Division of Dermatology and Dental Products
DMEPA = Division of Medication Error Prevention and Analysis
DPMH = Division of Pediatrics and Maternal Health
OND = Office of New Drugs
OSE = Office of Surveillance and Epidemiology

Reference ID: 3906220

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Taltz (ixekizumab) is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody produced by recombinant DNA technology. Ixekizumab selectively binds with interleukin-17A (IL-17A) and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Ixekizumab inhibits the release of proinflammatory cytokines and chemokines. Taltz (ixekizumab) is administered by subcutaneous injection, and supplied in a single-dose prefilled autoinjector or a single-dose prefilled syringe delivering 80 mg of ixekizumab.

I concur with the recommendation of the Division of Dermatology and Dental Products to approve Taltz (ixekizumab) injection for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Substantial evidence of effectiveness was demonstrated in three randomized controlled clinical trials, and the safety profile of ixekizumab was consistent with that of other approved systemic biologic therapies for adult patients with moderate-to-severe plaque psoriasis. The safety concerns identified with use of Taltz (ixekizumab) in clinical trials can be adequately managed by product labeling, a Medication Guide, that will be required as part of approved labeling to communicate important safety information to patients, and pharmacovigilance in the postmarket setting. A Risk Evaluation and Mitigation Strategy (REMS) will not be required.

Psoriasis is a common, chronically remitting and relapsing inflammatory disease. Skin and joint manifestations predominate. Approximately 20% of patients have moderate-to-severe disease affecting more than 5% of their body surface area. Patients with psoriasis face numerous social and psychological challenges. The incidence of clinical depression and suicidality is higher among patients with psoriasis than in the general population.

There are several FDA-approved therapies for adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy, including the tumor necrosis factor inhibitors, adalimumab and etanercept, apremilast (a phosphodiesterase 4 inhibitor), ustekinumab (an antagonist of IL-12 and IL-23), and secukinumab (an antagonist of IL-17A). Product efficacy, as measured by the PASI 75, ranges from highly efficacious (adalimumab, ustekinumab and secukinumab), to moderately efficacious (etanercept), to somewhat efficacious (apremilast). Approved systemic therapies for moderate-to-severe plaque psoriasis also have attendant serious side effects including risk of serious infections, and risk of malignancy/lymphoma. Thus, alternative efficacious therapies with potentially better safety profiles are needed.

Taltz (ixekizumab) injection was highly efficacious for the treatment of adults with moderate-to-severe plaque psoriasis in clinical trials. Evidence of ixekizumab efficacy included 1) superior clinical response at Week 12 compared to placebo, 2) superior clinical response at Week 60 among responding ixekizumab-treated patients receiving continued ixekizumab treatment compared to those switched to placebo maintenance therapy after Week 12, and 3) achievement of a second clinical response among ixekizumab-treated patients who responded initially and later relapsed on placebo maintenance therapy. In addition, clinical response to ixekizumab was superior to that of etanercept at Week 12.

Reference ID: 3906220

The overall safety profile of ixekizumab for the treatment of adult patients with moderate-to-severe plaque psoriasis is consistent with that of approved systemic biologic therapies for this disease. Infections, including serious infections, hypersensitivity reactions, including rare cases of angioedema, and inflammatory bowel disease were reported with ixekizumab therapy. These are known common, and potentially serious, adverse reactions associated with approved systemic biologic therapies for adult patients with moderate-to-severe plaque psoriasis. These reactions will be highlighted in the Warnings and Precautions section of product labeling and medical interventions that could be employed should these reactions occur will be described.

In addition, the risk of latent TB reactivation, and the need to complete immunizations prior to initiating ixekizumab and avoid live vaccines will be highlighted in product labeling, consistent with labeling for approved systemic biologic therapies.

The most common adverse reactions reported with ixekizumab therapy were injection site reactions (erythema and pain), upper respiratory tract infections, nausea, and tinea infections. Most injection site reactions were mild to moderate in severity and did not lead to discontinuation of ixekizumab.

Anti-drug antibodies to ixekizumab, including neutralizing antibodies can develop; higher antibody titers were associated with decreasing drug concentration and clinical response.

The evaluation of depression and suicidality in ixekizumab clinical trials was limited by the exclusion of patients with a history of prior suicide attempts, the relatively infrequent assessment for depression using the Quick Inventory of Depressive Symptoms, and the absence of active solicitation of information about suicidality, e.g., using the Columbia Suicide Severity Rating Scale. The available data however, do not support an association of ixekizumab with suicidality. There were no reports of completed suicide. The reports of suicidal ideation in ixekizumab-treated patients were confounded by other events, there was no temporal association of the events with the onset or duration of treatment, and the exposure-adjusted rate of suicide attempt in ixekizumab-treated patients was less than that for placebo-treated patients. In addition, there was no evidence for treatment-emergent worsening of depression, anxiety or other psychiatric adverse events.

The applicant will be required to conduct three observational studies under FDAAA in adults with moderate-to-severe plaque psoriasis exposed to ixekizumab. Comparisons to control population(s) will be made. These studies will further assess potential serious safety risks as follows:

- A prospective long-term observational safety study with malignancy as the primary outcome of interest;
- A prospective observational study in pregnant women of maternal, fetal and infant outcomes, including effects on postnatal growth and development;
- A retrospective observational study of pregnancy outcomes in pregnant women exposed to ixekizumab; this study will be complementary to the prospective observational study in pregnant women.

The Division has determined that full extrapolation of adult efficacy data to pediatric patients with moderate-to-severe plaque psoriasis is appropriate. The applicant will be required to conduct a pharmacokinetic, safety and efficacy study in pediatric patients ages 6 to less than 18 years with moderate-to-severe plaque psoriasis, with a duration of exposure to ixekizumab of at least one year. Weight-based dosing regimens have been determined based on simulations

Reference ID: 3906220

from adult pharmacokinetic and exposure-response data that are predicted to achieve pediatric exposures in the range of exposures achieved in adults with the labeled ixekizumab dosing regimen.

In addition, the applicant has agreed to conduct a drug-drug interaction clinical study to assess whether ixekizumab alters the metabolism or pharmacokinetics of CYP substrates in psoriasis patients treated with ixekizumab.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Psoriasis is a chronically remitting and relapsing inflammatory disease affecting 2-3% of the U.S. population. Skin and joint manifestations predominate. Plaque psoriasis (Psoriasis vulgaris) is the most common form, accounting for 85-90% of cases. Skin lesions are circumscribed, scaly and erythematous and often symmetrically distributed over the body. Affected skin may be painful, cracked or itchy. The majority of cases are mild to moderate, but 20% have moderate to severe disease affecting more than 5% of the body surface area. Patients with psoriasis face numerous social and psychological challenges. In a study conducted in the U.K.'s General Practice Research Database, the incidence of clinical depression and suicidality (including suicidal ideation, attempt or suicide completion) in patients with psoriasis was higher than in the general population. Among patients with psoriasis, the incidence of clinical depression and suicidality was higher for those on systemic therapy than for those who were not (i.e., for patients presumed to have severe vs. mild disease).[1]	Psoriasis is a common, chronically remitting and relapsing inflammatory disease. Skin and joint manifestations predominate. Approximately 20% of patients have moderate to severe disease affecting more than 5% of their body surface area. Patients with psoriasis face numerous social and psychological challenges. The incidence of clinical depression and suicidality is higher among patients with psoriasis than in the general population.
Current Treatment Options	Although numerous topical therapies are FDA-approved for plaque psoriasis, adult patients with moderate-to-severe plaque psoriasis have skin involvement that covers too large a surface area for these therapies to be practical or acceptable. Therefore, systemic therapies are typically indicated.	There are several FDA-approved therapies for adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy, including the tumor necrosis factor inhibitors, adalimumab and etanercept, apremilast (a phosphodiesterase 4

[1] Olivier C, Robert P. D., Daihung D., Urba G., Catalin P., Hywel W., Kurd S. K., Troxel A. B., Crits-Christoph P., Gelfand J. M. The risk of depression, anxiety, and suicidality in patients with psoriasis: A population-based cohort study. *Arch Dermatol* 2010; 146(8): 891-895.

Reference ID: 3906220

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Currently FDA-approved systemic therapies indicated for moderate-to-severe plaque psoriasis include the tumor necrosis factor inhibitors (adalimumab and etanercept), apremilast (a phosphodiesterase 4 inhibitor), ustekinumab (an antagonist of IL-12 and IL-23) and secukinumab (an antagonist of IL-17A). The following systemic therapies are indicated for severe plaque psoriasis: methotrexate (an antimetabolite), the tumor necrosis factor inhibitor infliximab, cyclosporine (a T cell inhibitor), acitretin (a retinoid), and phototherapy. Product efficacy, as measured by a 75% reduction in the Psoriasis Area and Severity Index from baseline (PASI 75), has been reported as follows: PASI 75 achieved in ≥ 70% of patients (highly efficacious) for cyclosporine, infliximab, adalimumab, ustekinumab, and secukinumab; PASI 75 achieved in ≥ 40% of patients (moderately efficacious) for methotrexate and etanercept; and PASI 75 achieved in ≥ 20% of patients (somewhat efficacious) for acitretin and apremilast. Phototherapy has been found to be highly efficacious as well. Attendant serious side effects of approved therapies include: hepatotoxicity (methotrexate); risk of serious infections (tumor necrosis factor inhibitors, ustekinumab, secukinumab, and cyclosporine); risk of malignancy/lymphoma (methotrexate, tumor necrosis factor inhibitors, ustekinumab, and cyclosporine); teratogenicity (acitretin); and skin aging/skin cancer (phototherapy).	inhibitor), ustekinumab (an antagonist of IL-12 and IL-23), and secukinumab (an antagonist of IL-17A). Product efficacy, as measured by the PASI 75, ranges from highly efficacious (adalimumab, ustekinumab and secukinumab), to moderately efficacious (etanercept), to somewhat efficacious (apremilast). Approved systemic therapies for moderate to severe plaque psoriasis also have attendant serious side effects including risk of serious infections, and risk of malignancy/lymphoma. Thus, alternative efficacious therapies with potentially better safety profiles are needed.
Benefit	The efficacy of Taltz (ixekizumab) was established in three randomized, double-blind, placebo-controlled clinical trials involving a total of 3866 adult patients with plaque psoriasis. Eligible patients had a minimum body surface area involvement of 10%, a static Physician Global Assessment (sPGA) score of 3 or greater (on a scale of 0 to 5), a Psoriasis Area and Severity Index (PASI) score of 12 or greater, and were candidates for systemic therapy or phototherapy. Overall, 44% had received prior phototherapy, 49% had prior conventional systemic therapy, and 26% had prior systemic biologic therapy.	Taltz (ixekizumab) injection was highly efficacious for the treatment of adults with moderate-to-severe plaque psoriasis in clinical trials. Evidence of ixekizumab efficacy included 1) superior clinical response at Week 12 compared to placebo, 2) superior clinical response at Week 60 among responding ixekizumab-treated patients receiving continued ixekizumab treatment compared to those switched to placebo maintenance therapy,

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	• **Dosing.** In all three trials, patients were randomized to either placebo or ixekizumab 80 mg every two weeks for 12 weeks, following a 160 mg starting dose. In two of the trials, patients were also randomized to receive etanercept 50 mg twice weekly for 12 weeks.[2] In two of the trials, patients treated with ixekizumab who were responders at Week 12 were re-randomized to an additional 48 weeks of either ixekizumab 80 mg every 4 weeks or placebo. • **Efficacy Endpoints.** In all three trials, clinical efficacy of ixekizumab was assessed as the changes from baseline to Week 12 in two co-primary endpoints: 1) the proportion of patients who achieved at least a 75% reduction in PASI score (PASI 75), and 2) the proportion of patients who achieved an sPGA score of "0" (clear) or "1" (minimal) and at least a 2-point improvement. • **Clinical Response at Week 12.** The proportions of ixekizumab-treated patients achieving PASI 75 were 89%, 90%, and 87% in the three trials, respectively. The proportions of patients achieving PASI 75 on placebo treatment were 4%, 2%, and 7% in these trials, respectively. The proportions of ixekizumab-treated patients achieving clinical response on the sPGA were 82%, 83%, and 81% in the three trials, respectively. The proportions of patients responding on placebo treatment were 3%, 2%, and 7% in these trials, respectively. Examination of age, gender, race, body weight, and previous treatment with a systemic biologic therapy did not identify differences in clinical response to ixekizumab among these subgroups at Week 12. At Week 12, ixekizumab-treated patients experienced reduced itch severity compared to placebo-treated patients, defined as at least a 4 point reduction on an 11 point itch Numeric Rating Scale.	and 3) achievement of a second clinical response among ixekizumab-treated patients who responded initially and later relapsed on placebo maintenance therapy. In addition, clinical response to ixekizumab was superior to that of etanercept at Week 12. The major efficacy findings were: In three clinical trials, at Week 12, the proportions of patients treated with ixekizumab 80 mg every 2 weeks who achieved at least a 75% reduction in PASI score, or an sPGA of "0" (clear) or "1" (minimal), were significantly greater than for placebo-treated patients. In two clinical trials, among ixekizumab-treated patients who were responders at Week 12, a greater proportion of patients who were re-randomized to additional ixekizumab (80 mg every four weeks) maintained response at Week 60 compared to those who were switched to placebo maintenance therapy. In two clinical trials, among ixekizumab-treated patients who were responders at Week 12 and who were re-randomized to placebo maintenance therapy, the median time to relapse (defined as an

[2] Patients enrolled at U.S. sites received U.S.-licensed etanercept whereas patients at non-U.S. sites received EU-approved etanercept. The applicant did not provide an adequate bridge to allow reliance on the data from the EU-approved product. Thus, labeling will include information only on the 287 patients treated with U.S.-licensed etanercept.

Reference ID: 3906220

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	In the two trials that included an active control group, ixekizumab-treated patients experienced superior responses on PASI and sPGA scores compared to patients treated with etanercept when assessed at Week 12. • **Maintenance and Durability of Response.** Among responders to ixekizumab at Week 12 (with an sPGA score of "0" or "1"), the proportion of patients who maintained this response at Week 60 (that is, 48 weeks post-re-randomization) was greater for patients treated with additional ixekizumab (80 mg every four weeks) compared to those who were switched to placebo maintenance therapy (75% vs. 7%), when results of the two trials that evaluated maintenance therapy are combined. • **Relapse upon Treatment Withdrawal.** Among responders to ixekizumab at Week 12 who were re-randomized to placebo maintenance therapy, the median time to relapse (defined as an sPGA score ≥ 3) was 164 days when the results of the two trials that evaluated treatment withdrawal are combined. Among relapsing patients, 66% regained a clinical response of at least "0" or "1" on the sPGA within 12 weeks of restarting treatment with ixekizumab 80 mg every four weeks.	sPGA score ≥ 3) was 164 days. Among relapsing patients, two-thirds regained a clinical response of at least "0" or "1" on the sPGA within 12 weeks of restarting treatment with ixekizumab 80 mg every four weeks.
Risk	In three clinical trials, a total of 1167 adult patients with moderate-to-severe plaque psoriasis received subcutaneous ixekizumab (160 mg at Week 0, then 80 mg every two weeks) for 12 weeks. The mean age was 45 years, 66% were male and 94% were Caucasian. A total of 332 of these patients also received the recommended maintenance regimen of ixekizumab 80 mg every 4 weeks. In two of the trials, a total of 287 adult patients with moderate-to-severe plaque psoriasis received active treatment with U.S.-licensed etanercept (50 mg every two weeks) for 12 weeks. The review identified the following serious risks that will be described in the Warnings and Precautions section of product labeling:	The overall safety profile of ixekizumab for the treatment of adult patients with moderate-to-severe plaque psoriasis is consistent with that of approved biologic systemic therapies for this disease. Infections, including serious infections, hypersensitivity reactions, including rare cases of angioedema, and inflammatory bowel disease were reported with ixekizumab therapy. These are known common, and potentially serious, adverse reactions associated with approved systemic

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	• **Risk of Infection.** In clinical trials, during the 12-week placebo-controlled period, ixekizumab-treated patients had a higher rate of infection than placebo-treated patients (27% vs. 23%), including upper respiratory tract infections, oral candidiasis, conjunctivitis and tinea infections. The infection rate per patient-year of follow-up was 1.2 and 1.0, respectively, in the two groups. Serious infections occurred in 0.4% of patients, or at a rate of 0.02 per patient-year of follow-up in both groups. In the two trials that included an active comparator during Weeks 0 - 12, the infection rate was 18% in etanercept-treated patients; serious infections occurred in 0.3% of patients in both etanercept and ixekizumab groups. During the 48-week maintenance period (Weeks 13-60), infections occurred in 57% of ixekizumab-treated patients, or at a rate of 0.70 per patient-year of follow-up compared to 32% of patients and a rate of 0.61 per patient-year of follow-up in placebo-treated patients. Serious infections occurred in 0.9% of ixekizumab-treated patients, at a rate of 0.01 per patient-year of follow-up; there were no serious infections in placebo-treated patients during the maintenance period. Labeling will recommend that for patients who develop a serious infection or do not respond to standard therapy, ixekizumab should be discontinued until the infection resolves. • **Hypersensitivity Reactions.** Serious hypersensitivity reactions occurred in ixekizumab-treated patients (angioedema in 0.1%, urticaria in 0.1%). Labeling will recommend that ixekizumab be discontinued if a serious hypersensitivity reaction occurs, and that appropriate therapy be initiated. • **Inflammatory Bowel Disease.** Crohn's disease and ulcerative colitis, including exacerbations, occurred at a greater frequency in ixekizumab-treated patients (Crohn's disease in 0.1%, ulcerative colitis in 0.2%) than in	biologic therapies for adult patients with moderate-to-severe plaque psoriasis. These reactions will be highlighted in the Warnings and Precautions section of product labeling and medical interventions that could be employed should these reactions occur will be described. In addition, the risk of latent TB reactivation, and the need to complete immunizations prior to initiating ixekizumab and avoid live vaccines will be highlighted in product labeling, consistent with labeling for approved systemic biologic therapies. The most common adverse reactions reported with ixekizumab therapy were injection site reactions (erythema and pain), upper respiratory tract infections, nausea, and tinea infections. Most injection site reactions were mild to moderate in severity and did not lead to discontinuation of ixekizumab. Anti-drug antibodies to ixekizumab, including neutralizing antibodies can develop; higher antibody titers were associated with decreasing drug concentration and clinical response. The evaluation of depression and suicidality in ixekizumab clinical trials was limited by the exclusion of patients with a history of prior suicide attempts, the relatively infrequent assessment for depression using the Quick Inventory of Depressive Symptoms, and the absence of active solicitation of

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	placebo-treated patients (0%) during the 12-week, placebo-controlled period. Labeling will recommend that patients be monitored for the onset or exacerbation of inflammatory bowel disease during ixekizumab treatment. • **Risk for Latent Tuberculosis Reactivation.** Labeling will recommend that patients be evaluated for tuberculosis (TB) infection prior to initiating treatment with ixekizumab. Patients with latent TB should be treated prior to initiating ixekizumab. Patients receiving ixekizumab should be monitored for signs and symptoms of active TB during and after treatment. Patients with active TB infection should not receive ixekizumab. • **Immunizations.** Labeling will recommend that patients complete all age appropriate immunizations prior to initiating therapy with ixekizumab. Use of live vaccines should be avoided. **Common Adverse Reactions.** The most common adverse reactions reported in ≥ 1% of ixekizumab-treated patients and occurring more frequently than in placebo-treated patients, through Week 12 were: injection site reactions (erythema and pain), upper respiratory tract infections, nausea, and tinea infections. Most injection site reactions were mild to moderate in severity and did not lead to discontinuation of ixekizumab. These were also the most common adverse reactions reported among etanercept-treated patients, however, no tinea infections were reported in this group. **Immunogenicity Findings.** By Week 12, approximately 9% of ixekizumab-treated patients developed anti-drug antibodies; approximately 22% developed anti-drug antibodies during the 60-week treatment period. Higher antibody titers were associated with decreasing drug concentration and clinical response. Of the patients who developed anti-drug antibodies on the recommended 60-week dosing regimen, approximately 2% had antibodies that were classified as neutralizing. Neutralizing antibodies were associated with reduced drug concentrations and loss of efficacy.	information about suicidality, e.g., using the Columbia Suicide Severity Rating Scale. The available data however, do not support an association of ixekizumab with suicidality. There were no reports of completed suicide. The reports of suicidal ideation in ixekizumab-treated patients were confounded by other events, there was no temporal association of the events with the onset or duration of treatment, and the exposure-adjusted rate of suicide attempt in ixekizumab-treated patients was less than that for placebo-treated patients. In addition, there was no evidence for treatment-emergent worsening of depression, anxiety or other psychiatric adverse events. There are no available data on ixekizumab use in pregnant women to inform any drug associated risks. Postmarketing studies will be required to assess maternal, fetal and infant outcomes among pregnant women with moderate-to-severe plaque psoriasis exposed to ixekizumab. 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. Labeling will state that the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ixekizumab and any

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	Depression and Suicidality. A comprehensive review of the risk of depression and suicidality in ixekizumab clinical trials was undertaken concurrent with a review of clinical trials for another anti-psoriatic agent targeting the IL-17 receptor that reported an excess of suicide completions. This review included staff from the Division of Psychiatry Products and the Division of Epidemiology I. The three ixekizumab clinical trials excluded patients with a history of suicide attempt, with significant uncontrolled neuropsychiatric disorders, or with frequent active suicidal ideation as assessed by the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR). During the trials, the QIDS was performed at Weeks 12, 24, 36, 52 and 60. Since the QIDS queries about events during the previous seven days, it is possible that events occurring at other times could have been missed. Nevertheless, these evaluations showed that most patients enrolled did not have depression or thoughts of death or suicide either at baseline or during the course of these trials. To further assess the risk of suicidality in ixekizumab-exposed patients, the Division requested that the applicant conduct a retrospective analysis using the Columbia Classification Algorithm of Suicide Assessment (C-CASA). A total of nine ixekizumab-treated patients reported suicidal ideation during treatment (and a tenth after treatment); one placebo-treated patient and one etanercept-treated patient reported suicidal ideation. Exposure-adjusted rates of suicide ideation were 0.14 per 100 patient-years for ixekizumab vs. 0.58 per 100 patient-years for placebo. There were no reports of completed suicides. Patients reporting suicide attempts also reported other risk factors, such as prior attempts, depression, bipolar disorder, anxiety, alcohol or other substance abuse or other psychosocial triggers. There was no temporal association of suicidal ideation events to either the onset or duration of treatment. In addition, there was no evidence for treatment-emergent worsening of depression, anxiety or other psychiatric adverse events. Taken together, the available data did not support an association of ixekizumab treatment with suicidality	potential adverse effects on the breastfed infant from ixekizumab or from the underlying maternal condition. The safety and effectiveness of ixekizumab have not been evaluated in pediatric patients with moderate-to-severe plaque psoriasis aged less than 18 years of age. Postmarketing studies will be required to further assess the safety and effectiveness of ixekizumab in pediatric patients ages 6 to less than 18 years.

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	Specific Populations. The safety of ixekizumab in specific populations can be summarized as follows: • **Pregnancy and Lactation.** 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 in pregnant cynomolgus monkeys administered ixekizumab weekly by subcutaneous injection during organogenesis at doses up to 19 times the maximum recommended human dose (MRHD) revealed no evidence of harm to the developing fetus. When drug exposure continued until parturition, neonatal deaths were observed at 1.9 times the MRHD. The clinical significance of these findings is unknown. 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. • **Pediatrics.** The safety and effectiveness of ixekizumab have not been evaluated in pediatric patients with moderate-to-severe plaque psoriasis aged less than 18 years of age. • **Elderly.** A total of 301 ixekizumab-treated patients were 65 years or older, and 36 were 75 years or older. Although no differences in safety or efficacy were observed between older and younger patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.	

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Risk Management	**Labeling.** Product labeling will address the serious safety concerns identified in clinical trials, including reports in ixekizumab-treated patients of: • Infections, including serious infections • Hypersensitivity reactions, including angioedema, and • Inflammatory bowel disease, including exacerbations In addition, the risk of latent TB reactivation, and the need to complete immunizations prior to initiating ixekizumab and avoid live vaccines will be highlighted in the Warnings and Precautions section. **Risk Mitigation.** A Risk Evaluation and Mitigation Strategy (REMS) will not be required for Taltz (ixekizumab). A Medication Guide will be required as part of approved labeling to communicate important safety information to patients. Ixekizumab shares many of the same serious risks as other systemic biologic therapies approved for plaque psoriasis. Infliximab, etanercept and adalimumab each had a REMS to address the risks of serious infections and malignancy. The activities supporting the Communication Plans to practitioners in these REMS were completed and REMS assessments demonstrated that the REMS goals were being met. In 2011, these products were released from their REMS requirements but continue to have Medication Guides as part of approved labeling. Ustekinumab was approved with a REMS in 2009 to address the risks of serious infections, malignancy and reversible posterior leukoencephalopathy syndrome. The Medication Guide was removed from the REMS in 2012. The Communication Plan was modified in 2013 to include rheumatologists when a supplemental indication of psoriatic arthritis was approved. Communication Plan activities were completed in 2014 and will be assessed in the next REMS assessment report. Thus, it is likely that practitioners who will prescribe ixekizumab for plaque psoriasis will be aware of the attendant risks of systemic biologic therapies.	The safety concerns identified with use of Taltz (ixekizumab) in clinical trials can be adequately managed by professional labeling, a Medication Guide, that will be required as part of approved labeling to communicate important safety information to patients, and pharmacovigilance in the postmarket setting. A Risk Evaluation and Mitigation Strategy (REMS) will not be required for Taltz (ixekizumab) to ensure that the benefits of the drug outweigh the risks. It is likely that practitioners who will prescribe ixekizumab for plaque psoriasis will be aware of the attendant risks of systemic biologic therapies. **Required Studies under FDAAA.** The applicant will be required to conduct three observational studies under FDAAA in adults with moderate-to-severe plaque psoriasis exposed to ixekizumab. Comparisons to control population(s) will be made. These studies will further assess potential serious safety risks as follows: • A prospective long-term observational safety study; the study will be of sufficient size and duration to assess the occurrence of long latency adverse events (e.g., malignancy) and relatively rare events (serious infections). • A prospective observational study in pregnant

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	Postmarketing Required Studies. Post-approval, the applicant will be required to conduct the following observational studies under the Food and Drug Administration Amendments Act (FDAAA) in adults with moderate-to-severe plaque psoriasis exposed to ixekizumab. Outcomes will be compared to control population(s): • A long-term prospective observational study to assess the occurrence of serious adverse events including malignancy, serious infections and opportunistic infections, serious hypersensitivity reactions and autoimmune disorders. Patients will be followed for a minimum of 8 years from the time of enrollment. • A prospective observational study in pregnant women exposed to ixekizumab to assess the occurrence of major congenital malformations, spontaneous abortions, stillbirths, and other adverse pregnancy outcomes. Maternal outcomes will be assessed throughout pregnancy; infant outcomes, including growth and development, will be assessed through at the least the first year of life. • A retrospective cohort study in pregnant women exposed to ixekizumab to assess to assess the occurrence of major congenital malformations, spontaneous abortions, stillbirths, and other adverse pregnancy outcomes. The Division has determined that full extrapolation of adult efficacy data for ixekizumab to pediatric patients with moderate-to-severe plaque psoriasis is appropriate. To this end, the applicant will be required to conduct the following pediatric study under the Pediatric Research Equity Act (PREA) in patients ages 6 to less than 18 years with moderate-to-severe plaque psoriasis: • A pharmacokinetic, safety, and efficacy study with a duration of exposure to ixekizumab of at least one year	women of maternal, fetal and infant outcomes, including effects on postnatal growth and development. Pregnant women were excluded from ixekizumab clinical trials; maternal, fetal and infant safety information is needed as women of childbearing potential may be prescribed ixekizumab once approved. • A retrospective observational study of pregnancy outcomes in pregnant women exposed to ixekizumab. Pregnant women were excluded from ixekizumab clinical trials; maternal, fetal and infant safety information is needed as women of childbearing potential may be prescribed ixekizumab once approved. This retrospective study will be complementary to the prospective observational study described above. Because it will rely on large claims databases or electronic medical record data it has the potential to address low enrollment in the prospective study, should that occur. **Required Studies under PREA.** The applicant will be required to conduct the following pediatric study under PREA in patients ages 6 to less than 18 years with moderate-to-severe plaque psoriasis: • A pharmacokinetic, safety and efficacy study with a duration of exposure to ixekizumab of at least one year

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Pediatric studies in patients 0 to less than 6 years of age will be waived because studies are impossible or highly impracticable. This is based on the lack of prevalence data for plaque psoriasis in this age group. In addition, live vaccines are usually administered to this age group. **Postmarketing Study Commitments.** The applicant has agreed to conduct a drug-drug interaction clinical study to assess whether ixekizumab alters the metabolism or pharmacokinetics of CYP substrates in psoriasis patients treated with ixekizumab. The applicant has also agreed to 1) perform a repeat microbial retention study (b) (4) (b) (4) using a suitable surrogate solution, and 2) provide data from two additional commercial drug product batches to support the maximum hold time for pooled drug substance.	The required pediatric study represents an evolution in the Division's thinking. Historically, due to concerns about serious safety risks, including malignancies, reported with other currently available systemic therapies (e.g., methotrexate, cyclosporine, the tumor necrosis factor inhibitors), the Division has either waived pediatric studies (e.g., for adalimumab, infliximab) or imposed delayed study timelines to allow for the collection of additional safety data in adults and from pediatric patients exposed *in utero* or via breastfeeding (e.g., ustekinumab). Since the highly efficacious IL-17 inhibitors, such as ixekizumab, may have a more favorable benefit/risk profile than other currently available systemic therapies, the Division has determined that timelines for initiating pediatric studies of ixekizumab may be accelerated. An accelerated timeline for pediatric studies has also been implemented for the recently approved IL-17 inhibitor, secukinumab. Furthermore, the Division has determined that full extrapolation of adult efficacy data to pediatric patients is appropriate. Weight-based dosing regimens have been determined based on simulations from adult pharmacokinetic and exposure-response data that are predicted to achieve pediatric exposures in the range of exposures achieved in adults with the labeled

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		ixekizumab dosing regimen. **Postmarketing Study Commitments.** The applicant has agreed to conduct a drug-drug interaction clinical study to assess whether ixekizumab alters the metabolism or pharmacokinetics of CYP substrates in psoriasis patients treated with ixekizumab. Patients with psoriasis have elevated levels of pro-inflammatory cytokines which can suppress the expression of some CYP enzymes; CYP enzyme expression could be normalized in responders to ixekizumab leading to reduced exposure of CYP substrates and potential loss of efficacy of concomitantly used small molecule CYP substrate drugs. I concur with the above-mentioned postmarketing study requirements and commitments.

2. Additional Comments

2.1 Application Review Milestones

A pre-submission meeting was held with the applicant on October 29, 2014. BLA 125521 was submitted on March 23, 2015. Key review milestones include:

June 24, 2015: the Division asked the applicant to perform a retrospective evaluation of suicidality in its clinical trial program using the Columbia Classification Algorithm of Suicide Assessment (C-CASA). Initial results, submitted on August 8, 2015, were later supplemented by additional responses to the Division's requests over a period of several weeks.

December 2, 2015: at the Late-Cycle meeting, the Division informed the applicant that it could submit a pediatric study plan with an accelerated timeline for study initiation. The pediatric study plan should assess the pharmacokinetic profile, safety and efficacy of ixekizumab in pediatric patients with moderate-to-severe plaque psoriasis.

January 27, 2016: at the Pediatric Review Committee (PeRC) meeting, the Division discussed a pediatric study plan for ixekizumab in which pediatric efficacy would be fully extrapolated from adult efficacy data, and that incorporated an accelerated timeline for initiation of pediatric studies. The PeRC endorsed the proposed plan and recommended that the Division harmonize with the EMA on a unified plan for the conduct of pediatric studies of ixekizumab.

2.2 Advisory Committee Meeting

The BLA for Taltz (ixekizumab) was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a biologic drug of this class.

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/s/

JULIE G BEITZ
03/22/2016