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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Deputy Director Decisional Memo

Date	January 20, 2015
From	Amy G. Egan, MD, MPH
Subject	Office Deputy Director Decisional Memo
NDA/BLA #	BLA 125504
Applicant Name	Novartis Pharmaceuticals Corporation
Date of Submission	October 22, 2013
PDUFA Goal Date	January 23, 2015
Proprietary Name / Established (USAN) Name	Cosentyx (secukinumab)
Dosage Forms / Strength	Lyophilized powder (150 mg) for reconstitution; solution for injection, 150 mg/mL
Proposed Indication(s)	For the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
Action:	Approval

Summary

Psoriasis is a chronic inflammatory skin disease. The most common form of the disease is plaque psoriasis, which is characterized by the development of chronic erythematous plaques covered with silvery white scales, most commonly appearing on the elbows, knees, scalp, umbilicus, and lumbar regions. The disease has a significant negative impact on a patient's quality of life. The cause of psoriasis is not fully understood; however, it is recognized that both the innate and adaptive immune pathways are involved in its pathogenesis. In the U.S., psoriasis affects approximately 7.4 million adults.[1]

Currently available therapies for psoriasis include TNF α-blockers (etanercept, adalimumab, and infliximab), an IL-12/IL-23 antagonist (ustekinumab); small molecule therapies (acitretin, methotrexate, cyclosporine, and apremilast); and phototherapy.

The subject of this BLA, Cosentyx (secukinumab) is a first-in-class human IgG1κ monoclonal antibody expressed in a recombinant Chinese Hamster Ovary cell line. Secukinumab selectively binds to the pro-inflammatory cytokine interleukin-17A (IL17-A) and inhibits its interaction with the IL-17 receptor, thus inhibiting the release of pro-inflammatory cytokines and chemokines. Secukinumab has a molecular mass of approximately 151 kDa.

This memo documents my concurrence with the Division of Dermatology and Dental Products' (DDDP) approval recommendation for Cosentyx (secukinumab) for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Dosing

Cosentyx is available as a single use pre-filled syringe containing 150 mg of secukinumab solution, a single use pen containing 150 mg of secukinumab solution, and a lyophilized powder (150 mg of secukinumab) in a single use vial for reconstitution. The recommended dose is 300 mg, administered as two subcutaneous injections of 150 mg, at weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. Patients may self-inject using the pen or prefilled syringe after proper training in subcutaneous injection technique.

Prior to injection, Cosentyx should be allowed to reach room temperature. The removable cap of the Cosentyx pen and the Cosentyx prefilled syringe contain rubber latex, therefore, product labeling will provide a precaution for latex-sensitive individuals.

Because of the observation that many subjects achieved the clinical endpoint at the lower dose of 150 mg, especially those with lower body weight (<90 kg) and lesser disease severity (IGA

[1] Rachakonda TD, Schupp CW, and Armstrong AW. Psoriasis prevalence among adults in the United States.*JAAD.*2014;70:512-516

of 3), product labeling will note that the 150 mg dose may be used at the healthcare provider's (HCP) discretion.

Regulatory History

A guidance meeting was held on March 2, 2011 to discuss the applicant's completed phase 1 and 2 trials, protocol synopses of the two pivotal phase 3 trials (Trial 1 and Trial 2), and plans for additional phase 3 trials. The Agency recommended further phase 2 study prior to moving into phase 3. There was no End of Phase 2 meeting, nor Special Protocol Assessment on any of the applicant's phase 3 protocols.

The pivotal trials were conducted using the lyophilized powder (LYO) formulation. Protocols to evaluate the comparability of the pre-filled syringe (PFS) presentation and the autoinjector (AI) presentation were the subject of several exchanges between the Agency and the applicant.

Discussions with the applicant were conducted regarding a human factor study of the AI, as well as patient reported outcomes (PRO).

On February 11, 2013, the applicant submitted an initial Pediatric Study Plan to address the Pediatric Research Equity Act (PREA).

On July 24, 2013 a pre-BLA meeting was conducted with the applicant. Discussion included Chemistry Manufacturing and Controls (CMC) requirements for the application, and the use of a European Union-sourced Enbrel (etanercept) product as the comparator in one of the phase 3 trials. The applicant was advised at that time that a superiority demonstration of Cosentyx over Enbrel would require two adequate and well-controlled clinical trials.

The BLA was submitted on October 22, 2013. The Agency issued a filing communication, dated December 17, 2013, identifying several CMC issues. The applicant's January 15, 2014 response constituted a major amendment to the application, triggering an extension of the PDUFA goal date to January 23, 2015.

On November 20, 2014, the European Medicines Agency's Committee for Medicinal Products for Human Use recommended marketing authorization for Cosentyx for all three presentations (LYO, PFS, and AI) for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Product Quality Considerations

Review of the original BLA submission identified several critical CMC issues related to control of the manufacturing process. These review issues were successfully resolved by the applicant.

The Division of Monoclonal Antibodies (DMA) concluded that "the manufacture of Cosentyx (secukinumab) is well-controlled and leads to a product that is pure and potent. The product is

free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs."

DMA has recommended an expiration dating period of (b) (4) months for secukinumab drug substance when stored (b) (4); an expiration dating period of 36 months for secukinumab lyophilized drug product when stored at 2-8°C; and an expiration dating period of 24 months for the pre-filled syringe and autoinjector presentations of secukinumab drug product when stored at 2-8°C.

Final reports of manufacturing facility inspections were completed on September 17, 2014, and were found acceptable.

The following CMC post-marketing commitments (PMCs) have been recommended, in order to allow for improvement in specifications after additional manufacturing experience has been gained:

1. Re-evaluate secukinumab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis will submit the corresponding data, the analytic and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

2. Re-evaluate secukinumab drug product (vial) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis will submit the corresponding data, the analytic and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

3. Re-evaluate secukinumab drug product (prefilled syringe) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

4. Conduct routine bioburden testing (b) (4). The bioburden method will be qualified with samples from the next production batches in 2015. Routine testing will be implemented for the 2016 manufacturing campaign.

5. Conduct routine bioburden testing (b) (4) The bioburden method will be qualified with samples from the next production batches in 2015. Routine testing will be implemented for the 2016 manufacturing campaign.

6. Conduct routine bioburden and endotoxin testing [redacted] (b) (4) Routine testing will be implemented for the 2015 manufacturing campaign.

7. Conduct additional hold time validation studies on two batches at commercial scale [redacted] (b) (4) validation will be conducted during the 2015 and 2016 commercial campaigns.

8. Evaluate feasibility of [redacted] (b) (4) secukinumab drug substance and update drug substance specification [redacted] (b) (4).

[redacted] (b) (4)

Secukinumab is considered to be a nonhazardous, biodegradable product. The environmental impact in terms of use and disposal is considered to be negligible.

Microbiology Product Quality Considerations

The product quality microbiology assessments of microbial controls of the drug product manufacturing process and sterility assurance of drug product described in the original BLA and amendments, as well as manufacturing site inspections, were deemed acceptable.

Non-clinical Considerations

Pharmacology studies demonstrated that secukinumab binds to human recombinant IL-17A with high affinity (K_D ~200 pM). The binding of secukinumab to all human IL-17 family members was assessed and no binding to IL-17B through IL-17E was detected, or binding to other unrelated human cytokines. A safety pharmacology study conducted in cynomolgus monkeys showed no evidence of treatment-related effects on neurological, cardiovascular or respiratory parameters.

Embryo-fetal development studies conducted in cynomolgus monkeys with secukinumab did not reveal evidence of treatment-related malformations or embryofetal toxicity in fetuses from pregnant monkeys at doses 30 times the maximum recommended human dose. A pre- and

post-natal development toxicity study conducted in mice with a murine analog of secukinumab did not demonstrate treatment-related adverse effects on fetal development. Based on the non-clinical and clinical data, an assignment of a pregnancy category B has been recommended.

Repeat dose toxicity studies in monkeys induced no treatment-related pathology. A NOAEL of 50 mg/kg/week was established based on clinical chemistry effects and immunotoxicity (decreases in total lymphocytes, B cells and T cells) observed at the high dose.

Because secukinumab does not cross-react with rodent IL-17A, the conduct of a standard 2-year carcinogenicity study was deemed impractical. No concerns relating to the oncogenic potential arise from the molecular structure or metabolites of secukinumab. Based on the size and binding of secukinumab, there is no reason to expect an effect on DNA integrity or any direct mutagenic effect. No tumors or histological evidence of pre-neoplastic changes were observed in organs or tissues in chronic toxicology studies. The non-clinical review team concluded that "Long term use of secukinumab may lead to increased risk of tumor development in psoriasis patients, particularly in those who have been exposed to other therapies which could increase the risk of tumor development, such as UVB, photodynamic therapy, and other immunosuppressive agents. Since secukinumab cannot be tested in a traditional 2-year rodent study to evaluate carcinogenic potential due to its species specific binding, the sponsor will monitor malignancy in psoriasis patients administered secukinumab as part of a comprehensive Risk Management Plan."

Clinical Pharmacology Considerations

The pharmacokinetic (PK) characteristics of secukinumab were determined in healthy subjects and in subjects with psoriasis. The absolute bioavailability in psoriasis patients was estimated to be 73%. The half-life is approximately 27 days. The PK comparability between the lyophilized product and the pre-filled syringe product was demonstrated in a dedicated PK study. The applicant did not conduct a dedicated PK study to evaluate the comparability between the auto-injector product and the lyophilized or pre-filled syringe products. Based on trough concentrations across the phase 3 trials (two conducted with LYO; one conducted with PFS; and one conducted with AI), patients achieved higher exposures (10%-30%) with the AI than the PFS and the LYO. The impact of this higher exposure will be further assessed in ongoing clinical trials with the AI.

Secukinumab concentration at Week 12 was a significant predictor of increasing IGA 0/1 response at Week 12. Body weight (a higher body weight resulted in a lower response) and the baseline IGA score (a higher baseline IGA score resulted in a lower response) were identified as significant covariates on the exposure-response relationship, and body weight was also a significant factor with regard to secukinumab exposure. Because of this effect, the sponsor will be asked to conduct the following PMC:

9. Conduct a clinical trial to evaluate the treatment effect and safety profile of a higher exposure (e.g., 450 mg) of secukinumab in psoriasis subjects with higher body weight and to explore the option of exposure escalation (e.g., 450 mg) for those who cannot achieve the therapeutic goal at the 300 mg dose.

The metabolic pathway of secukinumab has not been characterized. As a human IgG1κ monoclonal antibody secukinumab is expected to be degraded into small peptides and amino acids in the same manner as endogenous IgG.

Because significant drug-drug interactions (DDIs) between monoclonal antibodies and low molecular weight drugs are not expected, the DDI potential of secukinumab as a target or culprit was not investigated *in vitro* or in dedicated interaction clinical studies. However, psoriasis patients have elevated levels of pro-inflammatory cytokines which can suppress the expression of some CYP enzymes and the CYP enzyme expression could be normalized upon disease improvement following biologic treatment. For this reason, product labeling will note that upon initiation or discontinuation of Cosentyx in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, monitoring for therapeutic effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) should be considered, as should dosage modification of the CYP450 substrate. In addition, the applicant will be asked to conduct the following PMC:

10. Conduct a clinical trial to assess whether secukinumab alters the metabolism or pharmacokinetics of CYP substrates in psoriasis patients treated with secukinumab

Population PK analysis indicated that the clearance of secukinumab was not significantly influenced by age in adult subjects with plaque psoriasis. No formal trial of the effect of hepatic or renal impairment on the PK of secukinumab was conducted.

Due to the size of the molecule, QT assessments were not recommended by the Agency.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. In the phase 3 trials, 0.4% (10/2842) of Cosentyx-treated subjects developed anti-drug antibodies (ADA). Of these 10 subjects, 3 were classified as positive for neutralizing antibodies, 5 were classified as negative for neutralizing antibodies, and 2 were not characterized. There was no evidence of altered PK, efficacy or safety in subjects who developed Cosentyx treatment-emergent ADA; however, numbers are too small to allow for meaningful conclusions.

Efficacy

The efficacy of Cosentyx was assessed in four placebo-controlled phase 3 trials that included two pivotal trials (Trials 1 and 2) conducted with LYO and two exploratory trials (Trials 3 and 4) conducted with PFS and AI, respectively.

Trials 1 and 2 were conducted in 738 subjects and 1306 subjects, respectively, age 18 years and older with Psoriasis Area and Severity Index (PASI) score ≥12, Investigator's Global Assessment (IGA) score of at least 3, and body surface area (BSA) involvement ≥10% at baseline. The co-primary endpoints were the proportion of subjects achieving PASI 75 response (i.e., ≥75% reduction in PASI score) at Week 12 and scoring IGA 0 or 1 at Week 12. The key secondary endpoint was the proportion of subjects achieving PASI 90 (i.e., ≥90% reduction in PASI score) at Week 12. The applicant also included PRO measures of itching, scaling and pain as secondary endpoints.

The median age of enrolled subjects in Trial 1 was 45 years. The majority of subjects were male (69%) and Caucasian (70%). Of enrolled subjects, 37.7% were from the U.S.

In Trial 1, 738 subjects were randomized 1:1:1 to receive Cosentyx 300 mg (n=245) or Cosentyx 150 mg (n=245) or placebo (n=248) dosed as 2 injections of study treatment and/or placebo at baseline, Weeks 1, 2, 3, and 4, followed by dosing every 4 weeks. Subjects randomized to receive placebo who were non-responders at Week 12 were crossed over to receive Cosentyx 150 mg or 300 mg at Weeks 12, 13, 14, 15, and 16 followed by dosing every 4 weeks. All subjects were followed for up to 52 weeks following first administration of study treatment.

In Trial 1, the proportion of subjects achieving PASI 75 response at Week 12 was 82%, 71%, and 4% for Cosentyx 300 mg, 150 mg, and placebo, respectively. The proportion of subjects scoring IGA 0 or 1 at Week 12 was 65%, 51%, and 2%, for Cosentyx 300 mg, 150 mg, and placebo, respectively.

Table 1: Trial 1 – Proportion of subjects with PASI 75 response at Week 12 and proportion of subjects with IGA 0 or 1 at Week 12*

	Treatment		
	Cosentyx 300 mg (n=245)	Cosentyx 150 mg (n=245)	Placebo (n=248)
PASI 75 response	200 (82%)	174 (71%)	11 (4%)
IGA of clear or almost clear	160 (65%)	125 (51%)	6 (2%)

*Source: Adapted from Table 1 of the Statistical Review.

Subgroup analyses were conducted for gender, age, and race. No significant treatment differences were observed among these subgroups. In subgroup analyses based on weight (<90 kg vs. ≥90 kg) and/or baseline severity of disease (IGA 3 vs. IGA 4), patients weighing less

than 90 kg and/or with lesser severity of disease (IGA 3) who received Cosentyx 150 mg achieved acceptable IGA response rates, 54% for subjects with both IGA 3 and <90 kg. The marginal response rates for subjects who met either <90 kg or IGA 3 were 53% and 55%, respectively. The 150 mg dose may be considered an appropriate dose in these sub-populations.

Table 2: Trial 1 – Proportion of subjects with IGA 0 or 1 at Week 12 by baseline IGA and weight*

	150 mg			300 mg		
	IGA=3	**IGA =4**	**Marginal Response**	**IGA=3**	**IGA =4**	**Marginal Response**
<90 kg	53/99 (54%)	22/42 (52%)	53%	70/93 (75%)	33/49 (67%)	73%
≥90 kg	35/62 (56%)	15/42 (36%)	48%	39/61 (64%)	18/42 (43%)	55%
Marginal Response	55%	45%		71%	56%	

*Source: FDA statisticians' post-hoc analysis

Cosentyx also achieved a higher response rate than placebo on the key secondary endpoint of PASI 90 at Week 12: 57%, 40%, and 2% for Cosentyx 300 mg, 150 mg, and placebo group, respectively.

The median age of enrolled subjects in Trial 2 was 45 years. The majority of subjects were male (71%) and Caucasian (67%). Of enrolled subjects, 3.6% were from the U.S.

In Trial 2, 1306 subjects were randomized 1:1:1:1 to receive Cosentyx 300 mg (n=327) or Cosentyx 150 mg (n=327) or placebo (n=326) or active control (etanercept; n=323) dosed as 2 injections of study treatment and/or placebo at baseline, Weeks 1, 2, 3, and 4, followed by dosing every 4 weeks. Subjects randomized to receive placebo who were non-responders at Week 12 were crossed over to receive Cosentyx 150 mg or 300 mg at Weeks 12, 13, 14, 15, and 16 followed by dosing every 4 weeks. All subjects were followed for up to 52 weeks following first administration of study treatment.

In Trial 2, the proportion of subjects achieving PASI 75 response at Week 12 was 76%, 67%, 5%, and 44% for Cosentyx 300 mg, 150 mg, placebo, and etanercept, respectively. The proportion of subjects scoring IGA 0 or 1 at Week 12 was 62%, 51%, 3%, and 27% for Cosentyx 300 mg, 150 mg, placebo, and etanercept, respectively. While both doses of Cosentyx established non-inferiority, as well as superiority ($p<0.001$), to etanercept, no replication of study findings for the comparisons against etanercept was performed. (b) (4)

Table 3: Trial 2 – Proportion of subjects with PASI 75 response at Week 12 and proportion of subjects with IGA 0 or 1 at Week 12*

	Treatment			
	Cosentyx 300 mg (n=327)	Cosentyx 150 mg (n=327)	Placebo (n=326)	Etanercept (n=326)
PASI 75 response	249 (76%)	219 (67%)	16 (5%)	142 (44%)
IGA of clear or almost clear	202 (62%)	167 (51%)	9 (3%)	88 (27%)

*Source: Adapted from Table 1 of the Statistical Review.

Subgroup analyses were conducted for gender, age, and race. No significant treatment differences were observed among these subgroups. In subgroup analyses based on weight (<90 kg vs. ≥90 kg) and baseline severity of disease (IGA 3 vs. IGA 4), patients weighing less than 90 kg and with lesser severity of disease (IGA 3) who received Cosentyx 150 mg achieved acceptable IGA response rates, 60% for subjects with both IGA 3 and <90 kg. The marginal response rates for subjects who met either <90 kg or IGA 3 were 55% and 57%, respectively. The 150 mg dose may be considered an appropriate dose in these sub-populations.

Table 4: Trial 2 – Proportion of subjects with IGA 0 or 1 at Week 12 by baseline IGA and weight*

	150 mg			300 mg		
	IGA=3	IGA =4	Marginal Response	IGA=3	IGA =4	Marginal Response
<90 kg	80/133 (60%)	39/82 (48%)	55%	94/137 (69%)	46/83 (55%)	64%
≥90 kg	36/72 (50%)	12/40 (30%)	43%	39/66 (59%)	23/41 (56%)	58%
Marginal Response	57%	42%		66%	56%	

*Source: FDA statisticians' post-hoc analysis

Cosentyx also achieved a higher response rate than placebo and etanercept on the key secondary endpoint of PASI 90 at Week 12: 54%, 42%, 2%, and 21% for Cosentyx 300 mg, 150 mg, placebo, and etanercept, respectively.

PRO measures for itching, pain, and scaling were included in the protocols for Trials 1 and 2 as secondary endpoints; however, because the Psoriasis Diary instrument was not available at all sites, and because subjects could elect not to use the instrument, only 40% of subjects from each trial participated. It is therefore unclear whether this subset is a random sample of the total population to support generalizability of these findings to the overall population. Product labeling will acknowledge the improvements in itching, pain and scaling that were observed in this limited subset of subjects, but will not include statistical analyses.

Trials 3 and 4 were conducted to support the safety and efficacy of secukinumab in the PFS and AI presentations, respectively. Trial 3 randomized 177 subjects to Cosentyx 300 mg (n=59), or Cosentyx 150 mg (n=59), or placebo (n=59). Trial 4 randomized 182 subjects to Cosentyx 300 mg (n=60), or Cosentyx 150 mg (n=61), or placebo (n=61). These trials employed the same co-primary endpoints as the pivotal trials, and established that both presentations at both dosage strengths were superior to placebo.

Table 1: Trials 3 and 4 – Proportion of subjects with PASI 75 response at Week 12 and proportion of subjects with IGA 0 or 1 at Week 12*

	Trial 3 Treatment Assignment		
	Cosentyx 300 mg (n=59)	Cosentyx 150 mg (n=59)	Placebo (n=59)
PASI 75 response	44 (75%)	41 (69%)	0 (0)
IGA of clear or almost clear	40 (68%)	31 (53%)	0 (0)
	Trial 4 Treatment Assignment		
	Cosentyx 300 mg (n=60)	Cosentyx 150 mg (n=61)	Placebo (n=61)
PASI 75 response	52 (87%)	43 (70%)	2 (3%)
IGA of clear or almost clear	44 (73%)	32 (52%)	0 (0)

*Source: Adapted from Table 2 of the Statistical Review.

With continued treatment over 52 weeks, response was maintained in Trial 1 subjects who were PASI 75 responders at Week 12 in 81% of those treated with Cosentyx 300 mg and 72% of those treated with Cosentyx 150 mg. In Trial 1 subjects who achieved an IGA of clear or almost clear at Week 12, response was maintained in 74% of those treated with Cosentyx 300 mg and 59% of those treated with Cosentyx 150 mg. In Trial 2, among PASI 75 responders at Week 12, 84% of those treated with Cosentyx 300 mg, and 82% of those treated with Cosentyx 150 mg maintained their response. In Trial 2 subjects who achieved IGA of clear or almost clear at Week 12, 80% of those treated with Cosentyx 300 mg and 68% of those treated with Cosentyx 150 mg maintained their response.

The Office of Scientific Investigations (OSI) conducted inspections of two clinical sites. OSI concluded that the data generated by the clinical sites appear adequate for use in support of the proposed indication.

Safety

In the Cosentyx development program, 3430 psoriasis subjects were exposed to at least one dose of Cosentyx (1395 subjects at 150 mg and 1410 subjects at 300 mg). A total of 2751 subjects were treated for at least 6 months and 1641 subjects treated for at least 1 year.

The proportion of subjects with at least one adverse event was 55%, 60%, and 47% for Cosentyx 300 mg, 150 mg and placebo, respectively in the induction period of Trial 1, and 58%, 58%, 50% and 57% for Cosentyx 300 mg, 150 mg, placebo, and etanercept, respectively in the induction period of Trial 2. The most common adverse reactions across the phase 3 program were nasopharyngitis, diarrhea, and upper respiratory infection.

Six deaths occurred in the Cosentyx clinical development program – four on Cosentyx, one on placebo, and one prior to initiation of study treatment. None appear to be treatment-related.

Serious adverse events (SAEs) were reported in 2% of subjects treated with Cosentyx 300 mg, 2% of subjects treated with Cosentyx 150 mg, and 1.7% of subjects treated with placebo. No SAE was reported with greater than 1% frequency. The most common SAEs were overdose and pulmonary edema. The Division of Cardiovascular and Renal Products (DCRP) reviewed the cases of pulmonary edema and concluded that drug-induced congestive heart failure was not the likely etiology of these events.

Adverse events leading to discontinuation occurred in 1.2% of subjects treated with Cosentyx 300 mg, 1.3% of subjects treated with Cosentyx 150 mg, and 1.3% of subjects treated with placebo. The most frequent adverse events leading to discontinuation in Cosentyx-treated subjects were psoriasis, psoriatic arthropathy and thrombocytopenia. Of four subjects who discontinued Cosentyx for thrombocytopenia, three were documented to have low platelet counts at baseline. No data on baseline platelet count were available for the fourth subject.

Adverse events of special interest (AESI) included infections, major adverse cardiovascular events (MACE), malignancy, hypersensitivity, neutropenia, and Crohn's disease.

Common infections such as nasopharyngitis and upper respiratory tract infection were reported more frequently in the Cosentyx dose groups as compared to placebo. Serious infections were reported infrequently and included one subject (0.1%) in each of the Cosentyx dose groups (anal abscess in a subject receiving the 300 mg dose and pneumonia in a subject receiving the 150 mg dose) and two subjects (0.3%) in the placebo group (both with cellulitis). A higher rate of Candida infections was observed with Cosentyx, particularly the 300 mg dose. Herpes viral infections occurred in a higher proportion of subjects in the Cosentyx 300 mg group than the 150 mg group and the placebo group. No cases of disseminated or CNS herpes were reported.

DCRP identified no convincing cardiovascular safety concern in the clinical development program for Cosentyx.

There were rare reports of malignancy in the clinical trials; however, given the short duration of the trials and the long latency of malignancy, the absence of a clear safety signal is not in itself reassuring. This AESI will be further assessed in a post-marketing registry.

Hypersensitivity reaction adverse events were reported more frequently with Cosentyx compared to placebo and consisted primarily of cases of urticaria; one case led to treatment discontinuation. Angioedema was reported more frequently in placebo-treated subjects compared to Cosentyx-treated subjects. No cases of serious anaphylactic reactions considered related to Cosentyx occurred in the psoriasis development program, although one case of a serious immediate hypersensitivity reaction has been reported in the ankylosing spondylitis program.

The incidence of any grade neutropenia for Cosentyx-treated subjects was 9.0% (both doses) compared to 2.7% for placebo-treated subjects and appeared to be dose dependent. Neutropenia reported as an adverse event was also higher for Cosentyx arms compared to placebo arms. Two trial subjects receiving Cosentyx discontinued for neutropenia; however, most cases of neutropenia associated with Cosentyx were transient and reversible. A few adverse events of neutropenia were associated with non-serious infections.

SAEs of autoimmune disorders not related to psoriasis were reported only in Cosentyx-treated subjects. The event rate of autoimmune AEs observed in the Cosentyx clinical database is similar to the rate that was observed in the etanercept clinical development program. This may suggest that Cosentyx is also associated with the paradoxical development of autoimmune disease. Currently, the greatest concern based on the clinical trial data is for potential worsening or development of Crohn's disease with Cosentyx use. Product labeling will convey this potential risk.

AESIs will be further assessed in two ongoing clinical trials.

Pediatric Considerations

The safety and effectiveness of Cosentyx in pediatric patients have not been evaluated. DDDP concurred with the applicant's request for a waiver of pediatric studies for patients under 6 years of age because the necessary studies are impossible or highly impractical.

DDDP concurred with the applicant's request for a deferral of pediatric studies for patients ages 6 to 17 years because pediatric studies should be delayed until additional safety or effectiveness data have been collected. DDDP recommended a deferral until 2022. The applicant has agreed to conduct the following PREA PMR:

PMR 2848-1: Conduct a study to evaluate the safety and efficacy of secukinumab in pediatric subjects ≥ 6 years of age with plaque psoriasis.

Tradename Review

The Division of Medication Error Prevention and Analysis, in consultation with the Office of Prescription Drug Promotion, has concluded that the applicant's proposed proprietary name "Cosentyx" is acceptable from both a promotional and safety perspective. In a letter dated

May 12, 2014, FDA notified Novartis Pharmaceuticals Corporation that the proposed proprietary name was acceptable.

Advisory Committee

A meeting of the Dermatologic and Ophthalmologic Drugs Advisory Committee (DODAC) was held on October 20, 2014 to discuss the overall safety and efficacy of Cosentyx, as well as potential dosing regimens. The committee unanimously agreed that the available data support the approval of Cosentyx for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The majority of the committee agreed that the recommended dose should be the 300 mg dose, but that the 150 mg dose should be available for patients with exceptionally low body weight, and could be used at the prescriber's discretion. The majority of the committee agreed that the 450 mg dose in patients >90 kg, or in patients who do not respond to the 300 mg dose, could be an option, but further study post-approval is recommended.

Consults

Center for Devices and Radiological Health (CDRH)

In a consultative memo dated May 19, 2014, CDRH determined that the applicant had provided all necessary testing of the pre-filled syringe and auto-injector devices and there were no concerns regarding the device component of this combination product.

A human factors validation study for the AI configuration was conducted and the study results and analyses were found to be acceptable. Revisions to the IFU were requested, but given the nature of the revisions, no additional human factors validation study was deemed necessary.

In a memo dated June 20, 2014, the Office of Compliance at CDRH, after review of the facilities involved in the manufacturing and packaging of the proposed PFS and AI devices, supported the approvability of the BLA stating there were no other outstanding concerns pertaining to the Medical Device Regulations for the combination product.

Division of Risk Management (DRISK)

DRISK reviewed the applicant's proposed Risk Evaluation and Mitigation Strategy (REMS) which consisted of a communication plan only REMS to communicate to healthcare providers and pharmacists the risk of infections associated with Cosentyx treatment.

After discussion with the review team, it was agreed that the risk of infection could be effectively communicated through physician and patient labeling. Therefore, DRISK recommended that the product not have a REMS at this time.

Study Endpoints and Labeling Development (SEALD)

SEALD reviewed the applicant's 16-item PRO measure, the electronic Psoriasis Symptom Diary, for the measurement of itching, pain and scaling. SEALD concluded that the applicant provided sufficient evidence to support the validity and reliability of these three items to (b) (4) these parameters "provided that the clinical trial data are clinically meaningful and statistically robust as determined by the clinical and statistical review staff".

Center for Biologics Evaluation and Research (CBER) – Office of Vaccines Research and Review/Division of Vaccines and Related Products Application (DVRPA)

The applicant conducted an open-label, single dose study to evaluate whether exposure to Cosentyx affected antibody responses elicited by meningococcal and influenza vaccines. DVRPA reviewed the study and concluded that the study did not meet CBER's regulatory standards for an immunobridging demonstration of vaccine effectiveness in subjects treated with Cosentyx, and did not assess all components of the immune response involved in conferring protection against disease. Furthermore, a single dose of Cosentyx administered 2 weeks prior to vaccination may not affect vaccine immune responses as profoundly as the intended long-term treatment regimen of Cosentyx. DVRPA also noted that the exact role of IL-17 in initial and memory vaccine responses, and the effects of its inhibition, are not well defined. Product labeling will convey that age-appropriate immunizations should be completed prior to initiating Cosentyx therapy; patients treated with Cosentyx should not receive live vaccines; and non-live vaccinations received during a course of Cosentyx may not elicit an immune response sufficient to prevent disease.

Postmarketing Requirements under 505(o)

Section 505(o)(3) of the Food, Drug and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

FDA determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA would not be sufficient to assess a signal of a serious risk of malignancy which occurs infrequently and/or has a long latency.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA determined that the applicant is required to conduct the following:

PMR 2848-2: A postmarketing prospective, long-term, observational study to assess the long-term safety of secukinumab compared to other therapies used in the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy in a real world clinical setting. The study's primary outcome is malignancies. Describe and justify the choice of appropriate comparator population(s). Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate. Specify concise case definitions and validation algorithms for the primary outcome. Enroll patients over an initial 4-year period and follow for a minimum of 8 years from the time of enrollment. Provide progress updates on registry patient accrual and demographic summary data in your Annual Report, and provide registry safety data in your Periodic Benefit-Risk Evaluation Reports (PBERs) for the reporting period as well as cumulatively, and a complete final study report.

Finally, FDA has determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess signals of the serious risks of serious infection, tuberculosis, opportunistic infections, malignancy, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events. Therefore, the applicant will be required to complete and submit the following:

PMR 2848-3: Complete the treatment and evaluation of subjects enrolled in the ongoing CAIN457A2302E1 trial for a duration of 4 years, unless a safety signal is identified that indicates the potential risks of such continued long-term treatment outweigh the benefits. Evaluation of subjects should continue through the end of the trial when achievable (even if treatment is not continued for the duration). Subjects will be followed for the occurrence of serious infection, tuberculosis, opportunistic infections, malignancy, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events.

PMR 2848-4: Complete the treatment and evaluation of subjects enrolled in the ongoing CAIN457A2304E1 trial for a duration of 4 years, unless a safety signal is identified that indicates the potential risks of such continued long-term treatment outweigh the benefits. Evaluation of subjects should continue through the end of the trial when achievable (even if treatment is not continued for the duration). Subjects will be followed for the occurrence of serious infection, tuberculosis,

opportunistic infections, malignancy, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events.

Conclusions

Psoriasis is a chronic inflammatory skin disorder which has a significant negative impact on a patient's quality of life. Available therapies exist; however, Cosentyx (secukinumab) provides an additional treatment option and a novel mechanism of action.

Treatment with Cosentyx 150 mg and 300 mg demonstrated superiority to placebo in adult subjects with moderate to severe plaque psoriasis.

The safety of Cosentyx has been adequately characterized to support approval, although it should be acknowledged that while a clear safety signal was not identified in the clinical development program, there remains considerable uncertainty regarding long latency safety risks which can only be characterized by longer term exposure in a large population of patients. All of the safety risks associated with Cosentyx have yet to be elucidated, and more side effects are anticipated with longer term exposure and greater use. Physician and patient labeling will convey the known and potential safety concerns associated with Cosentyx therapy, including infections, exacerbations of Crohn's disease, and hypersensitivity reactions, and these and other AESIs will be further assessed in two ongoing clinical trials. The 8-year observational safety study will further assess any potential increased risk of tumor development in psoriasis patients treated with Cosentyx.

There has been considerable discussion within FDA and by the DODAC regarding the optimal dose of Cosentyx. Because many patients can achieve an acceptable degree of efficacy with the lower (150 mg) dose, and because of lingering safety concerns and the dose-dependent nature of the safety concerns, healthcare providers (HCP) should consider use of the 150 mg dose, particularly in patients at lower body weight and/or with moderate disease. However, HCPs should understand that while certain patients may respond to the 150 mg dose, it is unknown whether non-responders will benefit from up-titration of the dose as there are no data that demonstrate that if patients fail on low dose, they will succeed at a higher dose. Additionally, the safety of higher doses of Cosentyx (i.e., 450 mg), especially in patients with higher body weight, severe disease, and non-response to the 300 mg dose, will need to be further studied before it can be recommended.

DDDP has recommended approval of BLA 125504 for Cosentyx (secukinumab) for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. I concur with DDDP's recommendation for approval, the PMRs/PMCs detailed in this memo, and the agreed upon labeling. Cosentyx will be an important addition to available treatments for this chronic disease.

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/s/

AMY G EGAN
01/20/2015