ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Kyntheum 210 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 210 mg brodalumab in 1.5 ml solution.
1 ml solution contains 140 mg brodalumab.

Brodalumab is a human monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

The solution is clear to slightly opalescent, colourless to slightly yellow and free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kyntheum is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy.

4.2 Posology and method of administration

Kyntheum is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis.

Posology

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

Consideration should be given to discontinuing treatment in patients who have shown no response after 12-16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Elderly (aged 65 years and over)
No dose adjustment is recommended in elderly patients (see section 5.2).

Renal and hepatic impairment
Kyntheum has not been studied in these patient populations. No dose recommendations can be made.

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

Method of administration

Kyntheum is administered by subcutaneous injection. Each pre-filled syringe is for single use only. Kyntheum should not be injected into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by psoriasis. The pre-filled syringe must not be shaken.

After proper training in subcutaneous injection technique, patients may self-inject Kyntheum when deemed appropriate by a physician. Patients should be instructed to inject the full amount of Kyntheum according to the instructions provided in the package leaflet. Detailed instructions for use are included at the end of the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active Crohn's disease.

Clinically important active infections (e.g. active tuberculosis, see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Inflammatory bowel disease (including Crohn's disease and ulcerative colitis)

Cases of new or exacerbations of inflammatory bowel disease have been reported with IL-17 inhibitors. Therefore, brodalumab is not recommended in patients with inflammatory bowel disease (see section 4.8). If a patient develops signs and symptoms of inflammatory bowel disease, or experiences an exacerbation of pre-existing inflammatory bowel disease, treatment should be discontinued and appropriate medical management should be initiated.

Suicidal ideation and behaviour

Suicidal ideation and behaviour, including completed suicide, have been reported in patients treated with brodalumab. The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour. A causal association between treatment with brodalumab and increased risk of suicidal ideation and behaviour has not been established.

The risk and benefit of treatment with brodalumab should be carefully weighed for patients with a history of depression and/or suicidal ideation or behaviour, or for patients who develop such symptoms. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal ideation, anxiety, or other mood changes, and they should contact their healthcare provider if such events occur. If a patient suffers from new or worsening symptoms of depression and/or suicidal ideation or behaviour is identified, it is recommended to discontinue treatment.

Hypersensitivity reactions

Rare cases of anaphylactic reactions have been reported in the post-marketing setting. In the event of an anaphylactic reaction, or any other serious allergic reaction, administration of brodalumab should be discontinued and appropriate therapy initiated.

Infections

Brodalumab may increase the risk of infections.

During the 12-week placebo-controlled clinical trial period in patients with psoriasis, serious infections were observed in 0.5% of patients receiving brodalumab (see section 4.8).

Caution should be exercised when considering the use of brodalumab in patients with a chronic infection or a history of recurrent infection. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and brodalumab should not be administered until the infection resolves.

Brodalumab should not be given to patients with active tuberculosis. Anti-tuberculosis therapy should be considered prior to initiation of treatment in patients with latent tuberculosis.

Vaccinations

It is recommended that patients be brought up-to-date with all immunisations in accordance with local immunisation guidelines prior to initiation of treatment. Live vaccines should not be given concurrently with brodalumab (see section 4.5). No data are available on the response to live vaccines or the risk of infection, or transmission of infection after the administration of live vaccines in patients receiving brodalumab.

Vaccination of infants
Vaccination of infants with live vaccines following third trimester exposure to brodalumab should be discussed with a physician (see also section 4.6).

Concomitant immunosuppressive therapy

The safety and efficacy of brodalumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated.

4.5 Interaction with other medicinal products and other forms of interaction

Live vaccines should not be given concurrently with brodalumab (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, TNFα, 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 brodalumab.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use an effective method of contraception during treatment and for at least 12 weeks after treatment.

Pregnancy

There are no or limited amount of data from the use of brodalumab in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Human IgG2 is known to cross the placental barrier and brodalumab is a human IgG2, therefore, brodalumab has the potential to be transmitted from the mother to the developing foetus. As a precautionary measure, it is preferable to avoid the use of Kyntheum in pregnancy.

As the metabolism of brodalumab is unknown in infants, benefit risk for exposure of the infant to live vaccines following third trimester exposure to Kyntheum should be discussed with a physician.

Breast-feeding

It is unknown whether brodalumab is excreted in human milk. Brodalumab is a monoclonal antibody and is expected to be present in the first milk and at low levels afterwards.

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Kyntheum therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No data are available on the effect of brodalumab on human fertility. Animal studies did not show any effects on male and female reproductive organs and on sperm count, motility and morphology (see section 5.3).

4.7 Effects on ability to drive and use machines

Kyntheum has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are arthralgia (4.6%), headache (4.3%), fatigue (2.6%), diarrhoea (2.2%), and oropharyngeal pain (2.1%).

Tabulated list of adverse reactions

Adverse reactions from clinical trials and post-marketing experience (Table 1) are listed by MedDRA system organ class (SOC). Within each SOC, the adverse reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse reaction is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping adverse reactions are presented in order of decreasing seriousness.

Table 1: List of adverse reactions in clinical trials and post-marketing experience

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Common	Influenza Tinea infections (including tinea pedis, tinea versicolor, tinea cruris)
	Uncommon	Candida infections (including oral, genital, and oesophageal infections)
Blood and lymphatic system disorders	Uncommon	Neutropenia
Immune system disorders	Rare	Anaphylactic reaction
Nervous system disorders	Common	Headache
Eye disorders	Uncommon	Conjunctivitis
Respiratory, thoracic and mediastinal disorders	Common	Oropharyngeal pain
Gastrointestinal disorders	Common	Diarrhoea Nausea
Musculoskeletal and connective tissue disorders	Common	Arthralgia Myalgia
General disorders and administration site conditions	Common	Fatigue Injection site reactions (including injection site erythema, pain, pruritus, bruising, haemorrhage)
Skin and subcutaneous tissue disorders	Not known	Pyoderma gangrenosum

Description of selected adverse reactions

Inflammatory bowel disease
Cases of new or exacerbations of inflammatory bowel disease (including Crohn's disease and ulcerative colitis) have been reported with IL-17 inhibitors (see section 4.4).

Infections
During the 12-week placebo-controlled trial period in plaque psoriasis, infections were reported in 28.2% of patients treated with brodalumab compared with 23.4% of patients treated with placebo. The majority of infections consisted of nasopharyngitis, upper respiratory tract infection, pharyngitis, urinary tract infections, bronchitis, influenza and sinusitis, which did not necessitate treatment discontinuation. Serious infections occurred in 0.5% of patients treated with brodalumab and in 0.1% of patients treated with placebo. Higher rates of fungal infections, primarily non-serious skin and mucosal candida infections, were observed in brodalumab patients compared to placebo patients, 2.5% vs 1.0%, respectively.

Through week 52, the event rates per 100 patient-years for infections were 134.7 for patients treated with brodalumab and 124.1 for patients treated with ustekinumab. The event rates per 100 patient-years for serious infections were 2.4 for patients treated with brodalumab and 1.2 for patients treated with ustekinumab. One serious case of cryptococcal meningitis and one serious case of coccidioidies infection were observed in clinical trials (see section 4.4).

Neutropenia
During the 12-week placebo-controlled period of clinical trials, neutropenia was reported in 0.9% of patients treated with brodalumab compared with 0.5% of patients treated with placebo. Most of the brodalumab-associated neutropenias were mild, transient and reversible.

Neutropenia Grade 3 ($<1.0 \times 10^9$/L to 0.5×10^9/L) was reported in 0.5% of patients receiving brodalumab compared to none of the patients who received ustekinumab or placebo. No Neutropenia Grade 4 ($<0.5 \times 10^9$/L) was reported in patients who received either brodalumab or placebo, but in 0.2% of patients who received ustekinumab. No serious infections were associated with neutropenia.

Immunogenicity
Antibodies to brodalumab developed in 2.2% (88/3935) of patients treated with brodalumab for up to 52 weeks in psoriasis clinical trials (0.3% of the patients had anti-brodalumab antibodies at baseline). Of these patients, none had neutralising antibodies.

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with anti-brodalumab antibody development.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Doses up to 700 mg intravenously have been administered in clinical trials with no evidence of dose limiting toxicity. In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors, ATC code: L04AC12

Mechanism of action

Brodalumab is a recombinant fully human monoclonal immunoglobulin IgG2 antibody that binds with high affinity to human IL-17RA and blocks the biological activities of the pro-inflammatory cytokines IL-17A, IL-17F, IL-17A/F heterodimer, IL-17C and IL-17E (also known as IL-25), resulting in inhibition of the inflammation and clinical symptoms associated with psoriasis. IL-17RA is a protein expressed on the cell surface and is a required component of receptor complexes utilised by multiple IL-17 family cytokines. IL-17 family cytokine levels have been reported to be increased in psoriasis. IL-17A, IL-17F and IL-17A/F heterodimer have pleiotropic activities including the induction of pro-inflammatory mediators such as IL-6, GROα, and G-CSF from epithelial cells, endothelial cells and fibroblasts that promote tissue inflammation. IL-17C has been shown to induce similar responses as IL-17A and IL-17F in keratinocytes. Blocking IL-17RA inhibits IL-17 cytokine-induced responses resulting in normalisation of inflammation in the skin.

Pharmacodynamic effects

Elevated levels of IL-17A, IL-17C and IL-17F gene expression are found in psoriatic plaques. Elevated levels of expression of IL-12B and IL-23A, the genes for the two subunits of IL-23, an upstream activator of IL-17A and IL-17F expression, are also found in psoriatic plaques. Treatment with brodalumab in psoriasis patients has been shown to decrease levels of IL-17A and markers of cell proliferation and epidermal thickness in lesional skin biopsies to non-lesional skin biopsy levels up to 12 weeks post-treatment.

Clinical efficacy and safety

The efficacy and safety of brodalumab was assessed in 4373 adult plaque psoriasis patients across three multinational, randomised, double-blind, phase 3, placebo-controlled clinical trials (AMAGINE-

1, AMAGINE-2, and AMAGINE-3). AMAGINE-2 and AMAGINE-3 were also active comparator (ustekinumab)-controlled. All three trials included a 12-week placebo-controlled induction phase, a double-blind duration of 52 weeks, and an open-label long-term extension.

Patients enrolled were candidates for systemic therapy, including phototherapy, biologic and non-biologic systemic therapies. Approximately 21% of patients had a history of psoriatic arthritis. Approximately 30% of patients had previously received a biological and 13% of patients were biological failures.

Patients were predominantly men (70%) and white (91%), with a mean age of 45 years (18 to 86 years), of these 6.4% were ≥65 years of age and 0.3% were >75 years of age. Across treatment groups, the baseline Psoriasis Area Severity Index (PASI) score ranged from 9.4 to 72 (median: 17.4) and baseline involved body surface area (BSA) ranged from 10 to 97 (median: 21). Baseline static Physician Global Assessment (sPGA) score ranged from "3 (moderate)" (58%) to "5 (very severe)" (5%).

AMAGINE-1 was conducted in 661 patients. The trial included a 12-week double-blind, placebo-controlled induction phase followed by a double-blind withdrawal and retreatment phase up to 52 weeks. Patients randomised to brodalumab received 210 mg or 140 mg at Week 0 (day 1), Week 1, and Week 2 followed by same dose every 2 weeks. At Week 12, patients originally randomised to brodalumab who achieved sPGA success (0 or 1) were re-randomised to receive either placebo or continued brodalumab at their induction dose. Patients originally randomised to placebo and those who did not meet the criteria for re-randomisation received brodalumab 210 mg every two weeks beginning at Week 12. Retreatment was available at or after Week 16 for patients with return of disease and rescue treatment was available after 12 weeks of retreatment.

AMAGINE-2 and AMAGINE-3 were identical placebo- and ustekinumab-controlled trials conducted in 1831 and 1881 patients, respectively. Both trials included a 12-week double-blind, placebo- and ustekinumab-controlled induction phase followed by a double-blind maintenance phase up to 52 weeks. Patients randomised to brodalumab in the induction phase received 210 mg or 140 mg at Week 0 (day 1), Week 1, and Week 2 followed by same dose every 2 weeks. Patients randomised to ustekinumab received 45 mg for patients ≤100 kg and 90 mg for patients >100 kg at Weeks 0, 4, and 16 followed by same dose every 12 weeks. At Week 12, patients originally randomised to brodalumab were re-randomised to receive either 210 mg every 2 weeks, or 140 mg every 2 weeks, or 140 mg every 4 weeks, or 140 mg every 8 weeks during the maintenance phase. Patients originally randomised to placebo received brodalumab 210 mg every 2 weeks beginning at Week 12. At Week 12, patients in the ustekinumab group continued to receive ustekinumab and then were switched to brodalumab 210 mg every 2 weeks at Week 52. Rescue treatment was available at or after Week 16 for patients with an inadequate response single sPGA ≥3 or persistent sPGA of 2 over at least a 4-week period.

Table 2: Overview of the main efficacy results

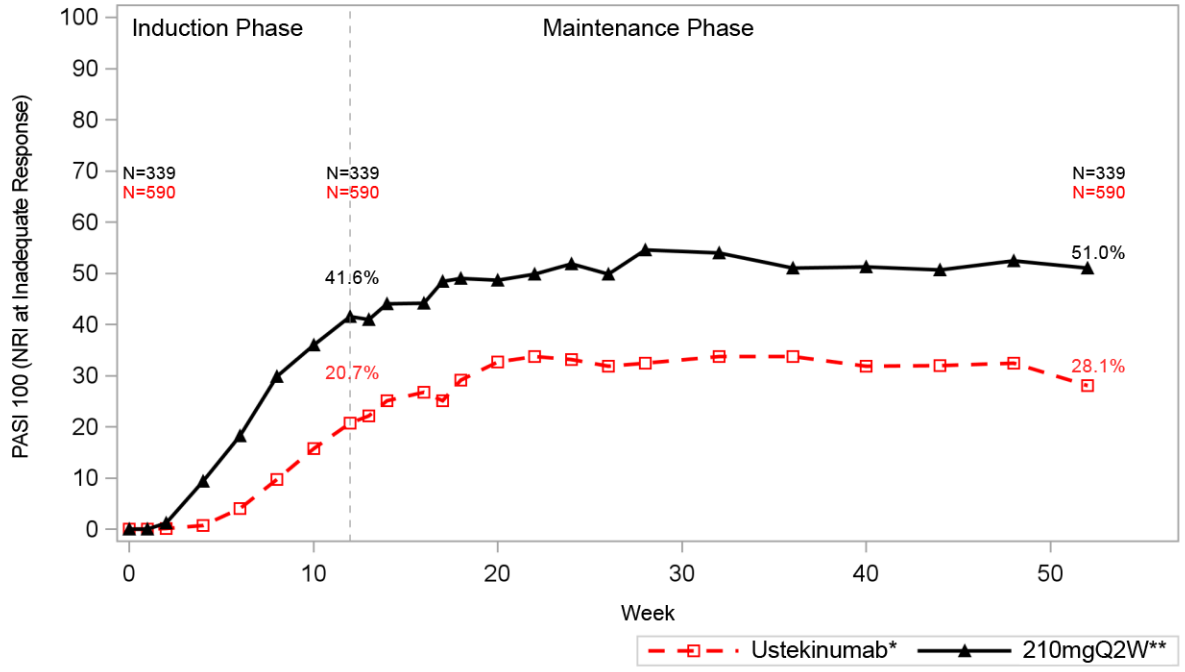
	AMAGINE-1		AMAGINE-2 and AMAGINE-3		
	Placebo	Brodalumab 210 mg Q2W	Placebo	Brodalumab 210 mg Q2W	Ustekinumab
$n_{\text{-randomised}}$	220	222	624	1236	613
$n_{\text{-completed Week 12}}$	209	212	601	1205	594
$n_{\text{-in maintenance}}$	84	83	NA	339	590
$n_{\text{-completed Week 52}}$	2	74	NA	236	300
PASI					
PASI $_{\text{Baseline score}}$ (mean±SD)	19.7±7.7	19.4±6.6	20.2±8.4	20.3±8.3	20.0±8.4
PASI 75 Week 12 (%)	3	83*	7	86*	70*
PASI 75 Week 52 (%)	0	87*	NA	65	48
sPGA (%)					
sPGA 0 or 1 Week 12	1	76*	4	79*	59*
sPGA 0 or 1 Week 52	0	83*	NA	65	45
PSI					
$PSI_{\text{Baseline score}}$ (mean±SD)	19.0±6.7	18.9±6.7	18.8±6.9	18.7±7.0	18.8±6.9
$PSI_{\text{responder Week 12}}$ (%)	4	61*	7	64*	54*

Q2W = every 2 weeks
PSI = Psoriasis Symptom Inventory. PSI responder: total score ≤8 with no item scores >1; SD: standard deviation.

Non-responder imputation is used to impute missing data.
Due to re-randomisation to other explored dose regimens, n-in maintenance is substantially lower than n-randomised in several arms. The maintenance phase in AMAGINE-2 and -3 did not include placebo.
*p-value vs. corresponding placebo, adjusted for stratification factors <0.001

PASI 75 response at 2 weeks ranged between 20% and 25% in the Phase 3 trials compared to placebo (0% to 0.6%) and ustekinumab (3% to 3.5%).

Figure 1: PASI 100 during induction and maintenance phase for brodalumab and ustekinumab (AMAGINE-2 and AMAGINE-3, pooled)



N = number of patients, which are presented at baseline, Week 12, and Week 52
Q2W = every 2 weeks
*Patients were administered ustekinumab in the induction phase and continued on ustekinumab in the maintenance phase
**Patients were administered brodalumab 210 mg every 2 weeks in the induction phase and re-randomised to brodalumab 210 mg every 2 weeks in the maintenance phase
NRI= Non-responder imputation

In all three clinical trials, examination of age, gender, race, use of prior systemic or photo therapy, use of prior biologics, and biologic failures did not identify differences in response in all key endpoints [PASI 75, PASI 100, sPGA success (0 or 1), and sPGA clear (0)] to brodalumab among these subgroups.

Along with primary efficacy endpoints, clinically important improvements were observed in Psoriasis Scalp Severity Index (PSSI) at Week 12 (AMAGINE-1) and in Nail Psoriasis Severity Index (NAPSI) at Week 12 and 52 (AMAGINE-1,-2, and -3).

Quality of life/patient reported outcomes
The proportion of patients who achieved a Psoriasis Symptom Inventory (PSI) score of 0 (not at all) or 1 (mild) on every item (itch, burning, stinging, pain, redness, scaling, cracking and flaking) at Week 12 are shown in Table 2.

The percentage of patients that at Week 12 achieved a DLQI (Dermatology Life Quality Index) score of 0 or 1 was 56%, 61%, 59% in the brodalumab 210 mg group and 5%, 5%, 7% in the placebo group in AMAGINE-1, -2 and -3, respectively (adjusted p-value <0.001) and 44% in the ustekinumab groups (AMAGINE-2 and -3).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with brodalumab in one or more subsets of the paediatric population in plaque psoriasis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Based on population pharmacokinetic modelling, the estimated accumulation ratio after 20 weeks of dosing is 2.5-fold. In moderate to severe plaque psoriasis patients following a single subcutaneous administration of brodalumab at 210 mg, the mean maximum serum concentration (C_{max}) was 13.4 mcg/ml (standard deviation [SD] = 7.29 mcg/ml). The median time to maximum concentration (T_{max}) was 3.0 days (range: 2.0 to 4.0 days) and the mean area under the concentration time curve to the last measurable concentration (AUC_{last}) was 111 mcg*day/ml (SD = 64.4 mcg*day/ml). The subcutaneous bioavailability of brodalumab estimated by population pharmacokinetic modelling was 55%.

The observed pharmacokinetic parameters during steady-state (weeks 10-12) were: mean steady-state area under the concentration time curve over the dosing interval (AUC_{tau}) was 227.4 mcg*day/ml (SD = 191.7 mcg*day/ml) corresponding to average concentration ($C_{av,ss}$) of 16.2 mcg/ml, mean C_{max} was 20.9 mcg/ml (SD = 17.0 mcg/ml) and Week 12 mean minimum serum concentration (C_{trough}) was 9.8 mcg/ml (SD = 11.2 mcg/ml).

Distribution

Based on population pharmacokinetic modelling, the estimated mean steady-state volume of distribution of brodalumab was approximately 7.24 L.

Biotransformation

As an IgG2 human monoclonal antibody brodalumab is expected to be degraded into small peptides and amino acids via catabolic pathways in a manner similar to endogenous IgG.

Elimination

Following subcutaneous administrations of 210 mg, brodalumab exhibits non-linear pharmacokinetics typical for a monoclonal antibody that undergoes target-mediated drug disposition.

Brodalumab clearance decreases with increasing dose and exposure increases in a greater than dose-proportional manner. For a 3-fold increase in SC brodalumab dose from 70 to 210 mg, the steady-state serum brodalumab C_{max} and AUC_{0-t} increased approximately 18- and 25-fold, respectively.

Following a single subcutaneous administration of brodalumab 210 mg in plaque psoriasis patients, the apparent clearance (CL/F) is 2.95 L/day.

Population pharmacokinetic modelling predicted that serum brodalumab concentrations dropped below the quantification limit (0.05 mcg/ml) 63 days after discontinuation of steady-state dosing of brodalumab 210 mg administered every 2 weeks in 95% of the patients. However, brodalumab concentrations below LLOQ (Lower Limit of Quantification) were associated with IL-17 receptor occupancy up to 81%.
Based on population pharmacokinetic modelling the estimated half-life of brodalumab was 10.9 days at steady-state after every other week subcutaneous dose of 210 mg.

Impact of weight on pharmacokinetics

Population pharmacokinetic modelling indicated that exposure decreased as body weight increased. No dose adjustment is recommended.

Elderly patients

Population pharmacokinetic modelling indicated that age did not have an effect on brodalumab pharmacokinetics, which was co-based on 259 (6%) patients being 65-74 years old and on 14 (0.3%) patients being ≥75 years old, within a total PK population of 4271 plaque psoriasis patients.

Renal or hepatic impairment

No pharmacokinetic data are available in patients with impaired renal or hepatic function. Renal elimination of intact brodalumab, an IgG monoclonal antibody, is expected to be low and of minor consequence. Brodalumab is expected to be mainly eliminated via catabolism and hepatic impairment is not expected to influence clearance.

Other populations

The pharmacokinetics of brodalumab was similar between Japanese and non-Japanese patients with psoriasis.

Population pharmacokinetic analysis indicated that gender did not have an effect on brodalumab pharmacokinetics.

Pharmacokinetic/pharmacodynamic relationship(s)

A population pharmacokinetic/pharmacodynamic model, developed using all available data indicated that at a dose of 210 mg every 2 weeks, 90% of all patients would be predicted to maintain a trough concentration greater than the estimated IC_{90} value of 1.51 mcg/ml. Based on an exploratory descriptive analysis, no relationship was observed between exposure and incidence of serious infections and infestations, candida infections, viral infections, and suicidal ideation and behaviour events. Exposure-response analysis indicates that higher brodalumab concentrations are related to better PASI and sPGA response.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity (including safety pharmacology endpoints and assessment of fertility-related endpoints), and toxicity to reproduction and development.

Carcinogenicity studies with brodalumab have not been conducted. However, there were no proliferative changes in cynomolgus monkeys administered weekly subcutaneous doses of brodalumab at 90 mg/kg for 6 months (AUC exposure 47-fold higher than in human patients receiving brodalumab 210 mg every 2 weeks). The mutagenic potential of brodalumab was not evaluated; however, monoclonal antibodies are not expected to alter DNA or chromosomes.

In cynomolgus monkeys there were no effects on male and female reproductive organs and on sperm count, motility and morphology following administration of brodalumab at dose levels up to 90 mg/kg once weekly for 6 months, (AUC exposure up to 47-fold higher than in human patients receiving brodalumab 210 mg every 2 weeks).

In cynomolgus monkeys, no effects on embryo-foetal or postnatal (up to 6 months of age) development were observed when brodalumab was dosed subcutaneously throughout pregnancy at exposure levels up to 27-fold higher than those achieved in human patients receiving brodalumab 210 mg every 2 weeks based on the area under the concentration curve (AUC). Serum concentrations

in monkey infants and in foetal rabbits indicated considerable passage of brodalumab from the mother to the foetus at the end of pregnancy.

In cynomolgus monkeys, after weekly subcutaneous dosing of brodalumab at dose levels up to 90 mg/kg for 6 months, brodalumab-related effects were limited to injection site reactions and mucocutaneous inflammation that was consistent with pharmacologic modulation of host surveillance to commensal microflora. There were no effects on peripheral blood immunophenotyping and the T-cell dependent antibody response assay. In a local tolerance test in rabbits, moderate to severe edema was observed after subcutaneous injection of a formulation containing brodalumab at the clinical concentration of 140 mg/ml.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Proline
Glutamate
Polysorbate 20
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

4 years

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

Kyntheum may be stored at room temperature (up to 25°C) once, in the outer carton, for a maximum single period of 14 days. Once Kyntheum has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 14 days or discarded.

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.

Kyntheum is available in unit packs containing 2 pre-filled syringes and in multipacks containing 6 (3 packs of 2) pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

To avoid discomfort at the site of injection, at least 30 minutes should be allowed for the pre-filled syringe to reach room temperature before injecting. The pre-filled syringe should not be warmed in any other way. The pre-filled syringe should not be shaken. The needle cap on the pre-filled syringe should not be removed while allowing to reach room temperature.

Kyntheum should be visually inspected for particles and discoloration prior to administration. This medicinal product should not be used if the solution is cloudy or discoloured or contains lumps, flakes, or particles.

The pre-filled syringe should not be used if it has been dropped on a hard surface.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1155/001
EU/1/16/1155/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 July 2017
Date of latest renewal: 25 April 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Immunex Rhode Island Corporation
40 Technology Way, West Greenwich,
Rhode Island, 02817
United States

Name and address of the manufacturers responsible for batch release

Laboratoires LEO
39 route de Chartres
28500 Vernouillet
France

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Kyntheum 210 mg solution for injection in pre-filled syringe
brodalumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 210 mg brodalumab in 1.5 ml solution (140 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: proline, glutamate, polysorbate 20 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

2 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use
For single use only
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the outer package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1155/001 Pack containing 2 pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kyntheum 210 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kyntheum 210 mg solution for injection in pre-filled syringe
brodalumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 210 mg brodalumab in 1.5 ml solution (140 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: proline, glutamate, polysorbate 20 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 6 (3 packs of 2) pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use
For single use only
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the outer package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1155/002 Multipack containing 6 (3 x 2) pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kyntheum 210 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kyntheum 210 mg solution for injection in pre-filled syringe
brodalumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 210 mg brodalumab in 1.5 ml solution (140 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: proline, glutamate, polysorbate 20 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

2 pre-filled syringes. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use
For single use only
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the outer package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1155/002 Multipack containing 6 (3 x 2) pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kyntheum 210 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kyntheum 210 mg injection
brodalumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Kyntheum 210 mg solution for injection in pre-filled syringe
brodalumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Kyntheum is and what it is used for
2. What you need to know before you use Kyntheum
3. How to use Kyntheum
4. Possible side effects
5. How to store Kyntheum
6. Contents of the pack and other information

1. What Kyntheum is and what it is used for

Kyntheum contains the active substance brodalumab. Brodalumab is a monoclonal antibody, a specialised type of protein that recognises and attaches to certain proteins in the body.

Brodalumab belongs to a group of medicines called interleukin (IL) inhibitors. This medicine works by blocking the activity of IL-17 proteins, which are present at increased levels in diseases such as psoriasis.

Kyntheum is used to treat a skin condition called "plaque psoriasis", which causes inflammation and scaly plaque formation on the skin. Kyntheum is used in adults with moderate to severe plaque psoriasis affecting large areas of the body.

Using Kyntheum will benefit you by leading to improvements of skin clearance and reducing psoriasis signs and symptoms, such as itch, redness, scaling, burning, stinging, cracking, flaking and pain.

2. What you need to know before you use Kyntheum

Do not use Kyntheum
- if you are allergic to brodalumab or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice before using Kyntheum
- if you have active Crohn's disease
- if you have an infection which your doctor thinks is important (for example, active tuberculosis).

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before using Kyntheum:
- if you have an inflammatory disease affecting the gut named Crohn's disease
- if you have an inflammation of the large intestine named ulcerative colitis
- if you have ever had or are having suicidal thoughts or actions, depression, anxiety, or mood problems
- if you have an infection now or often get infections

- if you have a long-term (chronic) infection
- if you have tuberculosis (TB), have had a positive TB test, or have been in close contact with someone with TB. You may be treated with another medicine for TB before you begin treatment with Kyntheum
- if you have recently received or are scheduled to receive a vaccination. You should not be given certain types of vaccines (called 'live vaccines') while being treated with Kyntheum
- if you have used Kyntheum during the last three months of your pregnancy, you should talk to your doctor before vaccinating your baby
- if you are receiving any other treatment for psoriasis, such as another immunosuppressant or phototherapy with ultraviolet (UV) light.

After starting Kyntheum, tell your doctor, pharmacist or nurse immediately:
- if you have been told by your doctor that you have developed Crohn's disease
- if you feel depressed, anxious, or have thoughts of suicide, or have unusual mood changes
- if you have an infection or have any signs of infection listed in Section 4 "Possible side effects"
- if you have been told you have tuberculosis.

Inflammatory bowel disease (Crohn's disease or ulcerative colitis)
Stop using Kyntheum and tell your doctor or seek medical help immediately if you notice abdominal cramps and pain, diarrhoea, weight loss or blood in the stool (any signs of bowel problems).

Look out for allergic reactions
Kyntheum can potentially cause serious side effects, including allergic reactions. You must look out for signs of these conditions while you are taking Kyntheum.

Stop using Kyntheum and tell your doctor or seek medical help immediately if you notice any signs indicating an allergic reaction. Such signs are listed under "Serious side effects" in section 4.

Children and adolescents
Kyntheum is not recommended for children and adolescents (below 18 years of age) because it has not been studied in this age group.

Other medicines and Kyntheum
Tell your doctor or pharmacist:
- if you are taking, have recently taken or might take any other medicines.
- if you have recently had or you or your baby are going to have a vaccination, see "Warnings and precautions" in section 2 "What you need to know before using Kyntheum".

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Kyntheum has not been tested in pregnant women and it is not known if this medicine can harm your unborn baby. It is therefore preferable to avoid the use of Kyntheum during pregnancy. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and should use adequate contraception while using Kyntheum and for at least 12 weeks after the last dose of Kyntheum.

It is not known whether brodalumab passes into breast milk. Tell your doctor if you are breast-feeding or plan to breast-feed. Your doctor will then help you decide whether to stop breast-feeding or stop using Kyntheum. Together you will consider the benefit of breast-feeding to the baby and the benefit of Kyntheum to you.

Driving and using machines
Kyntheum is unlikely to affect your ability to drive and use machines.

3. How to use Kyntheum

Kyntheum should be prescribed to you by a doctor with experience in diagnosing and treating psoriasis.

Always use this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much Kyntheum is given
- Your doctor will decide how much Kyntheum you need and for how long. The recommended dose is 210 mg (one injection).
- After the first dose you will need to have a weekly injection at Week 1 (one week after the first dose) and Week 2 (two weeks after the first dose). After that, you will need to have an injection every two weeks.
- Kyntheum is for long-term treatment. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect. Tell your doctor if you think your signs and symptoms of psoriasis are not improving after using Kyntheum.

How is Kyntheum given
Kyntheum is given as an injection under the skin (known as a subcutaneous injection).

Self-administration instructions
See the detailed "Instructions for Use" that comes with this medicine for information on the right way to store, prepare, and give your injections at home.
- If your doctor decides that you or a caregiver can give the injections at home, you or your caregiver should receive training on the right way to prepare and inject Kyntheum. Do not try to inject Kyntheum until you or your caregiver have been shown how to inject Kyntheum by your doctor or nurse.
- Do not shake the pre-filled syringe before use.
- Kyntheum is injected in your upper legs (thighs) or stomach area (abdomen) by you or a caregiver. A caregiver may also give you an injection in your upper, outer arm.
- Do not inject into an area of the skin that is tender, bruised, red, hard or in an area of skin that is affected by psoriasis.

If you use more Kyntheum than you should
If you use more of this medicine than prescribed or take the dose sooner than required, tell your doctor.

If you forget to use Kyntheum
If you have forgotten to inject a dose of Kyntheum, inject the next dose as soon as you can after the missed dose. Then, talk to your doctor about when you should inject the next dose. Do not take a double dose to make up for a forgotten dose.

If you stop using Kyntheum
You should not stop using Kyntheum without speaking to your doctor first. If you stop treatment, symptoms of psoriasis may come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Stop using Kyntheum and tell your doctor or seek medical help immediately if you get any of the following side effects. Your doctor will decide if and when you may restart the treatment:

Serious allergic reaction (may affect up to 1 in 1,000 people), the signs may include:
- difficulty breathing or swallowing
- low blood pressure, which can cause dizziness or light-headedness
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps.

Possible serious infections (may affect up to 1 in 100 people), the signs may include:
- fever, flu-like symptoms, night sweats
- feeling tired or short of breath, cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters.

Other side effects

Common (may affect up to 1 in 10 people)
- diarrhoea
- feeling sick
- redness, pain, itching, bruising, or bleeding at injection site
- tiredness
- mouth or throat pain
- tinea (fungal) skin infections (including on feet and groin)
- flu (influenza)
- headache
- joint pain
- muscle pain.

Uncommon (may affect up to 1 in 100 people)
- candida (fungal) infection in the mouth, throat or genitals
- discharge from the eye with itching, redness and swelling (conjunctivitis)
- low white blood cell count.

Not known (frequency cannot be estimated from the available data)
- painful swelling and skin ulceration (pyoderma gangrenosum).

Most of these side effects are mild to moderate. If any of these side effects becomes severe, tell your doctor, nurse, or pharmacist.

Abdominal cramps and pain, diarrhoea, weight loss or blood in the stool (signs of bowel problems) have also been reported with IL-17 inhibitors, such as Kyntheum.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Kyntheum

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and label of the pre-filled syringe after EXP. The expiry date refers to the last day of that month.

Keep the pre-filled syringe in the outer carton in order to protect from light.

Store in a refrigerator (2°C to 8°C). Do not freeze.

Kyntheum can be kept at room temperature up to 25°C in the outer carton for 14 days. Throw away Kyntheum if it is not used within 14 days of storage at room temperature.

Do not use this medicine if you notice the solution is cloudy or discoloured or contains lumps, flakes or particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Kyntheum contains
- The active substance is brodalumab. Each pre-filled syringe contains 210 mg brodalumab in 1.5 ml solution.
- The other ingredients are proline, glutamate, polysorbate 20 and water for injections.

What Kyntheum looks like and contents of the pack
Kyntheum is a solution for injection that is a clear to slightly pearly, colourless to slightly yellow liquid, with no particles.

Kyntheum is available in unit packs containing 2 pre-filled syringes and in multipacks comprising 3 cartons, each containing 2 pre-filled syringes. Not all pack sizes may be marketed.

Marketing Authorisation Holder
LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

Manufacturer
Laboratoires LEO
39 route de Chartres
28500 Vernouillet
France

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu..

Instructions for Use:
Kyntheum 210 mg
solution for injection in pre-filled syringe
brodalumab

For subcutaneous use

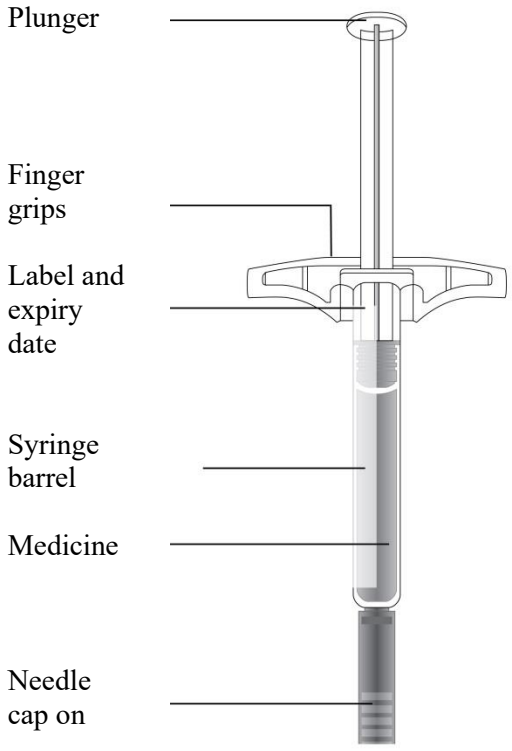
Kyntheum is available as a single-use pre-filled syringe. Each syringe contains one 210 mg dose of Kyntheum. Your doctor, pharmacist or nurse will tell you how often to inject the medicine. **Each Kyntheum pre-filled syringe can only be used once.**

If your doctor decides that you or a caregiver can give you injections at home, you should receive training on the right way to prepare and inject Kyntheum. Do not try to inject yourself until your healthcare provider has shown you the right way to give the injections.

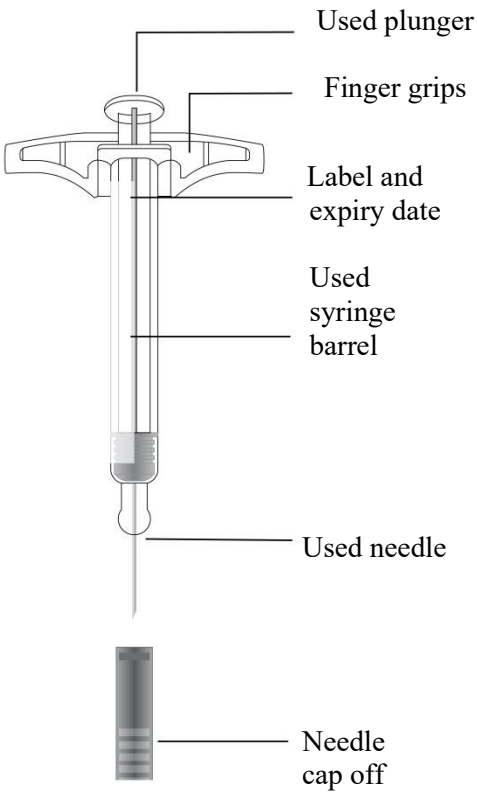
Please read all the instructions before using the Kyntheum pre-filled syringe. Call your doctor, pharmacist or nurse if you or your caregiver have any questions about the right way to inject Kyntheum.

Guide to parts

Before use



After use



Important: Needle is inside

Before you use a Kyntheum pre-filled syringe, read this important information:

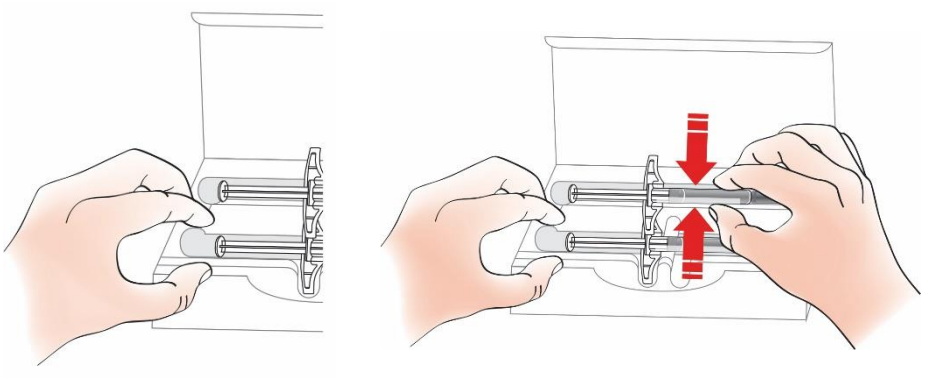
Storing your Kyntheum pre-filled syringes
- Keep out of the sight and the reach of children.

- Keep the pre-filled syringe in the original carton in order to protect from light or physical damage.
- Keep in the refrigerator (2°C to 8°C).
- If needed, you may store the Kyntheum pre-filled syringe at room temperature up to 25°C for up to 14 days. Throw away Kyntheum that has been stored at room temperature for longer than 14 days.
- **Do not** freeze.

Using your Kyntheum pre-filled syringe
- **Do not** use after the expiry date on the label.
- **Do not** shake.
- **Do not** remove the needle cap until you are ready to inject.
- **Do not** use a Kyntheum pre-filled syringe if it has been dropped on a hard surface. This is in case the syringe is broken.

Step 1: Preparing

A. Remove the Kyntheum pre-filled syringe from the box
Grab the syringe barrel to remove the syringe from the tray.



Place finger or thumb on edge of tray to secure it while you remove syringe.

Put the box with any unused syringes back in the refrigerator.

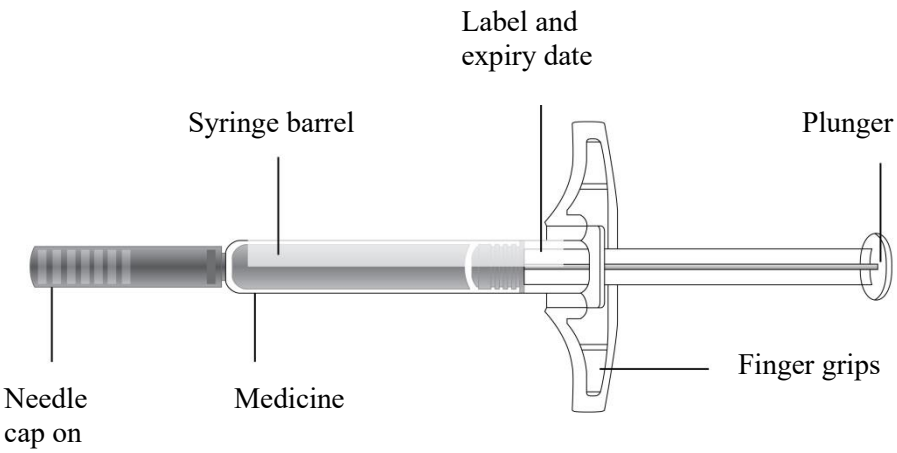
For safety reasons:
- **Do not** hold the plunger.
- **Do not** grasp the needle cap.
- **Do not** remove the needle cap until you are ready to inject.
- **Do not** remove the finger grips. They are part of the syringe.

Leave the syringe at room temperature for at least **30** minutes before injecting.

- **Do not** put the syringe back in the refrigerator once it has reached room temperature.
- **Do not** try to warm the syringe by using a heat source such as hot water or a microwave.
- **Do not** leave the syringe in direct sunlight.
- **Do not** shake the syringe.

Important: Always hold the pre-filled syringe by the syringe barrel.

B. Check the Kyntheum pre-filled syringe



Make sure the medicine in the syringe is clear to slightly pearly and colourless to slightly yellow.

- **Do not** use the syringe if:
  - the medicine is cloudy or discoloured or contains flakes or particles
  - any part appears cracked or broken.

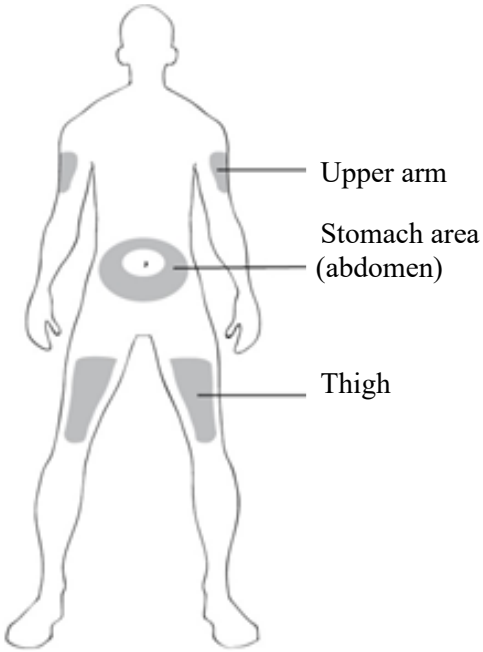
C. Collect all the materials you need

Wash your hands thoroughly with soap and water.

On a clean, well-lit work surface, place the:

- new syringe
- alcohol wipes
- cotton ball or gauze pad
- plaster
- sharps disposal container (colour and appearance of container may differ depending on national requirements).

D. Prepare and clean the area where you will inject



You or your caregiver can use:

- your thigh
- your stomach area (abdomen), except for a 5-centimetre area right around your belly button (navel).

Only your caregiver can use:

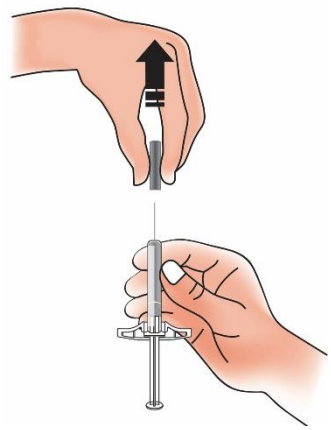
- your outer area of upper arm.

About the injection area:

- **Do not** inject into areas where the skin is tender, bruised red, or hard.
- Avoid injecting into areas with scars or stretch marks.
- Avoid injecting directly into raised, thick, red or scaly skin patches or lesions.
- Clean the area where you plan to inject with an alcohol wipe. Let your skin dry.
- **Do not** touch this area again before injecting.
- If you want to use the same injection area each time, make sure it is not exactly the same spot that you used for a previous injection.

Step 2: Getting ready to inject

E. When you are ready to inject, pull the needle cap straight out and away from your body

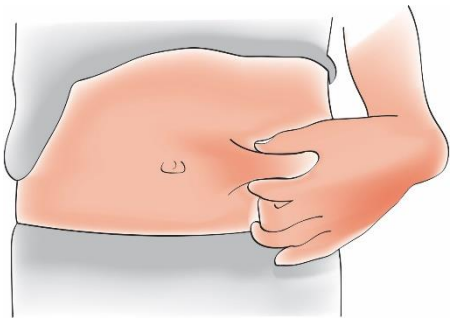


Throw the needle cap into the sharps disposal container provided.

- **Do not** twist or bend the needle cap.
- **Do not** put the needle cap back onto the syringe.

You may notice a small air bubble in the syringe or a drop of liquid at the end of the needle. Both are normal and do not need to be removed.

F. Pinch your skin to create a firm surface



Pinch the skin firmly between your thumb and fingers, creating an area about 5 centimetres wide.

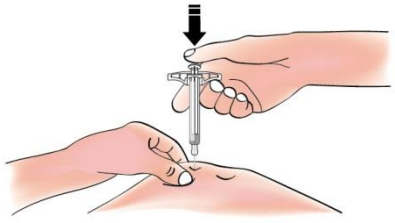
Important: Keep the skin pinched until after you have injected.

Step 3: Injecting

G. Hold the pinched skin. With the needle cap off, insert the syringe into your skin at somewhere between 45 and 90 degrees

Do not place your finger on the plunger while inserting the needle.

H. Using slow and constant pressure, push the plunger all the way down until it stops moving



I. When you have finished, release your thumb. Then, gently remove the syringe from your skin

Important: When you remove the syringe, if it looks like the medicine is still in the syringe barrel, this means you have not received a full dose. Call your doctor, pharmacist or nurse immediately.

Step 4: Finishing up

J. Throw away the used syringe

- Put your used pre-filled syringe in a puncture resistant sharps disposal container straight after use.
- **Do not** re-use the syringe.
- **Do not** recycle the syringe or sharps disposal container or throw them into household rubbish.

Important: Always keep the sharps disposal container out of the sight and the reach of children.

K. Check the injection site
If there is blood, press a cotton ball or gauze pad on your injection site. **Do not** rub the injection site. Cover with plaster if needed.