

## เอกสารกำกับยาสำหรับบุคลากรทางการแพทย์

### 1. NAME OF THE MEDICINAL PRODUCT

**LUMICEF® Subcutaneous Injection 210 mg Syringe**

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each syringe contains Brodalumab 210 mg in 1.5 mL solution.

Brodalumab is a fully human IgG2 monoclonal antibody against human interleukin (IL)-17 receptor A expressed in a Chinese hamster ovary cell line.

### 3. PHARMACEUTICAL FORM

Solution for subcutaneous injection in pre-filled syringe

Colorless to pale yellow, transparent to slightly opaque liquid

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

“LUMICEF® is indicated for (1) treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. (2) treatment of generalized pustular psoriasis in adult patients who have had an inadequate response to conventional therapies”

#### 4.2 Posology and method of administration

##### Posology

The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.

Patients generally achieve a response to treatment with LUMICEF® within 12 weeks of treatment initiation. If no response to treatment is achieved within 12 weeks, carefully reconsider whether to continue the treatment protocol with LUMICEF®.

##### Special populations

###### Use in the Elderly

The elderly generally have reduced physiological functions. Observe such patients carefully and be mindful of possible adverse reactions such as infections.

###### Pediatric population

The safety and efficacy of LUMICEF® in children and adolescents below the age of 18 years have not yet been established. No data are available.

###### Renal and hepatic impairment

LUMICEF® has not been studied in these patient populations. No dose recommendations can be made.

## Method of administration

The administration of LUMICEF® must be initiated by a physician or under the direct supervision of a physician in a medical institution. After proper training in subcutaneous injection technique, patients may self-inject LUMICEF® when deemed appropriate by a physician. Patients should be instructed to inject the full amount of LUMICEF®.

Use a different site for each injection. Moreover, do not inject areas of the skin that are sensitive or abnormal (scratch, redness, sclerosis, thickness, scaling, or other abnormalities), or sites of psoriasis. (See “Precautions concerning Use”)

### 4.3 Contraindications

1. Patients with a serious infection
2. Patients with active tuberculosis
3. Patients with a history of hypersensitivity to any of the ingredients of LUMICEF®.

### 4.4 Special warnings and precautions for use

#### WARNINGS

1. Use LUMICEF® only at a medical institution capable of providing adequate responses to emergencies including tuberculosis and other infections, under the supervision of a physician who has thorough knowledge of LUMICEF® and is well versed and experienced in treating psoriasis, for patients for whom the benefits outweigh the risks of treatment with LUMICEF®. LUMICEF® is associated with increased risks of infections and may activate tuberculosis in patients with a history of tuberculosis. There have also been reports of malignant tumors, although it is unclear whether they are causally related to LUMICEF®. Before commencing treatment, make sure patients are well informed and understand the efficacy and risks of LUMICEF®, including the fact that it is not curative.
2. Serious infection  
Given reports of serious viral, bacterial, and fungal infections, instruct patients to observe closely or otherwise pay attention to any onset of infection and to contact their attending physician immediately when any signs or symptoms of infection occur after the administration of LUMICEF®.
3. Before commencing treatment with LUMICEF®, fully consider the use of phototherapies or other existing systemic therapies (except biologics).

#### PRECAUTIONS

1. Careful Administration
  - (1) Patients with infections or suspected infections (See “Important Precautions”)
  - (2) Patients with a history of tuberculosis (See “Important Precautions”)
  - (3) Patients with depression, in a state of depression, or with such a history or patients with a history of suicidal ideation or suicidal attempt (See “Other Precautions”)
  - (4) Patients with active Crohn’s disease (See “Important Precautions”)
  - (5) Elderly patients (See “Use in the Elderly”)
2. Important Precautions
  - (1) LUMICEF® is associated with increased risks of infections. Thus, patients undergoing treatment with LUMICEF® should be observed carefully, with attention paid to any onset or worsening of infections. Instruct patients to contact their attending physician promptly should

any signs or symptoms of infection develop. Moreover, in the event of a serious infection, take appropriate actions. (See “Clinically significant adverse reactions”)

- (2) Before administering LUMICEF<sup>®</sup>, confirm whether a patient has a tuberculous infection by detailed medical interview about tuberculosis and performing a chest X-ray exam, an interferon- $\gamma$  release assay or a tuberculin test, and a chest CT scan, as appropriate, among other tests. Consult a physician who is experienced in treating tuberculosis if the patient has a history of tuberculosis or a suspected tuberculous infection. Any of the following patients, in principle, should be treated with an anti-tuberculosis drug before receiving LUMICEF<sup>®</sup>.
- Patients whose chest imaging results show shadows consistent with or presumed to be old tuberculosis
  - Patients with a medical history of tuberculosis (including extrapulmonary tuberculosis)
  - Patients whose interferon- $\gamma$  release assay, tuberculin test, or any other exam shows a strong suspicion of existing infection
  - Patients with a history of close contact with a tuberculosis patient

Furthermore, perform appropriate tests such as chest X-ray regularly to closely monitor potential onset of tuberculosis in patients even while they are undergoing treatment with LUMICEF<sup>®</sup>, and instruct patients to contact their attending physician promptly should they develop symptoms indicating suspected tuberculosis (such as persistent coughs, weight decreased, or fever, among other symptoms). For patients who have a confirmed diagnosis of active tuberculosis, the tuberculosis treatment should be given priority, with the LUMICEF<sup>®</sup> treatment withheld. (See “CONTRAINDICATIONS” and “Careful Administration”)

- (3) There have been reports of events related to worsening of Crohn’s disease in Europe and the US clinical studies conducted in subjects with Crohn’s disease. Observe patients with active Crohn’s disease carefully before administering LUMICEF<sup>®</sup> and be mindful of possible worsening of Crohn’s disease. Instruct patients to contact their attending physician promptly should any worsening of symptoms is noted. Moreover, in the event of worsened Crohn’s disease, take appropriate actions. (See “Careful Administration”)
- (4) There have been reports of malignant skin and non-skin tumors in clinical studies. Although it is unclear whether they are causally related to LUMICEF<sup>®</sup>, be mindful of possible onset of malignant tumors. (See “Clinical studies”)
- (5) A risk of developing infection associated with live vaccines cannot be ruled out. Thus, no live vaccines are to be given to patients undergoing treatment with LUMICEF<sup>®</sup>.
- (6) The safety and efficacy of the concomitant use of LUMICEF<sup>®</sup> and another biologic have not been established. Any such concomitant use, therefore, should be avoided. Moreover, patients switching from another biologic to LUMICEF<sup>®</sup> should be observed closely for signs of infection.
- (7) Patients who are allowed to self-administer LUMICEF<sup>®</sup> should be given instructions on the injection procedure and the safe disposal procedure.
- 1) Self-administration should only be allowed under the control and direction of a physician after a careful assessment of the appropriateness by the physician, extensive education and training for the patient, understanding by the patient of the risks associated with LUMICEF<sup>®</sup> treatment and countermeasures, and the confirmation that the patient is able to properly self-administer the drug. Furthermore, after beginning self-administration, patients are to suspend self-administration immediately if LUMICEF<sup>®</sup> is suspected of causing adverse reactions such as infection or if they have difficulty with continuing self-administration. Physicians are to take appropriate actions such as placing such patients under careful physician-managed observation.

2) Provide patients with strict training and guidance to alert them not to reuse any used injection devices (with built-in needle) and to educate them on how to dispose the injection devices safely. Instruct patients on how to dispose all injection devices safely.

### 3. Other Precautions

- (1) In Japanese clinical studies, suicide attempt was reported in 1 of 177 subjects (0.6%). In Europe and the US clinical studies, suicidal ideation, suicide attempt, etc. were reported in 16 of 4,625 subjects (0.3%) exposed to brodalumab, and suicide was reported in 3 (0.06%). Moreover, in an Europe and the US clinical study in subjects with rheumatoid arthritis, suicide was reported in 1 of 211 subjects (0.5%).
- (2) In Japanese and Europe and the US clinical studies in subjects with psoriasis, anti-brodalumab binding antibodies were noted in 3 of 177 Japanese subjects (1.7%) and in 122 of 4,461 European and American subjects (2.7%), but no anti-brodalumab neutralizing antibodies production has been reported. In an Europe and the US clinical study in subjects with rheumatoid arthritis, production of anti-brodalumab neutralizing antibodies was reported in 2 of 211 subjects (0.9%).
- (3) The safety and efficacy of concomitant use with an immunosuppressant or phototherapy have not been established.

### 4.5 Interaction with other medicinal products and other forms of interaction

Live vaccines should not be given concurrently with LUMICEF® (see section 4.4).

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g. IL-1, IL-6, IL-10, TNF $\alpha$ , IFN) during chronic inflammation. Although a role for interleukin (IL)-17A and IL-17RA in the regulation of CYP450 enzymes has not been reported, the effect of brodalumab on CYP3A4/3A5 activity was evaluated in a disease-drug-drug interaction study.

In patients with moderate to severe plaque psoriasis, a single subcutaneous dose of 210 mg brodalumab increased the exposure of midazolam, a CYP3A4/3A5 substrate by 24%. Based on the magnitude of change in exposure of midazolam, no dose adjustment of CYP3A4/3A5 substrates is necessary when administered concomitantly with LUMICEF®.

### 4.6 Pregnancy and lactation

Use during Pregnancy, Delivery, or Lactation

- (1) Do not administer to women who are pregnant or may possibly be pregnant unless the expected therapeutic benefits of treatment are judged to outweigh the possible risks. (Safety of the treatment in pregnancy has not been established.)
- (2) Avoid breast feeding while receiving LUMICEF® treatment. (It is unknown whether brodalumab penetrates into breast milk in humans, but animal experiments [monkeys] have indicated penetration into breast milk.)

### 4.7 Effects on ability to drive and use machines

There is no evidence to indicate that treatment with this product alters the ability to drive and use machines.

### 4.8 Undesirable effects

Of all subjects in the Japanese and Europe and the US safety evaluation studies combined (177 Japanese subjects with psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, or psoriatic

erythroderma; 4,625 European and American subjects with psoriasis vulgaris or psoriatic arthritis; a total of 4,802 subjects), adverse reactions (including laboratory data abnormalities) occurred in 1,711 subjects (35.6%). Common adverse reactions (with an incidence of 1.5% or more) were upper respiratory tract infection (5.1%), nasopharyngitis (3.7%), headache (2.1%), arthralgia (2.1%), pruritus (1.9%), fatigue (1.7%), and oral candidiasis (1.6%).

(1) Clinically significant adverse reactions

1) **Serious infection (0.8%)**

Serious viral, bacterial, fungal, or other microbial infections may occur. Observe patients carefully and take appropriate actions when infections are suspected.

2) **Neutrophil count decreased (0.7%)**

Neutrophil count decreased may occur. Observe patients carefully and take appropriate actions such as interrupting or discontinuing treatment when abnormalities are noted.

3) **Serious hypersensitivity (0.02%)**

Serious hypersensitivity such as anaphylaxis may occur. Observe patients carefully; upon noting any abnormalities, immediately discontinue the injection and take appropriate actions.

(2) Other adverse reactions

	≥5%	1% to <5%	<1%
Infection	Upper respiratory tract infection	Nasopharyngitis, candidiasis, sinusitis, bronchitis, influenza, urinary tract infection, herpes infection	Folliculitis, cellulitis, ear infection, tinea, rhinitis, conjunctivitis, herpes zoster
Skin		Pruritus, rash, psoriasis	Dermatitis, alopecia, dry skin, skin papilloma, erythema, hypersensitivity
Musculoskeletal		Arthralgia	Psoriatic arthritis, pain in extremity, myalgia, arthritis, back pain
Gastrointestinal			Nausea, diarrhoea, gastroenteritis, abdominal pain, cheilitis
Respiratory			Cough, oropharyngeal pain
Hepatic		Liver function test abnormal	
Hematologic			White blood cell decreased
Psychoneurotic		Headache	Dizziness, depression, paraesthesia, sleep loss
Others		Injection site reaction (including pain, erythema, haemorrhage, pruritus, swelling, and induration), malaise	Hypertension, weight increased, pyrexia

#### 4.9 Overdose

No serious adverse events have been noted after a single intravenous dose of brodalumab up to 700 mg. In case of an overdosage, observe patients with close attention for signs or symptoms of adverse reactions. Should symptoms develop, promptly administer appropriate symptomatic treatments.

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

#### PHARMACOLOGY

Brodalumab is a monoclonal antibody against human IL-17 receptor A (IL-17RA) that selectively binds to the human IL-17RA and blocks the signaling of the proinflammatory cytokines IL-17A, IL-17F, IL-17A/F heterodimer, IL-25 (also known as IL-17E), and IL-17C with IL-17RA.

##### 1. IL-17RA Inhibitory Effect

- (1) In *in vitro* studies, brodalumab showed a high binding affinity for human IL-17RA and bound to human IL-17RA competitively with human IL-17A.
- (2) In *in vitro* studies, brodalumab bound to the cell surface of human lymphocytes, monocytes, granulocytes, and various human fibroblasts and inhibited IL-17RA-mediated biological activities induced by human IL-17A, IL-17F, IL-17A/F heterodimer, IL-25, and IL-17C stimulations.

##### 2. Effects on Psoriasis

- (1) In a mouse model of psoriasis, the intraperitoneal injection of an anti-mouse IL-17RA antibody inhibited the psoriasis-like skin symptoms (epidermal hyperplasia, intra-epidermal neutrophilic pustule formation, and parakeratotic scaling) and the mRNA expressions for various inflammatory chemokines and cytokines at the sites of skin lesion.
- (1) Brodalumab inhibited the mRNA expressions for IL-17A, IL-17F, IL-17C, IL-12B, and IL-23A, the proliferation of keratinocytes, acanthosis, and the accumulation of inflammatory T-cells (Europe and the US study data) at the site of skin lesion in psoriasis patients.

##### 3. Effects on Arthritis

In a mouse model of inflammatory arthritis, the intraperitoneal injection of an anti-mouse IL-17RA antibody inhibited arthritic symptoms (redness and swelling) in the total paw as well as the associated bone loss and jointcartilage erosion.

#### CLINICAL STUDIES

##### 1. Japanese Double-blind Comparative Study (subjects with psoriasis vulgaris and subjects with psoriatic arthritis)

A randomized, placebo-controlled, double-blind, parallel-group comparative study was conducted in subjects with moderate to severe psoriasis vulgaris and subjects with psoriatic arthritis (with plaque lesions covering  $\geq 10\%$  of body surface area [BSA] and a PASI<sup>Note 1)</sup> score of  $\geq 12$ ). Subjects received either placebo or brodalumab at 70, 140, or 210 mg\* by subcutaneous injection at Weeks 0, 1, and 2 and at 2-week intervals thereafter for 12 weeks. The Week-12 PASI score improvement rates and percentages of subjects achieving an improvement from baseline in PASI score of  $\geq 75\%$ ,  $\geq 90\%$ , and 100% (hereafter, PASI 75/90/100 responses) are shown in the table below. The PASI score improvement rate was significantly higher in the brodalumab-treated groups than in the placebo group. Moreover, the proportion of subjects diagnosed with psoriatic arthritis and who achieved an improvement from baseline in ACR response<sup>Note 2)</sup> of  $\geq 20\%$  (ACR

20) was 0% (0 of 5 subjects) in the placebo group and 100% (4 of 4 subjects) in the 210-mg group.

Note 1) Psoriasis Area and Severity Index

Note 2) A set of criteria defined by the American College of Rheumatology to assess joint symptoms

	Placebo n = 38	70 mg n = 39	140 mg n = 37	210 mg n = 37
PASI score improvement rate (%) <sup>#</sup>				
Mean ± SD	9.4 ± 45.4	37.7 ± 46.8	82.2 ± 28.1	96.8 ± 7.4
Difference from placebo (95% CI)	–	28.3 (12.1, 44.5)	72.8 (56.4, 89.2)	87.3 (70.9, 103.8)
P-value	–	<.001	<.001	<.001
Percentage of PASI 75 responders <sup>##</sup> (n)	7.9% (3/38)	25.6% (10/39)	78.4% (29/37)	94.6% (35/37)
Percentage of PASI 90 responders <sup>##</sup> (n)	2.6% (1/38)	15.4% (6/39)	64.9% (24/37)	91.9% (34/37)
Percentage of PASI 100 responders <sup>##</sup> (n)	0% (0/38)	2.6% (1/39)	35.1% (13/37)	59.5% (22/37)

# Missing data were imputed with the baseline value. The 95% confidence intervals were determined by the analysis of variance. The p-values were determined by the Williams' test.

## Dropouts and withdrawals are included in the analysis set as non-responders.

## 2. Europe and the US Double-blind Comparative Studies (subjects with plaque psoriasis)

A randomized, placebo- and ustekinumab-controlled, double-blind, parallel-group comparative study was conducted in subjects with moderate to severe plaque psoriasis (with plaque lesions covering ≥ 10% BSA and a PASI score of ≥ 12). Subjects received either placebo or brodalumab at 210 mg by subcutaneous injection at Weeks 0, 1, and 2 and at 2-week intervals thereafter for 12 weeks, with the brodalumab treatment continuing up to Week 52. Moreover, ustekinumab (45 mg for those weighing ≤ 100 kg and 90 mg for those weighing > 100 kg) was subcutaneously administered at Weeks 0, 4, 16, 28, and 40. As shown in the table below, the percentages of those achieving a PASI 75/100 response after 12 weeks of treatment were significantly higher in the brodalumab-treated group than those in either the placebo or the ustekinumab group.

	Placebo	Ustekinumab	210 mg
Percentage of PASI 75 responders (n)	6.0% (19/315)	69.3% (217/313)	85.1% (531/624)
95% CI	(3.7, 9.3)	(63.9, 74.4)	(82.1, 87.8)
Difference from placebo (95% CI)	–	–	79.1% (74.4, 83.4), <.001
P-value vs. placebo <sup>#</sup>			

Difference from ustekinumab (95% CI) P-value vs. ustekinumab <sup>#</sup>	–	–	15.8% (9.0, 22.4), 0.007
Percentage of PASI 100 responders (n)	0.3% (1/315)	18.5% (58/313)	36.7% (229/624)
95% CI	(0.0, 1.8)	(14.4, 23.3)	(32.9, 40.6)
Difference from placebo (95% CI) P-value vs. placebo <sup>#</sup>	–	–	36.4% (32.9, 40.6), <.001
Difference from ustekinumab (95% CI) P-value vs. ustekinumab <sup>#</sup>	–	–	18.2% (11.4, 24.8), <.001

Dropouts and withdrawals are included in the analysis set as non-responders.

# P-values were determined by the Cochran-Mantel-Haenszel test stratified by baseline weight ( $\leq 100$  kg,  $> 100$  kg), history of biologic use, region, and baseline PASI score ( $\leq$  median,  $>$  median). The primary and key secondary endpoints were adjusted for multiplicity in the comparisons against the placebo group and the ustekinumab group

### 3. Japanese Study (subjects with pustular psoriasis and subjects with psoriatic erythroderma)

An open-label study was conducted in 12 subjects with pustular psoriasis and 18 subjects with psoriatic erythroderma. Subjects received brodalumab 140 mg by subcutaneous injection at Weeks 0, 1, and 2 and once every 2 weeks thereafter for 52 weeks. If the response at Week 4 or beyond was unsatisfactory, a dose increase to 210 mg was allowed.

Among subjects with pustular psoriasis, “remission” or “improved,” in terms of change from baseline in Clinical Global Impression, was observed in 11 subjects by Week 10. At the final evaluation time point (Week 52 or discontinuation), “remission” was noted in 58.3% (7 of 12), “improved” in 33.3% (4 of 12), and “worsened” in 8.3% (1 of 12) of the subjects. Among subjects with psoriatic erythroderma, the Clinical Global Impression was assessed as “improved” or better across all subjects at Week 4 and beyond, with 66.7% (12 of 18 subjects) achieving “remission” and 33.3% (6 of 18 subjects) achieving “improved” at the final evaluation time point.

### 4. Incidences of malignant tumors (Europe and the US clinical studies)

In the Europe and the US clinical studies conducted in subjects with plaque psoriasis, the incidence of malignant tumors (excluding nonmelanoma skin cancers, the same hereafter) among 4,461 subjects (5,574.01 subject-years) treated with brodalumab was 0.4 per 100 subject-years (23 of 4,461 subjects). The malignant tumors included prostate cancer and adenocarcinoma pancreas, among other tumors. The incidence of malignant tumors was similar to that expected in the general population (standardized incidence rate, 0.91 [95% CI: 0.58, 1.37]). The incidence of nonmelanoma skin cancers was 0.5 per 100 subject-years (28 of 4,461 subjects).

## 5.2 Pharmacokinetic properties

### 1. Serum Concentrations

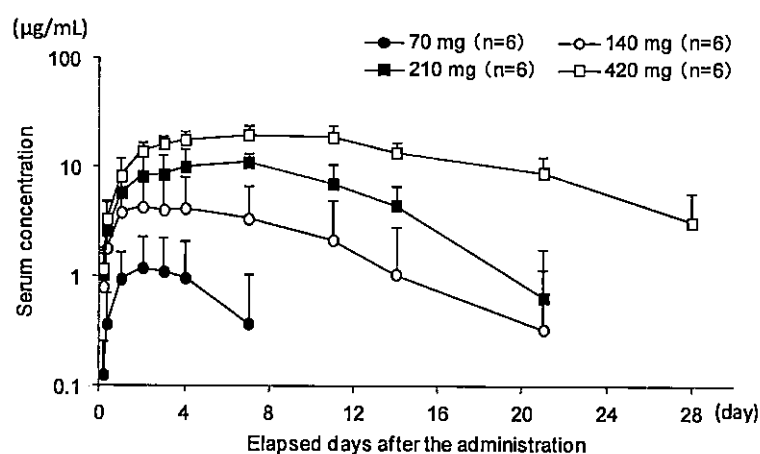
#### (1) Single dose

The time courses of serum concentration and pharmacokinetic parameters in healthy Japanese adults after a single subcutaneous dose of brodalumab at 70, 140, 210, or 420 mg are as



follows.  $C_{max}$  and  $AUC_{0-t}$  increased more than dose-proportionally, indicating that brodalumab has a nonlinear pharmacokinetic profile.

#### Time courses of serum concentration (mean + SD)



#### Pharmacokinetic parameters after single subcutaneous dose

Dose	n	$t_{max}$ (day)	$C_{max}$ (µg/mL)	$AUC_{0-t}$ (µg·day/mL)
70 mg	6	1.00 (1.00, 2.99)	1.30 ± 1.10	5.40 ± 6.24
140 mg	6	2.00 (1.00, 4.00)*	4.48 ± 3.99	53.2 ± 47.6*
210 mg	6	4.00 (4.00, 7.00)	10.0 ± 4.7	119 ± 58
420 mg	6	7.00 (4.00, 10.99)	21.6 ± 5.2	349 ± 80

Mean ± SD ( $t_{max}$  is shown as medians [min, max])

\*: n = 5

#### (2) Repeated doses

The Weeks 8 to 10 pharmacokinetic parameters in Japanese subjects with moderate to severe plaque psoriasis who received brodalumab subcutaneously at 70, 140, or 210 mg as the initial dose, once every week up to Week 2, and once every 2 weeks thereafter are as follows.

#### Weeks 8 to 10 pharmacokinetic parameters after repeated subcutaneous doses

Dose	n	$t_{max}$ (day)	$C_{max}$ (µg/mL)	$AUC_{0-\tau}$ (µg·day/mL)
70 mg	15	2.93 (1.96, 4.16)	2.34 ± 1.71	14.3 ± 12.9
140 mg	15	3.22 (1.84, 7.02)	5.97 ± 3.60	56.1 ± 49.6

Dose	n	$t_{max}$ (day)	$C_{max}$ ( $\mu\text{g/mL}$ )	$AUC_{0-\tau}$ ( $\mu\text{g}\cdot\text{day/mL}$ )
210 mg	11	2.90 (1.90, 6.92)	27.3 $\pm 11.1$	319 $\pm$ 136

Mean  $\pm$  SD ( $t_{max}$  is shown as medians [min, max])

## 2. Distribution

Based on the results of a population pharmacokinetic analysis, the volume of distribution of brodalumab was estimated to be approximately 6.52 L, indicating that non-plasma distributions are limited.

## 5.3 Preclinical safety data

No single dose toxicity studies were conducted. In the repeat-dose toxicity studies in cynomolgus monkeys and a dose-range finding for an embryo-fetal developmental toxicity study in rabbits, no toxicity was observed after the first dose (up to 350 mg/kg).

In repeat-dose toxicity studies in cynomolgus monkeys, brodalumab was repeatedly administered once weekly for 1 month (up to 350 mg/kg), 3 months (up to 350 mg/kg), and 6 months (up to 90 mg/kg). Brodalumab was well-tolerated in cynomolgus monkeys. Brodalumab-related effects included only injection site reactions, and slight to mild dermatitis and glossitis.

No genotoxicity studies were conducted. No carcinogenicity studies of brodalumab were conducted, because brodalumab does not cross-react with rodent receptors. Based on comprehensive review on reported findings, brodalumab was considered unlikely to have a carcinogenetic risk either directly or indirectly.

In a 6-month repeat-dose toxicity study in sexually matured cynomolgus monkeys, no effects of brodalumab on sperm (motility, density, and morphology), or male or female reproductive organs were observed at doses up to 90 mg/kg (highest dose). In pregnant cynomolgus monkeys which received brodalumab at a dose of 90 mg/kg (highest dose) from gestation day 20-22 to delivery throughout the pregnancy period including the organogenesis phase, none of the toxicity in dams and brodalumab-related effects on maternal function, and embryo-fetal and infant development (including immune function) up to 6 months post-partum were observed.

A single-subcutaneous-dose local tolerance study in rabbits was conducted. As a result, local irritation reactions (edema and erythema) at the injection site were observed, but a resolving trend was observed at 72 hours post-dose. The local irritation reaction at the injection site was considered to be a non-specific change attributable to the protein load injected locally but not a change attributable to the pharmacological action of brodalumab.

In all of the toxicity studies, brodalumab was well-tolerated in cynomolgus monkeys. Brodalumab-related effects were injection site reactions, and dermatitis and glossitis. Dermatitis and glossitis were considered as consequences of the pharmacologic action of brodalumab on host immunomodulation on commensal microorganisms on the skin and tongue.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

L-Glutamic acid, L-Proline, Polysorbate 20, and Water for injections

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

Store protected from light at 2°C to 8°C

**6.5 Nature and contents of container**

1.5 ml solution in a type I glass pre-filled syringe with stainless steel 27G x ½" needle, covered with an elastomeric needle cap.

**6.6 Special precautions for disposal and other handling****Route of administration**

Use LUMICEF® only by subcutaneous administration.

**Administration**

1. Before use, remove from the refrigerator and return to room temperature.
2. Do not inject areas of the skin that are sensitive or abnormal (scratch, redness, sclerosis, thickness, scaling, or other abnormalities), or sites of psoriasis.
3. It is recommended to administer the injection to the thigh, abdomen, or upper arm. Avoid repeated injections to the same site; use a different injection site for each injection.
4. LUMICEF® is a single-use formulation; never reuse.

**Handling**

1. To avoid light exposure, store LUMICEF® in its outer box. Moreover, continue to store protected from light even after the outer box has been opened.
2. Use immediately after opening the blister pack.

**7. Marketing Authorization Holder**

Kyowa Hakko Kirin (Thailand) Co., Ltd. Bangkok.

**8. Marketing Authorization Numbers**

XXXX

**9. Date of First Authorization**

XXXX

**10. DATE OF REVISION OF THE TEXT**

July 2018 (version 1)