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) and 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 HPRA Pharmacovigilance, Website: www.hpra.ie.

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

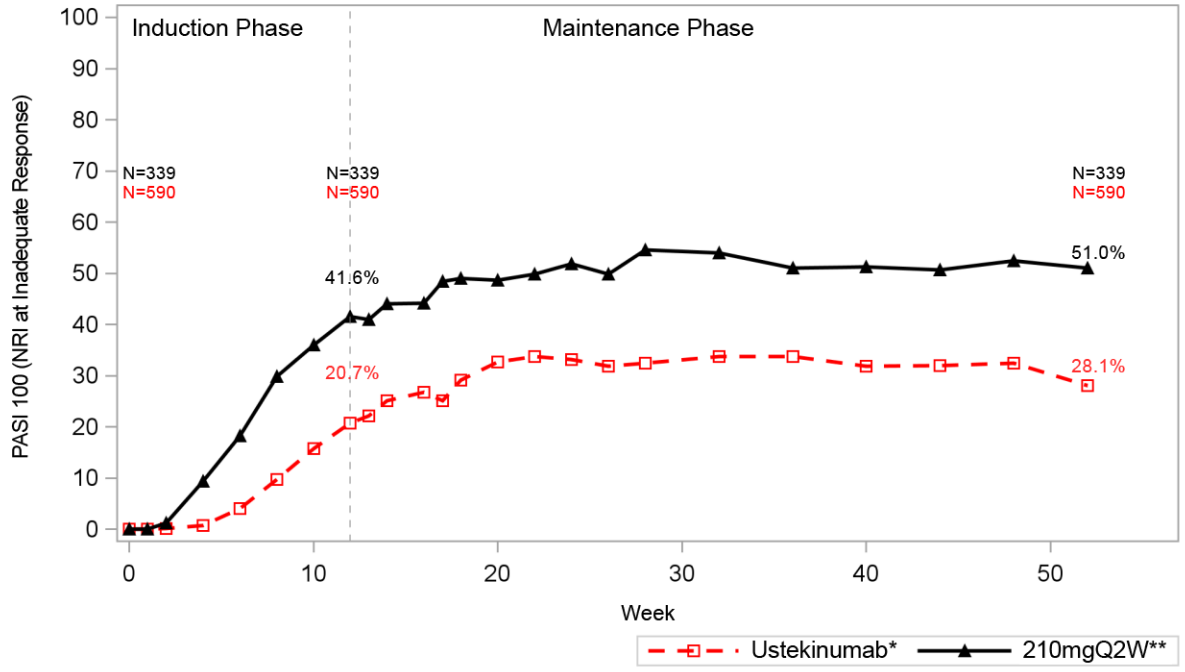
	AMAGINE-1		AMAGINE-2 and AMAGINE-3		
	Placebo	Brodalumab 210 mg Q2W	Placebo	Brodalumab 210 mg Q2W	Ustekinumab
$n_{\text{-randomised}}$	220	222	624	1236	613
$n_{\text{-completed Week 12}}$	209	212	601	1205	594
$n_{\text{-in maintenance}}$	84	83	NA	339	590
$n_{\text{-completed Week 52}}$	2	74	NA	236	300
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

August 2025

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