

## Review Report

November 12, 2015

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	(a) Cosentyx for Subcutaneous Injection 150 mg Syringe (b) Cosentyx for Subcutaneous Injection 150 mg
[Non-proprietary name]	Secukinumab (Genetical Recombination) (JAN*)
[Applicant]	Novartis Pharma K.K.
[Date of application]	March 3, 2015
[Dosage form/Strength]	(a) Solution for injection in a pre-filled syringe: Each syringe contains 150 mg of Secukinumab (Genetical Recombination) in 1 mL. (b) Powder for injection in a vial for reconstitution before use: <sup>1</sup> Each vial contains 180 mg of Secukinumab (Genetical Recombination).
[Application classification]	Prescription drug, (4) Drug with a new indication
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug IV

*\*Japanese Accepted Name (modified INN)*

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<sup>1</sup> The product is designed to ensure an extractable volume of 1.0 mL of solution for injection containing 150 mg of Secukinumab (Genetical Recombination) after the lyophilized powder is reconstituted with 1.0 mL of Water for Injection (Japanese Pharmacopoeia [JP]), and contains a 20% overage to compensate for loss during reconstitution. Doses of the product in this report are expressed in terms of Secukinumab (Genetical Recombination).

*This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.*

## Review Results

November 12, 2015

[Brand name] (a) Cosentyx for Subcutaneous Injection 150 mg Syringe  
(b) Cosentyx for Subcutaneous Injection 150 mg  
[Non-proprietary name] Secukinumab (Genetical Recombination)  
[Applicant] Novartis Pharma K.K.  
[Date of application] March 3, 2015

### [Results of review]

Based on the submitted data, a certain level of efficacy of the product is expected in the treatment of pustular psoriasis (generalized) in patients who have had an inadequate response to conventional therapy, and its safety is acceptable in view of its observed benefits. Since the number of patients assessed in a clinical study was extremely limited, the safety and efficacy of the product, etc. in clinical use should be further investigated via post-marketing surveillance.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for “Indications” and “Dosage and administration” as shown below, with the following condition.

### [Indications]

Treatment of the following diseases in patients who have had an inadequate response to conventional therapy:  
Psoriasis vulgaris, psoriatic arthritis, and pustular psoriasis (generalized)

(Words underlined are additions.)

### [Dosage and administration]

The usual adult dosage is 300 mg of Secukinumab (Genetical Recombination) by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. A dose of 150 mg may be acceptable for some patients, depending on their body weight.

### [Condition for approval]

The applicant is required to develop and appropriately implement a risk management plan.

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## Review Report (1)

October 22, 2015

### I. Product Submitted for Registration

[Brand name] (a) Cosentyx for Subcutaneous Injection 150 mg Syringe  
(b) Cosentyx for Subcutaneous Injection 150 mg

[Non-proprietary name] Secukinumab (Genetical Recombination)

[Applicant] Novartis Pharma K.K.

[Date of application] March 3, 2015

[Dosage form/Strength] (a) Solution for injection in a pre-filled syringe: Each syringe contains 150 mg of Secukinumab (Genetical Recombination) in 1 mL.  
(b) Powder for injection in a vial for reconstitution before use:<sup>2</sup> Each vial contains 180 mg of Secukinumab (Genetical Recombination).

#### [Proposed indications]

Treatment of the following diseases in patients who have had an inadequate response to conventional therapy: Psoriasis vulgaris, psoriatic arthritis, and pustular psoriasis (generalized)

(Words underlined are additions.)

#### [Proposed dosage and administration]

The usual adult dosage is 300 mg of Secukinumab (Genetical Recombination) by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. A dose of 150 mg may be acceptable for some patients, depending on their body weight.

(No changes)

### II. Summary of the Submitted Data and Outline of the Review by the Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

The current application is for a new indication. “Data relating to quality” or “non-clinical data” have not been submitted.

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<sup>2</sup> The product is designed to ensure an extractable volume of 1.0 mL of solution for injection containing 150 mg of Secukinumab (Genetical Recombination) after the lyophilized powder is reconstituted with 1.0 mL of Water for Injection (JP), and contains a 20% overage to compensate for loss during reconstitution. Doses of the product in this report are expressed in terms of Secukinumab (Genetical Recombination).

## 1. Origin or history of discovery and usage conditions in foreign countries etc.

The active substance of Cosentyx for Subcutaneous Injection 150 mg Syringe and Cosentyx for Subcutaneous Injection 150 mg is Secukinumab (Genetical Recombination) (hereinafter referred to as secukinumab), a human immunoglobulin G 1/κ monoclonal antibody against human interleukin-17 (IL-17) A, developed by Novartis Pharma AG (Switzerland). In Japan, secukinumab was approved in December 2014 for the treatment of psoriasis vulgaris and psoriatic arthritis in patients who have had an inadequate response to conventional therapy.

Pustular psoriasis (generalized) is a variant of psoriasis with acute or chronic sterile pustules appearing on erythematous skin (skin lesion common to all types of psoriasis). It is a systemic inflammatory disease characterized by repeated episodes. Patients with pustular psoriasis (generalized) present with skin symptoms (erythema, pustules, edema), laboratory abnormalities associated with systemic inflammation (i.e., abnormalities in white blood cell [WBC] count, serum C-reactive protein [CRP] level, and serum albumin level), and fever. Pustular psoriasis (generalized) is often complicated by mucosal symptoms, arthritis, and, in rare cases, respiratory failure, eye disease, or secondary amyloidosis (Iwatsuki K, et al. *Pustular psoriasis (generalized type) clinical practice guidelines 2010: Treatment guidelines incorporating TNFα inhibitors*, 2010). In Japan, the number of patients with pustular psoriasis (generalized) is approximately 1800 (approximately 1% of patients with psoriasis of all types) (*Data for Sub-committee on designated intractable diseases, Disease Committee, Health Sciences Council [3rd]*, 2014), and pustular psoriasis (generalized) is a “designated intractable disease” as per Article 5 of Act on Medical Care for Patients with Rare/Intractable Disease (Act No.50 of 2014). The disease is usually treated with drug therapy. In Japan, cyclosporine, etretinate, and Infliximab (Genetical Recombination) have been approved for the treatment of pustular psoriasis (generalized); cyclosporine and etretinate are first-line drugs (Iwatsuki K, et al. *Pustular psoriasis (generalized type) clinical practice guidelines 2010: Treatment guidelines incorporating TNFα inhibitors*, 2010).

Although the mechanism of development of pustular psoriasis (generalized) has not fully been elucidated, IL-17A is considered to contribute to the pathogenesis of psoriasis (Di Cesare A, et al. *J Invest Dermatol.* 2009;129:1339-1350, Weaver CT, et al. *Annu Rev Pathol Mech Dis.* 2013;8:477-512). Since serum IL-17A and IL-17A mRNA levels were higher in lesional skin samples of patients with pustular psoriasis (generalized) than of those with plaque psoriasis (Yilmaz SB, et al. *Arch Dermatol Res.* 2012;304:465-469), IL-17A is assumed to contribute to the pathogenesis of pustular psoriasis (generalized) as well. Secukinumab binds to IL-17A, a human IL-17 family member, and inhibits the binding of IL-17A to the IL-17 receptor, thereby neutralizing its bioactivity. Therefore, secukinumab was developed as a treatment option for pustular psoriasis (generalized).

In the EU and the US, secukinumab was approved for the treatment of moderate to severe plaque psoriasis in January 2015.

In Japan, the clinical development of secukinumab for the treatment of pustular psoriasis (generalized) began in August 2013. Currently, an application for partial change has been filed for an additional indication of pustular psoriasis (generalized) in patients who have had an inadequate response to conventional therapy, based

on the results from a Japanese clinical study.

## **2. Non-clinical data**

Although the current application is for an additional new indication, no new pharmacology data have been submitted with the application, because there was no appropriate animal model to assess the effects of secukinumab on pustular psoriasis (generalized).

## **3. Clinical data**

### **3.(i) Summary of biopharmaceutical studies and clinical pharmacology studies**

#### **3.(i).A Summary of the submitted data**

As evaluation data on the pharmacokinetics of secukinumab, the results from a Japanese clinical study in patients with pustular psoriasis (generalized) (5.3.5.2-2, Study A1302) were submitted.

Secukinumab concentrations in serum (lower limit of quantification, 80 ng/mL) were determined by enzyme-linked immunosorbent assay (ELISA) using anti-idiotypic anti-secukinumab antibodies coated on a plate. Anti-secukinumab antibodies were measured by a Meso Scale Discovery assay (lower limit of quantification, 4 ng/mL).

Unless otherwise specified, measurements are expressed as the mean  $\pm$  standard deviation (SD).

#### **3.(i).A.(1) Japanese clinical study (5.3.5.2-2, Study A1302 [ongoing since August 2013 (data cutoff date of March 11, 2015; Week 52 data)])**

The pharmacokinetics of secukinumab were evaluated in an open-label, uncontrolled study in 12 subjects with pustular psoriasis (generalized). Secukinumab 150 mg was subcutaneously administered once weekly for the first 4 weeks and subsequently every 4 weeks. The trough serum secukinumab concentrations were  $54.6 \pm 11.4$   $\mu\text{g/mL}$  at Week 4 (11 subjects),  $30.1 \pm 9.63$   $\mu\text{g/mL}$  at Week 8 (6 subjects),  $19.8 \pm 9.08$   $\mu\text{g/mL}$  at Week 16 (9 subjects),  $20.9 \pm 8.87$   $\mu\text{g/mL}$  at Week 24 (7 subjects), and  $18.4 \pm 5.93$   $\mu\text{g/mL}$  at Week 52 (6 subjects).

In subjects rated as “worsened,” “no change,” or “minimally improved” in Clinical Global Impression (CGI), secukinumab was up-titrated to 300 mg at the discretion of the investigator (sub-investigator). Two subjects underwent up-titration. Their trough serum secukinumab concentrations were 27.1  $\mu\text{g/mL}$  (Week 8) before up-titration and 22.3  $\mu\text{g/mL}$  (Week 16) after up-titration (in one subject); and 8.25  $\mu\text{g/mL}$  (Week 24) before up-titration and 10.3  $\mu\text{g/mL}$  (Week 52) after up-titration (in the other).

None of the 12 subjects treated with secukinumab were tested positive for anti-secukinumab antibodies between the start of treatment and Week 52.

#### **3.(i).B Outline of the review**

PMDA’s view:

There were no major differences in the time course of serum secukinumab concentration between patients with

pustular psoriasis (generalized) in Study A1302 and patients with psoriasis vulgaris or psoriatic arthritis (the approved indications) who have had an inadequate response to conventional therapy (see the Review Report of Cosentyx for Subcutaneous Injection 150 mg Syringe/Cosentyx for Subcutaneous Injection 150 mg dated November 14, 2014). No particular clinical pharmacological problems have been suggested in patients with pustular psoriasis (generalized).

### **3.(ii) Summary of clinical efficacy and safety**

#### **3.(ii).A Summary of the submitted data**

The applicant submitted efficacy and safety evaluation data, namely the results from a Japanese clinical study in patients with pustular psoriasis (generalized) (5.3.5.2-2, Study A1302).

#### **3.(ii).A.(1) Japanese clinical study (5.3.5.2-2, Study A1302 [ongoing since August 2013 (data cutoff date of March 11, 2015; Week 52 data)])**

An open-label, uncontrolled study was conducted at 9 sites in Japan to evaluate the efficacy and safety of secukinumab in patients with moderate to severe pustular psoriasis (generalized)<sup>3</sup> who had erythema with pustules (target sample size,  $\geq 7$ ).

Secukinumab 150 mg was subcutaneously administered at Weeks 0, 1, 2, 3, and 4, and subsequently every 4 weeks until Week 136. Subjects rated as “worsened,” “no change,” or “minimally improved” in CGI prior to treatment at Week 8 received subcutaneous secukinumab 300 mg at Weeks 8, 9, and 12 and thereafter every 4 weeks until Week 136, only when up-titration was considered necessary by the investigator (sub-investigator). Of subjects remaining on secukinumab 150 mg at Week 8, those who were rated as “worsened,” “no change,” or “minimally improved” in CGI prior to any treatment between Weeks 16 and 48 received subcutaneous secukinumab 300 mg every 4 weeks until Week 136, only when up-titration was considered necessary by the investigator. From Week 52 onward, however, subjects on secukinumab 300 mg continued treatment with 300 mg or switched to 150 mg, both administered subcutaneously every 4 weeks, at the discretion of the investigator.

All of 12 subjects treated with secukinumab were included in the Safety Analysis Set and the Full Analysis Set (FAS), and the FAS was used for efficacy analyses. There were 3 withdrawals (25%).

The primary endpoint, CGI, was defined, as shown in Table 1, based on the total score of the severity index for Generalized Pustular Psoriasis (GPP)<sup>4</sup> of the Japanese Dermatological Association (JDA) (JDA total score).

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<sup>3</sup> Key eligibility criteria: patients who met all of the following criteria: (a) a diagnosis of Generalized Pustular Psoriasis based on the Japanese Dermatological Association diagnostic criteria, (b) erythema with pustules affecting  $\geq 10\%$  of total body surface area and JDA total score  $< 14$ , and (c) absence of erythrodermic psoriasis, guttate psoriasis, and subcorneal pustular dermatosis at screening.

<sup>4</sup> Each item of skin lesions (areas of erythema with pustules, erythema, and edema), was rated from 0 to 3, and systemic manifestations and laboratory findings (fever, WBC count, CRP, serum albumin) from 0 to 2. A total score of 1-6 was defined as mild, 7-10 as moderate, and 11-17 as severe.

Table 1. Definitions of CGI

	Change in JDA total score		Other criteria
Very much improved	Decreased by $\geq 3$ points	or	Clear or almost clear of symptoms of GPP
Much improved	Decreased by 1 or 2 points	or	Erythema area with pustules (%) decreased by $\geq 30\%$ from baseline; or Clinically meaningful improvement in at least 2 other items of the JDA severity index for GPP (erythema area, edema area, WBC count, CRP, fever, serum albumin)
Minimally improved	0 points (No change)	and	Erythema area with pustules (%) decreased by $\geq 20\%$ from baseline; or Clinically meaningful improvement in at least 1 other item of the JDA severity index for GPP (erythema area, edema area, WBC count, CRP, fever, serum albumin)
No change	0 points (No change)	and	Not meeting the other criteria for “minimally improved”
Worsened	Increased by $\geq 1$ point	—	—

The proportion of subjects who responded to the treatment at Week 16 (rated as “minimally improved,” “much improved,” or “very much improved” in CGI), the primary efficacy endpoint, was 83.3% (10 of 12 subjects). The proportion of subjects who responded to the treatment at Week 52, a secondary endpoint, was 83.3% (10 of 12 subjects).

The incidence of adverse events was 100% (12 of 12 subjects). Major events are shown in Table 2. There were no deaths. Serious adverse events occurred in 25.0% (3 of 12) of subjects: cellulitis and Bowen’s disease (after up-titration to secukinumab 300 mg) in 1 subject; drug-induced liver injury in 1 subject; and upper gastrointestinal haemorrhage, hypoglycaemia, and hepatic function abnormal in 1 subject. Although a causal relationship to study drug could not be ruled out for drug-induced liver injury and hepatic function abnormal, the outcomes of these events were reported as resolved. Adverse events leading to the discontinuation of treatment occurred in 16.7% (2 of 12) of subjects: drug-induced liver injury and renal impairment in 1 subject each. Although a causal relationship to study drug could not be ruled out for both events, the outcomes of these events were reported as resolved.

The incidence of adverse drug reactions was 33.3% (4 of 12 subjects).

Table 2. Adverse events reported by  $\geq 2$  subjects (through Week 52, Safety Analysis Set, N = 12)

Nasopharyngitis	6 (50.0)
Urticaria	2 (16.7)
Diabetes mellitus	2 (16.7)
Arthralgia	2 (16.7)

n (%)

### 3.(ii).B Outline of the review

#### 3.(ii).B.(1) Efficacy and dosage and administration

##### 3.(ii).B.(1).1 Study A1302

The applicant’s explanation on the design of a Japanese clinical study (Study A1302) based on the pathology of pustular psoriasis (generalized) and currently available treatment of the disease, etc.:

- Control group and target sample size

As of 2012, the cumulative number of recipients of medical certificates for specific disease in patients with pustular psoriasis (generalized) was 1843 (website of the Japan Intractable Diseases Information Center, <http://www.nanbyou.or.jp> [October 2015]). According to a survey conducted by the Japanese Society for

Psoriasis Research, the proportion of patients with pustular psoriasis (generalized) among newly registered patients with psoriasis each year was 0.6% (12 of 1948 patients) in 2009, 2.1% (47 of 2248 patients) in 2010, and 1.6% (39 of 2434 patients) in 2011 (the proceedings of the annual meetings of the Japanese Society for Psoriasis Research [25th annual meeting in 2010, 26th annual meeting in 2011, 27th annual meeting in 2012]). Given the extremely limited number of patients with pustular psoriasis (generalized) in Japan, the feasibility of a large-scaled controlled clinical study was low. An open-label study was therefore designed for the evaluation of the efficacy and safety of secukinumab in patients with pustular psoriasis (generalized), with a target sample size of 7 (up to 15, allowing for withdrawals).

- Study population and concomitant medications

Secukinumab is expected to be used in patients with pustular psoriasis (generalized) who have had an inadequate response to, or are intolerant of, conventional therapy and require systemic therapy. In order to evaluate efficacy, the study should include subjects with the disease of a certain severity. Therefore, the inclusion criteria were defined as a diagnosis of pustular psoriasis (generalized) with the area of erythema with pustules  $\geq 10\%$  of total body surface.

Of note, for patients with pustular psoriasis (generalized), the discontinuation of concomitant systemic therapy prior to the start of the study is life-threatening, possibly leading to acute exacerbation of systemic symptoms. Thus, the use of concomitant systemic drugs such as cyclosporine, etretinate, methotrexate, and oral corticosteroids was permitted, but no dose increase was allowed during the study<sup>5</sup>. This meant that the study would have a possibility to enroll patients with well-controlled systemic symptoms. Patients were therefore allowed to be enrolled even if they did not meet the following diagnostic criterion for pustular psoriasis (generalized) at screening: “With systemic symptoms such as fever or general malaise.”

- Dosage and administration

Because of the extremely limited number of patients with pustular psoriasis (generalized) in Japan, it is difficult to conduct a clinical study to evaluate a dose-response relationship of secukinumab in these patients. IL-17A is considered to contribute to the pathogenesis of psoriasis (Di Cesare A, et al. *J Invest Dermatol.* 2009;129:1339-1350, Weaver CT, et al. *Annu Rev Pathol Mech Dis.* 2013;8:477-512). Since serum IL-17A and IL-17A mRNA levels were higher in lesional skin samples of patients with pustular psoriasis (generalized) than those with plaque psoriasis (Yilmaz SB, et al. *Arch Dermatol Res.* 2012;304:465-469), IL-17A should also contribute to the pathogenesis of pustular psoriasis (generalized). All types of psoriasis are characterized by systemic inflammation, and psoriasis vulgaris may convert to pustular psoriasis (generalized) (Hashimoto T, et al. *2011 Update on Generalized Pustular Psoriasis, Research Committee for Rare/Intractable Skin Disease,* 2011), etc. Considering these facts, the dosing regimen of secukinumab for Study A1302 was determined, based on the design of a clinical study of secukinumab in patients with psoriasis vulgaris, the most common psoriasis. In Study A1302, the starting dose of 150 mg was selected and up-titration to 300 mg was allowed for patients with an inadequate response, for the following reasons: (1) Secukinumab was administered every

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<sup>5</sup> Infliximab (Genetical Recombination), Adalimumab (Genetical Recombination), Etanercept (Genetical Recombination), photochemotherapy, phototherapy, and granulocyte apheresis were prohibited.



4 weeks at 150 or 300 mg in a confirmatory study in patients with psoriasis vulgaris or psoriatic arthritis (Study A2302), which was ongoing when Study A1302 was being planned. (2) Generally, patients with pustular psoriasis (generalized) have poorer general condition than those with psoriasis vulgaris or psoriatic arthritis. (3) The tolerability of secukinumab in patients with pustular psoriasis (generalized) was unclear.

- Efficacy endpoint and timing of endpoint assessment

There is no consensus about the efficacy endpoint in clinical studies of pustular psoriasis (generalized). Therefore, the CGI criteria were established based on the JDA total score, which is widely used for assessment of patient condition in clinical settings (Table 1 [see 3.(ii).A Summary of the submitted data]). The primary endpoint was defined as response rate (the proportion of subjects rated as “minimally improved,” “much improved,” or “very much improved” in CGI). The individual items of the JDA severity index for GPP (assessment of skin lesions and systemic manifestations and laboratory findings) were chosen as secondary endpoints.

The primary endpoint was evaluated at Week 16 for the following reasons. A simulation was performed between exposure to secukinumab and its efficacy against skin plaques common to all types of psoriasis (the psoriasis area and severity index [PASI] 75 response rate), using a model established based on clinical study data from patients with plaque psoriasis. According to the simulation, when the dose was up-titrated to 300 mg at Week 8 and an additional dose of 300 mg was administered at Week 9, the effect of secukinumab on plaque psoriasis would become almost constant at Week 16. The duration to evaluate the long-term efficacy and safety of secukinumab was determined as 52 weeks, because pustular psoriasis (generalized) is characterized by remissions and exacerbations.

PMDA’s view:

Given the extremely limited number of patients with pustular psoriasis (generalized) in Japan, the applicant had no choice but to conduct Study A1302 as an open-label, uncontrolled study. The dosing regimen of secukinumab for Study A1302 was determined based on the design of the ongoing clinical study in patients with psoriasis vulgaris, the most common form of psoriasis, because all types of psoriasis are characterized by systemic inflammation; this is acceptable. Efficacy endpoints for the treatment of pustular psoriasis (generalized) have not been established. Therefore, the efficacy of treatment should be assessed comprehensively based on the JDA total score, which is commonly used for the assessment of patient condition in clinical practice, and based on each JDA severity criterion, skin lesions such as area of erythema or edema, and systemic manifestations and laboratory findings such as fever, WBC count, and CRP.

### **3.(ii).B.(1).2) Efficacy**

The applicant’s explanation on the efficacy of secukinumab in the treatment of pustular psoriasis (generalized): The results of efficacy endpoints in the Japanese clinical study (Study A1302) are shown in Table 4. The response rate at Week 16, the primary endpoint, was 83.3% (10 of 12 subjects) and the response rate at Week 52, a secondary endpoint, was 83.3% (10 of 12 subjects). The trend towards improvement continued through Week 52 in most subjects including those who underwent up-titration to 300 mg due to exacerbated skin lesions.

The proportion of subjects rated as “much improved” or “very much improved” in CGI was 83.3% (10 of 12 subjects) at Week 16 and 75% (9 of 12 subjects) at Week 52.

Table 4 shows the evaluation results of skin-related items of the JDA severity index for GPP (areas of erythema with pustules, erythema, and edema) through Week 52. In many subjects, skin lesions improved following the start of treatment with secukinumab and remained improved through Week 52, although none of the subjects achieved complete response.

Table 4 also shows the evaluation results of systemic items of the JDA severity index for GPP (fever, WBC count, CRP, serum albumin) through Week 52. A trend towards improvement was observed following treatment with secukinumab in many subjects rated as  $\geq 1$  in any of the evaluation items. No subjects experienced exacerbation with a  $>1$ -point increase in score through Week 52 and their pathological condition tended to be mostly stable.

Table 4. Results of main efficacy endpoints for treatment of pustular psoriasis (generalized) (OC<sup>a</sup>)

Endpoint	Baseline (N = 12)	Week 1 (N = 11)	Week 4 (N = 12)	Week 8 (N = 12)	Week 12 (N = 12)	Week 16 (N = 11)	Week 24 (N = 11)	Week 36 (N = 11)	Week 52 (N = 10)
No. of subjects who responded to the treatment	—	10	12	11	11	10	10	10	10
CGI (n [%])									
Very much improved	—	4 (36.4)	10 (83.3)	9 (75.0)	10 (83.3)	9 (81.8)	8 (72.7)	7 (63.6)	7 (70.0)
Much improved	—	5 (45.5)	2 (16.7)	2 (16.7)	1 (8.3)	1 (9.1)	1 (9.1)	3 (27.3)	2 (20.0)
Minimally improved	—	1 (9.1)	0	0	0	0	1 (9.1)	0	1 (10.0)
No change	—	1 (9.1)	0	1 (8.3)	1 (8.3)	1 (9.1)	0	1 (9.1)	0
Worsened	—	0	0	0	0	0	1 (9.1)	0	0
JDA total score (Mean $\pm$ SD)	5.9 $\pm$ 1.62	3.5 $\pm$ 1.69	1.9 $\pm$ 1.83	2.1 $\pm$ 1.88	2.3 $\pm$ 1.71	2.1 $\pm$ 1.58	2.2 $\pm$ 1.99	1.7 $\pm$ 1.74	1.9 $\pm$ 1.37
Skin-related items of JDA severity index for GPP (Mean $\pm$ SD)									
Erythema with pustules (%)	13.08 $\pm$ 7.48	6.00 $\pm$ 10.22	2.75 $\pm$ 7.38	2.17 $\pm$ 5.13	1.33 $\pm$ 3.37	1.00 $\pm$ 3.32	1.09 $\pm$ 3.30	0.91 $\pm$ 3.02	0.00 $\pm$ 0.00
Erythema (%)	32.92 $\pm$ 21.48	28.14 $\pm$ 23.84	13.38 $\pm$ 17.48	10.08 $\pm$ 16.80	10.50 $\pm$ 16.68	11.64 $\pm$ 17.43	11.82 $\pm$ 17.76	10.37 $\pm$ 14.75	3.60 $\pm$ 4.48
Edema (%)	9.58 $\pm$ 9.08	2.64 $\pm$ 3.53	1.25 $\pm$ 3.11	1.08 $\pm$ 3.75	1.17 $\pm$ 3.22	1.09 $\pm$ 3.30	1.73 $\pm$ 3.58	1.27 $\pm$ 3.13	1.00 $\pm$ 1.70
Systemic items of JDA severity index for GPP (Mean $\pm$ SD)									
Fever ( $^{\circ}$ C)	36.7 $\pm$ 0.3	36.6 $\pm$ 0.4	36.5 $\pm$ 0.3	36.6 $\pm$ 0.3	36.5 $\pm$ 0.4	36.6 $\pm$ 0.4	36.6 $\pm$ 0.5	36.5 $\pm$ 0.3	36.7 $\pm$ 0.5
WBC count (/ $\mu$ L)	9342 $\pm$ 3867	8064 $\pm$ 2617	7992 $\pm$ 2822	7917 $\pm$ 2559	8108 $\pm$ 3859	6946 $\pm$ 2610	7336 $\pm$ 1738	7627 $\pm$ 2297	6820 $\pm$ 2089
CRP (mg/dL)	1.43 $\pm$ 3.74	0.18 $\pm$ 0.20	0.18 $\pm$ 0.24	0.20 $\pm$ 0.26	0.72 $\pm$ 1.87	0.19 $\pm$ 0.20	0.15 $\pm$ 0.18	0.30 $\pm$ 0.53	0.21 $\pm$ 0.31
Serum albumin (g/dL)	4.3 $\pm$ 0.2	4.3 $\pm$ 0.3	4.3 $\pm$ 0.2	4.3 $\pm$ 0.2	4.3 $\pm$ 0.2	4.3 $\pm$ 0.3	4.3 $\pm$ 0.2	4.3 $\pm$ 0.2	4.3 $\pm$ 0.4

<sup>a)</sup>, Observed Cases

—, Not available

Of the 12 subjects, 8 were receiving a concomitant systemic medication at baseline. Table 5 shows the concomitant medications in these subjects. Of the 8 subjects on a concomitant systemic medication, 6 subjects responded to secukinumab at Week 16, and 7 subjects at Week 52. Of the 8 subjects, 5 reduced the dose of concomitant systemic medication and responded to secukinumab by Week 16. In the 5 patients, the effect of secukinumab was sustained through Week 52, but only 1 of them was able to discontinue concomitant medication.

Table 5. Changes in dose of concomitant systemic medication (mg) and CGI rating by subject

Subject ID Concomitant medication	Baseline (N = 8)	Week 1 (N = 8)	Week 8 (N = 8)	Week 16 (N = 8)	Week 24 (N = 8)	Week 36 (N = 8)	Week 52 (N = 8)
1011002 Etretinate Prednisolone	40 30	40 30	40 15	(Responded) 40 10	30 10	30 10	(Responded) 30 10
1001002 Etretinate	20	20	10	(Responded) 10	10	10	(Responded) 10
1002001 Cyclosporine	150	100	25	(Responded) 25	25	25	(Responded) 25
1013001 Cyclosporine	250	250	250	(Responded) 250	250	250	(Responded) 250
1012003 Cyclosporine	150	100	0	(Responded) 0	0	0	(Responded) 0
1004002 Methotrexate	7.5	7.5	2.5	(Responded) 2.5	2.5	2.5	(Responded) 2.5
1014002 Cyclosporine	150	—	150	—	—	—	—
1009001 <sup>a)</sup> Etretinate	30	30	30	30	30	30	(Responded) 30

<sup>a)</sup> Up-titrated to secukinumab 300 mg at Week 8

—, Not available

As described above, the treatment with secukinumab demonstrated improved clinical symptoms and sustained effect through Week 52, leading to the reduction or discontinuation of a concomitant systemic medication in some patients. The results suggested the efficacy of secukinumab in the treatment of pustular psoriasis (generalized).

#### PMDA's view:

The small number of patients in the Japanese clinical study hinders the study data-based evaluation of the efficacy of secukinumab in the treatment of pustular psoriasis (generalized). Meanwhile, many patients with pustular psoriasis (generalized) (characterized by exacerbations and remissions) experienced improvement in the JDA total score and skin lesion-related JDA severity index for GPP following the treatment with secukinumab; the improvement was mostly sustained through Week 52. No patient experienced exacerbation in systemic manifestations or laboratory findings (i.e., a >1-point score increase in a systemic item of the JDA severity index for GPP) through Week 52. These findings suggest that secukinumab have a certain level of efficacy in the treatment of pustular psoriasis (generalized). Because of the extremely small number of patients in the Japanese clinical study, the efficacy of secukinumab in patients with pustular psoriasis (generalized) should be further investigated via post-marketing surveillance.

The above conclusions by PMDA on the efficacy of secukinumab will be discussed at the Expert Discussion.

#### 3.(ii).B.(1).3 Dosage and administration

PMDA's view on the dosage and administration for pustular psoriasis (generalized):

Due to the extremely limited number of subjects, data from Study A1302 (a Japanese clinical study) are too inadequate to fully examine the appropriateness of the dose of secukinumab for patients with pustular psoriasis (generalized). On the other hand, 10 of 12 subjects remained on secukinumab 150 mg and responded to secukinumab, achieving reduced JDA total score and improved skin lesions. These improvements were mostly sustained through Week 52. Secukinumab was up-titrated to 300 mg by Week 52 in 2 of 12 subjects. In 1 of

the 2 subjects, skin lesions improved after up-titration to 300 mg at Week 24, and the effect was sustained through Week 52. These findings suggest a certain level of efficacy of secukinumab 150 and 300 mg in the treatment of pustular psoriasis (generalized). No major safety concern have been identified. [see “3.(ii).B.(2) Safety”].

In clinical studies in patients with plaque psoriasis (Studies A2302, A2303, A2308, and A2309), the PASI 75, 90, and 100 response rates were higher with secukinumab 300 mg than with 150 mg, and there were no differences in safety profile between the 2 doses (see Review Report of Cosentyx for Subcutaneous Injection 150 mg Syringe/Cosentyx for Subcutaneous Injection 150 mg dated November 14, 2014). Pustular psoriasis (generalized) is a severe form of psoriasis. The majority of subjects enrolled into Study A1302 had mild symptoms. (Of the 12 subjects, 9 had mild pustular psoriasis [generalized] and 3 moderate pustular psoriasis [generalized]). Psoriasis vulgaris may convert to pustular psoriasis (generalized) (Hashimoto T, et al. *2011 Update on Generalized Pustular Psoriasis, the Research Team on Rare/Intractable Skin Disease*, 2011). The extremely limited number of patients with pustular psoriasis (generalized) limits the feasibility of a dose-finding study. Given all these factors, the following dosage and administration for pustular psoriasis (generalized) (proposed based on the approved labeling for psoriasis vulgaris or psoriatic arthritis) is acceptable: The usual dosage is 300 mg of secukinumab administered by subcutaneous injection every 4 weeks and a dose of 150 mg may be considered for patients with low body weight,  $\leq 60$  kg.

However, because of a severe lack of clinical experience with secukinumab 300 mg in patients with pustular psoriasis (generalized), the efficacy and safety of secukinumab should be further investigated via post-marketing surveillance. Healthcare professionals should be advised to avoid chronic use of secukinumab in patients not responding to the treatment or presenting with clear worsening of symptoms.

The above conclusions by PMDA on dosage and administration will be discussed at the Expert Discussion.

### **3.(ii).B.(2) Safety**

#### **3.(ii).B.(2).1 Safety in patients with pustular psoriasis (generalized)**

The applicant’s explanation on the safety of secukinumab in patients with pustular psoriasis (generalized): Table 6 shows the occurrence of adverse events through Week 52 in Study A1302 and safety data for secukinumab used in patients with psoriasis vulgaris and psoriatic arthritis (the approved indications). Although the number of subjects in Study A1302 was limited, no major differences were observed in the safety profile of secukinumab between patients with pustular psoriasis (generalized) and those with psoriasis vulgaris/psoriatic arthritis. No safety concerns specific to pustular psoriasis (generalized) have been identified.

Table 6. Adverse events occurring after 52 weeks of treatment with secukinumab in patients with pustular psoriasis (generalized) and in patients with psoriasis vulgaris/psoriatic arthritis

	Pustular psoriasis (generalized) (Study A1302) (N = 12)	Psoriasis vulgaris and psoriatic arthritis (Pooled data)		
		150 mg (N = 1395)	300 mg (N = 1410)	any Dose (N = 3430)
Adverse events	12 (100)	1066 (76.4)	1091 (77.4)	2637 (76.9)
Adverse drug reactions	4 (33.3)	373 (26.7)	377 (26.7)	892 (26.0)
Serious adverse events	3 (25.0)	76 (5.5)	85 (6.0)	207 (6.0)
Adverse events leading to discontinuation	2 (16.7)	43 (3.1)	46 (3.3)	118 (3.4)
Infections	7 (58.3)	653 (46.8)	704 (49.9)	1640 (47.8)
Serious infections	1 (8.3)	12 (0.9)	16 (1.1)	40 (1.2)
Hypersensitivity	3 (25.0)	115 (8.2)	132 (9.4)	287 (8.4)
Malignancy	1 (8.3)	11 (0.8)	9 (0.6)	26 (0.8)
Cardiovascular/cerebrovascular events	2 (16.7)	30 (2.2)	38 (2.7)	82 (2.4)
Administration site reactions or immune reactions	4 (33.3)	292 (20.9)	318 (22.6)	782 (22.8)
Drug related hepatic disorders	2 (16.7)	57 (4.1)	62 (4.4)	143 (4.2)

n (%)

Subjects in Study A1302 experienced infections, hypersensitivity reaction, malignancy, cardiovascular /cerebrovascular events, and administration site reactions/immune reactions. (These events are among the noteworthy major risks in the use of secukinumab for the approved indications). None of these events led to the discontinuation of the study drug, and many resolved with or without treatment.

In Study A1302, drug related hepatic disorders<sup>6</sup> occurred in 2 of 12 subjects (drug-induced liver injury and hepatic steatosis in one subject, hepatic function abnormal in the other). The drug-induced liver injury was reported as a serious adverse event. Its relationship to study drug could not be ruled out, and the study drug was discontinued. The event resolved with hospitalization and medical treatment. The hepatic steatosis occurred after the discontinuation of study drug. The hepatic function abnormal occurred twice in 1 subject; the first episode occurred on Day 29 and the second episode on Day 260. The first episode was considered not related to the study drug and resolved on Day 92. The second episode was reported as a serious adverse event because aspartate aminotransferase was  $\geq 5$  times the upper limit of normal, and its relationship to study drug could not be ruled out. The event resolved with drug therapy on Day 470. In clinical studies for the approved indications, the incidences of drug related hepatic disorders were 1.3% in the 150 mg group, 1.9% in the 300 mg group, 0.9% in the placebo group, and 2.5% in the etanercept group during the induction period, and 4.1% in the 150 mg group, 4.4% in the 300 mg group, and 5.0% in the etanercept group during the entire treatment period. Serious events occurred in 3 subjects in the 150 mg group and 4 subjects in the 300 mg group. Taking account of these findings, secukinumab is considered unlikely to cause hepatic disorders that would pose a clinically significant problem in patients with pustular psoriasis (generalized) at present.

PMDA's view:

A comparison of adverse events between patients with pustular psoriasis (generalized) and those with psoriasis vulgaris and psoriatic arthritis (the approved indications) suggested no new safety concerns in the use of secukinumab for pustular psoriasis (generalized). However, because of the extremely limited number of patients assessed in Study A1302 and lack of experience with secukinumab for severe symptoms, patients on

<sup>6</sup> Drug related hepatic disorders - comprehensive search (SMQ)

secukinumab should be carefully monitored for adverse events specific to pustular psoriasis (generalized) as well as for known adverse drug reactions. Safety of secukinumab in patients with pustular psoriasis (generalized) should be further investigated via post-marketing surveillance.

### **3.(ii).B.(2).2 Safety of secukinumab in combination with other systemic therapies**

The applicant's explanation on the safety of secukinumab in combination with other systemic therapies:

In patients with acute or worsening pustular psoriasis (generalized), biologics including secukinumab are expected to be used in combination with other systemic therapies including immunosuppressants, to prevent further worsening of the disease. The use of concomitant systemic medications (cyclosporine, etretinate, methotrexate, oral corticosteroids) was also allowed in Study A1302 to prevent acute worsening of systemic symptoms due to discontinued treatment. In Study A1302, 8 of 12 subjects were receiving a systemic concomitant medication at baseline (etretinate [3 subjects], cyclosporine [4 subjects], methotrexate [1 subject], and prednisolone [1 subject]); one of the 8 subjects were receiving 2 concomitant medications [etretinate and prednisolone]). Adverse events and severity of these events did not tend to significantly differ between patients with and without systemic concomitant medication, although both subgroups (defined by the presence or absence of systemic concomitant medication) had only a small number of subjects. Study A1302 showed no trend towards increased safety risk such as infections in patients receiving secukinumab in combination with immunosuppressants.

PMDA's view:

Study A1302 suggested no clinically significant problems in the use of secukinumab with other systemic therapies. However, because of the extremely limited number of patients assessed and no enrollment of patients with severe symptoms, the safety of secukinumab in combination with other systemic therapies should be further investigated via post-marketing surveillance.

### **3.(ii).B.(3) Indication**

Based on the data submitted by the applicant and "3.(ii).B.(1) Efficacy and dosage and administration" and "3.(ii).B.(2) Safety," PMDA concluded that the proposed indication, "Treatment of the following disease in patients who have had an inadequate response to conventional therapy: pustular psoriasis (generalized)" is acceptable.

### **3.(ii).B.(4) Post-marketing safety measures**

PMDA asked the applicant to explain post-marketing safety measures for patients with pustular psoriasis (generalized).

The applicant's explanation:

The safety profile of secukinumab in patients with pustular psoriasis (generalized) suggested no particular concerns as compared with the approved indications. The ongoing safety measures in the use of secukinumab for the approved indications will also be taken in patients with pustular psoriasis (generalized). The package insert will advise that the concomitant use of conventional systemic therapy (excluding biologics) should be

carefully considered prior to the treatment with secukinumab and that secukinumab should be used under the supervision of a knowledgeable and experienced physician in the treatment of psoriasis, etc. Informative materials will be prepared for healthcare professionals, etc. to promote the proper use of secukinumab. Serious infections and other adverse drug reactions should be addressed in cooperation with other departments or medical institutions. Post-marketing surveillance, etc. will also be used to check for such cooperation in the clinical use of secukinumab.

PMDA's view:

The ongoing safety measures in the use of secukinumab for the approved indications should also be taken in the use for pustular psoriasis (generalized). Due to the extremely limited number of patients assessed in the Japanese clinical study, the safety and efficacy of secukinumab in clinical use in patients with pustular psoriasis (generalized), including those with severe symptoms and those on long-term treatment, should be further investigated via post-marketing surveillance. New findings should be communicated to healthcare professionals in an appropriate manner.

### **III. Results of Compliance Assessment Concerning the Data Submitted in the Application and Conclusion by PMDA**

#### **1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment**

Document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics for the data submitted in the application. PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

#### **2. PMDA's conclusion on the results of GCP on-site inspection**

GCP on-site inspection was conducted in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics for the data submitted in the application (5.3.5.2-2). PMDA concluded that since the clinical study was conducted generally in compliance with GCP, there should be no problem with proceeding to a regulatory review based on the submitted application documents. The following issue associated with the sponsor was identified, and the applicant (the sponsor) was notified of the issue as an area for improvement. However, the issue did not affect the outcome of the overall assessment of the study significantly.

[Area for improvement]

Sponsor

- Some of serious, unexpected adverse drug reactions, etc. were not appropriately notified to the investigators or the heads of the medical institutions (the study sites).





#### **IV. Overall Evaluation**

Based on the submitted data, a certain level of efficacy of secukinumab is expected in the treatment of pustular psoriasis (generalized) of patients who have had an inadequate response to conventional therapy, and its safety is acceptable in view of its observed benefits. Secukinumab has clinical significance as a new therapeutic option for patients with pustular psoriasis (generalized) who have had an inadequate response to conventional therapy. No particular concerns regarding the safety profile of secukinumab have been identified in patients with pustular psoriasis (generalized), as compared with patients with psoriasis vulgaris or psoriatic arthritis, the approved indications. Nevertheless, because of the extremely limited number of patients assessed in the clinical study, the safety and efficacy of secukinumab in clinical use, including the occurrence of adverse events such as serious infections in long-term treatment, should be further investigated via post-marketing surveillance.

This application may be approved if secukinumab is not considered to have any particular problems based on comments from the Expert Discussion.

## Review Report (2)

November 12, 2015

### I. Product Submitted for Registration

[Brand name]	(a) Cosentyx for Subcutaneous Injection 150 mg Syringe (b) Cosentyx for Subcutaneous Injection 150 mg
[Non-proprietary name]	Secukinumab (Genetical Recombination)
[Applicant]	Novartis Pharma K.K.
[Date of application]	March 3, 2015

### II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for registration, in accordance with the provisions of the “Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

#### (1) Efficacy, indications, and dosage and administration

PMDA’s conclusions on the efficacy, indications, and dosage and administration for “Cosentyx for Subcutaneous Injection 150 mg Syringe and Cosentyx for Subcutaneous Injection 150 mg,” as per the Review Report (1), were supported at the Expert Discussion.

#### (2) Safety and draft risk management plan

The expert advisors supported PMDA’s conclusions regarding the safety of secukinumab described in the Review Report (1), making the following comment:

- Given the extremely limited number of patients assessed in a Japanese clinical study (Study A1302), the safety profile of secukinumab in patients with pustular psoriasis (generalized) should be further assessed in a careful manner via post-marketing surveillance, etc.

Based on the Review Report (1) “II.3.(ii).B.(2) Safety” and “II.3.(ii).B.(4) Post-marketing safety measures” and the expert advisors’ comments at the Expert Discussion, PMDA concluded that the safety and efficacy specification listed in Table 7 should be included in the current draft risk management plan, and that additional pharmacovigilance activities and risk minimization activities listed in Table 8 should be performed.

Table 7. Safety and efficacy specification of the draft risk management plan

Safety specification		
Important identified risks	Important potential risks	Important missing information
<ul style="list-style-type: none"> <li>· Serious infections</li> <li>· Neutropenia</li> <li>· Hypersensitivity reactions</li> </ul>	<ul style="list-style-type: none"> <li>· Malignancy</li> <li>· Cardiovascular/cerebrovascular events</li> <li>· Tuberculosis</li> <li>· Immunogenicity</li> <li>· Inflammatory bowel disease</li> </ul>	<ul style="list-style-type: none"> <li>· None</li> </ul>
Efficacy specification		
<ul style="list-style-type: none"> <li>· Efficacy in clinical use in patients with psoriasis vulgaris, psoriatic arthritis, or pustular psoriasis (generalized)</li> </ul>		

Table 8. Summary of additional pharmacovigilance activities and risk minimization activities in the draft risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
<ul style="list-style-type: none"> <li>· Specified drug use-results survey (psoriasis vulgaris and psoriatic arthritis)</li> <li>· Specified drug use-results survey (pustular psoriasis [generalized])</li> <li>· Post-marketing clinical studies<sup>a)</sup></li> </ul>	<ul style="list-style-type: none"> <li>· Develop a guidance book for the proper-use of the product for healthcare professionals.</li> <li>· Ensure that information on the proper use of the product is communicated before the delivery of the product.</li> </ul>

<sup>a)</sup> After approval of the product, clinical studies in patients with psoriasis vulgaris/psoriatic arthritis (Studies A2302E1 and A2304E1) and a clinical study in patients with pustular psoriasis (generalized) (Study A1302) will be reclassified as post-marketing clinical studies to assess the long-term safety and efficacy of secukinumab.

Accordingly, PMDA instructed the applicant to conduct post-marketing surveillance to investigate the above issues.

The applicant's response:

Table 9 is a specified drug use-results survey plan. The survey is to be conducted in patients with pustular psoriasis (generalized) inadequately responding to conventional therapy, with a target sample size of 100 (as safety analysis population) and an observation period of 52 weeks, aiming to evaluate the safety and efficacy of secukinumab in clinical use. Priority investigation items are serious infections, tuberculosis, neutropenia, fungal infection, hypersensitivity reactions, malignancy, inflammatory bowel disease, and cardiovascular/cerebrovascular events. After the completion of the observation period, patients will be followed for serious infections and malignancy until 3 years after the start of treatment for the further evaluation of the long-term safety of secukinumab.

Table 9. Outline of the draft specified drug use-results survey plan

Objective	To confirm the long-term safety and efficacy of secukinumab in clinical use.
Method	Central registry system
Population	Patients with pustular psoriasis (generalized) inadequately responding to conventional therapy
Observation period	52 weeks (after the completion of the observation period, patients will be followed until 3 years after the start of treatment.)
Target sample size	100 (safety analysis population)
Priority investigation items	Serious infections, tuberculosis, neutropenia, fungal infection, hypersensitivity reactions, malignancy, inflammatory bowel disease, cardiovascular/cerebrovascular events
Main investigation items	Patient characteristics (duration of disease, severity, complications, medical history, previous therapy, etc.) Concomitant medications/therapies Use of secukinumab Efficacy assessment (clinical global impression, PASI, body surface area, etc.) Adverse events Clinical laboratory tests

PMDA considers that the survey should be conducted promptly and that survey results should be communicated to healthcare professionals in an appropriate manner.

### III. Overall Evaluation

As a result of the above review, PMDA has concluded that secukinumab may be approved for “Indications” and “Dosage and Administration” as shown below, with the following condition. The re-examination period for this application is the remainder of the ongoing re-examination period for the initial approval of secukinumab (until December 25, 2022).

#### [Indications]

Treatment of the following diseases in patients who have had an inadequate response to conventional therapy: Psoriasis vulgaris, psoriatic arthritis, and pustular psoriasis (generalized)

(Words underlined are additions.)

#### [Dosage and administration]

The usual adult dosage is 300 mg of Secukinumab (Genetical Recombination) by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. A dose of 150 mg may be acceptable for some patients, depending on their body weight.

(No changes)

#### [Condition for approval]

The applicant is required to develop and appropriately implement a risk management plan.