

Medicinal product no longer authorised

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rilonacept Regeneron 80 mg/ml powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains 220 mg of rilonacept. After reconstitution, each ml of solution contains 80 mg rilonacept.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is white to off-white.

The solvent is a clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rilonacept Regeneron is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) with severe symptoms, including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), in adults and children aged 12 years and older.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a specialist physician experienced in the diagnosis and treatment of CAPS.

After proper training in the correct injection technique, patients may self-inject Rilonacept Regeneron if their physician determines that it is appropriate and with medical follow-up as necessary.

Posology

Adults

Treatment in adults should be initiated with a loading dose of 320 mg. Dosing should be continued with a once-weekly injection of 160 mg. Rilonacept Regeneron should not be given more often than once weekly.

Paediatric population (12 to 17 years old)

Treatment should be initiated with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg. Dosing should be continued with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg (see Table 1). Dosing in children must be adjusted as the child grows. The patient or care giver should be advised to speak to the treating physician before adjusting the dose. The experience in children is limited. In the clinical program for CAPS, 8 adolescents aged 12-17 were treated for up to 18 months.

Paediatric population (up to 12 years old)

No data are available on the use of Riloncept Regeneron in children with CAPS under 12 years of age, therefore it is not recommended in this paediatric age group.

Elderly (65 years old or older)

Available data indicate that dose modification is not required based on advanced age. However, clinical experience in patients above 65 years is limited, therefore caution is recommended (see section 5.1).

Renal impairment

No dose adjustment is required in patients with mild, moderate, or severe renal impairment, or end stage renal disease. However, clinical experience in such patients is limited.

Hepatic impairment

Riloncept Regeneron has not been studied in patients with hepatic impairment.

Method of administration

Riloncept Regeneron is for subcutaneous use only. It is not intended for intravenous or intramuscular use.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

The adult loading dose should be administered as two 2 ml subcutaneous injections (320 mg of riloncept in total) given on the same day at different sites. The subsequent doses are administered as a 2 ml (160 mg of riloncept) subcutaneous injection once a week.

For paediatric patients, the dose is delivered as one or two (for loading dose) subcutaneous injections with a maximum single-injection volume of 2 ml.

For convenience, the corresponding dose volume for weekly injection in paediatric patients is presented in Table 1 below.

Table 1: Riloncept Regeneron dose volume (after reconstitution) by body weight for paediatric patients aged 12-17 years

Weight range (kg)	Dose volume (ml)
23.6 to 27.2	0.7
27.3 to 30.8	0.8
30.9 to 34.4	0.9
34.5 to 38.1	1
38.2 to 41.7	1.1
41.8 to 45.4	1.2
45.5 to 49.0	1.3
49.1 to 52.6	1.4
52.7 to 56.3	1.5
56.4 to 59.9	1.6
60.0 to 63.5	1.7
63.6 to 67.2	1.8
67.3 to 70.8	1.9
70.9 or greater	2

4.3 Contraindications

Hypersensitivity to rilonacept or to any of the excipients.
Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Serious infections

Interleukin-1 (IL-1) blockade may interfere with immune response to infections. Serious, life-threatening infections have been reported uncommonly in patients taking Rilonacept Regeneron.

In an open-label extension study, one patient developed bacterial meningitis and died. Rilonacept Regeneron should be discontinued if a patient develops a serious infection. Treatment should not be initiated in patients with an active or chronic infection (see section 4.3) and physicians should exercise caution when administering Rilonacept Regeneron to patients with a history of recurring infections or with underlying conditions that may predispose them to infections.

Because Rilonacept Regeneron dampens an inflammatory response, vigilance in excluding underlying infection in unwell patients is required.

Tumour necrosis factor (TNF) inhibitors have been associated with an increased risk of reactivation of latent tuberculosis (TB). It is unknown whether the use of IL-1 inhibitors like rilonacept increases the risk of reactivation of TB or of opportunistic infections. Before starting treatment with Rilonacept Regeneron, all patients should be evaluated for both active and inactive (latent) tuberculosis.

Combinations not recommended

The combination of Rilonacept Regeneron with TNF inhibitors has not been evaluated in clinical studies. An increased incidence of serious infections has been associated with administration of another IL-1 inhibitor, in combination with a TNF inhibitor.

Rilonacept Regeneron should not be used with TNF inhibitors because of increased risk of serious infections (see section 4.5).

The concomitant use of Rilonacept Regeneron with other IL-1 inhibitors is not recommended (see section 4.5).

Hypersensitivity

Although hypersensitivity reactions related to treatment with Rilonacept Regeneron were not seen in the initial clinical program, if a hypersensitivity reaction occurs, administration should be stopped immediately and permanently, and appropriate therapy initiated.

The risk for severe hypersensitivity reactions, which is not uncommon for injectable proteins, cannot be excluded (see section 4.3).

Immunogenicity

Antibodies directed against the receptor domains of rilonacept were detected by an ELISA assay in 35% of patients (19 out of 55) treated for at least 6 weeks in the clinical study. There was no correlation of antibody activity with either clinical efficacy or safety.

Neutropenia

Neutropenia (absolute neutrophil count [ANC] $< 1.5 \times 10^9/l$) has been observed commonly with another medicinal product that inhibits IL-1 used in a patient population (rheumatoid arthritis) other than CAPS. Neutropenia was observed commonly in patients with rheumatoid arthritis (not an approved use) who were administered Riloncept Regeneron subcutaneously in clinical studies. None of these patients had serious infections associated with the neutropenia. Although neutropenia was observed uncommonly in CAPS patients, the numbers studied are small. Treatment with Riloncept Regeneron should not be initiated in patients with neutropenia. It is recommended that neutrophil counts be assessed prior to initiating treatment, after 1 to 2 months, and periodically thereafter while receiving Riloncept Regeneron. If a patient becomes neutropenic the ANC should be monitored closely and treatment discontinuation should be considered.

Malignancies

The impact of treatment with Riloncept Regeneron on the development of malignancies is not known. However, treatment with immunosuppressants, including Riloncept Regeneron, may result in an increase in the risk of malignancies.

Vaccines

Live vaccines should not be given concurrently with Riloncept Regeneron (see section 4.5). Prior to initiation of Riloncept Regeneron therapy, adult and paediatric patients should receive all recommended vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine.

Lipid profile changes

Patients should be monitored for changes in their lipid profiles and provided with medical treatment if warranted (see section 4.8).

Mutation in NLRP3 gene

All cases in the clinical trials had a confirmed mutation in the NLRP3 gene. The efficacy was not evaluated in patients without a confirmed NLRP3 gene mutation.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The concomitant administration of Riloncept Regeneron with any TNF inhibitor is not recommended (see section 4.4), because an increased incidence of serious infections has been associated with administration of another IL-1 blocker in combination with TNF inhibitors.

The concomitant administration of Riloncept Regeneron with other IL-1 inhibitors has not been studied and is therefore not recommended.

The formation of CYP450 enzymes is suppressed by increased levels of cytokines during chronic inflammation. Thus it is expected that for a molecule that binds to IL-1, such as riloncept, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g. warfarin). Upon initiation of Riloncept Regeneron, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect or plasma levels should be performed and the individual dose of the medicinal product may need to be adjusted as needed.

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving Riloncept Regeneron. Therefore, live vaccines should not be given

concurrently with Rilonacept Regeneron, unless the benefits clearly outweigh the risks. Should vaccination with live vaccines be indicated after initiation of Rilonacept Regeneron treatment, the recommendation is to wait for at least 6 weeks after the last Rilonacept Regeneron injection and before the next one (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from use of rilonacept in pregnant women. Reproductive toxicity studies have been conducted in animals and have shown no effects on fertility or foetal morphology; however a study in pregnant monkeys showed reduced levels of oestrogen (see section 5.3). The risk for the foetus/mother is unknown. Women should use effective contraceptives during treatment with Rilonacept Regeneron and for up to 6 weeks after the last dose. Women who are pregnant or who desire to become pregnant should therefore only be treated after a thorough benefit-risk evaluation.

Breast-feeding

It is unknown whether rilonacept is excreted in human or animal breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Rilonacept Regeneron should be made taking into account the benefit of breast-feeding to the child and the benefit of Rilonacept Regeneron therapy to the woman.

4.7 Effects on ability to drive and use machines

The ability to drive and operate machines may be impaired by some symptoms associated with CAPS. Patients who experience vertigo during Rilonacept Regeneron treatment should wait for this to resolve completely before driving or operating machines.

4.8 Undesirable effects

The majority of the related adverse events in the clinical trials were classified as injection site reactions, experienced by approximately 50% of the patients in the Phase 3 study. Reported ISRs were generally mild to moderate in severity. No patients withdrew from the study due to ISRs.

ADRs to Rilonacept Regeneron reported during the Phase 2/3 program in a total of 109 patients, some treated for longer than 2 years, are listed below using the following categories of frequency: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$).

Due to the small patient population, an ADR reported in 2 or more patients is classified as “common.”

Table 2: Adverse reactions with Riloncept Regeneron in CAPS patients

MedDRA System Organ Class	Adverse reaction	Frequency
General disorders and administration site conditions	Injection site reactions, including erythema, bruising, pruritus, swelling, inflammation, pain, dermatitis, oedema, urticaria, vesicles	very common
	Fatigue	common
Infections and infestations	Upper respiratory tract infection; sinusitis	very common
	Bronchitis; gastroenteritis; viral infections; skin, eye and ear infections; pneumonia	common
	Bacterial meningitis	uncommon
Investigations	Eosinophil count increased	common
Nervous system disorders	Headache	very common
	Dizziness	common
Vascular disorders	Hypertension, flushing	common
Ear and labyrinth disorders	Vertigo	common
Eye disorders	Iritis	uncommon
Psychiatric disorders	Anxiety, insomnia	common
Immune system disorders	Hypersensitivity	common

Infections and infestations

During Part A of the pivotal study (see section 5.1), the incidence of patients reporting infections and considered by the investigator as related to treatment was greater with Riloncept Regeneron (9%) than with placebo (0%). In Part B, randomised withdrawal, the incidence of infections were similar in the Riloncept Regeneron (0%) and the placebo patients (4%). Part A of the trial was initiated in the winter months, while Part B was predominantly performed in the summer months.

In placebo-controlled studies across a variety of patient populations encompassing 336 patients treated with riloncept and 165 treated with placebo, the incidence of infections was 6.8% and 3% (0.44 per patient-exposure year and 0.19 per patient-exposure year), respectively, for riloncept and placebo.

Serious infections

One patient in an open-label study of CAPS died after developing sinusitis and bacterial (*Streptococcus pneumoniae*) meningitis.

In a study in patients with adult Still's disease, one patient developed an infection in his elbow with *Mycobacterium intracellulare* after an intraarticular glucocorticoid injection and subsequent local exposure to a suspected source of mycobacteria. In a study in patients with polymyalgia rheumatica, one patient developed bronchitis and sinusitis, which resulted in hospitalization.

Blood and lymphatic system disorder

During the initial placebo-controlled portion of the pivotal trial, mean values increased for haemoglobin and decreased for neutrophils and platelets in the patients treated with Riloncept Regeneron. These

changes were not deemed as clinically significant and were potentially due to a decrease in the chronic inflammatory state present in CAPS with an attendant decrease in acute-phase response.

General disorders and administration site conditions

In patients with CAPS, the most common and consistently reported adverse event associated with treatment was injection-site reaction (ISR). The ISRs included erythema, swelling, pruritus, and bruising. Most ISRs lasted for one to two days. In studies of patients with CAPS, no ISRs were assessed as severe, and no patient discontinued study participation due to an ISR.

Immunogenicity

Antibodies directed against the receptor domains of riloncept were detected by an ELISA assay in patients with CAPS after treatment with Riloncept Regeneron in clinical studies. Nineteen of 55 patients (35%) who had received Riloncept Regeneron for at least 6 weeks tested positive for treatment-emergent binding antibodies on at least one occasion. Of the 19 patients, 7 tested positive at the last assessment (Week 18 or 24 of the open-label extension period), and 5 patients tested positive for neutralising antibodies on at least one occasion. There was no correlation of antibody activity and either clinical efficacy or safety.

The data reflect the percentage of patients whose test results were positive for antibodies to riloncept in specific assays, and are highly dependent on the sensitivity and specificity of the assays. The observed incidence of antibody positivity in an assay may be influenced by several factors including assay sensitivity and specificity, sample handling, concomitant medicinal products, and underlying disease. For these reasons, comparison of the incidence of antibodies to riloncept with the incidence of antibodies to other products may be misleading.

Changes in lipid parameters

Cholesterol and lipid levels may be reduced in patients with chronic inflammation. Patients with CAPS treated with Riloncept Regeneron experienced mean increases from baseline for total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides of 19 mg/dl, 2 mg/dl, 10 mg/dl, and 57 mg/dl respectively after 6 weeks of open-label therapy. Physicians should monitor the lipid profiles of their patients (for example after 2-3 months) and consider lipid-lowering therapies as needed based upon cardiovascular risk factors and current guidelines.

4.9 Overdose

No case of overdose has been reported. The maximum amount of product that can be safely administered has not been determined.

Intravenous administration of Riloncept Regeneron at doses of up to 2000 mg monthly in another patient population for up to six months was generally well-tolerated. One patient in a study of osteoarthritis developed transient neutropenia (absolute neutrophil count $< 1 \times 10^9/l$) after receiving a very large dose (2000 mg). Maximum weekly doses of up to 320 mg have been administered subcutaneously for up to approximately 2 years or more in a small number of patients with CAPS and up to 6 months in patients with RA in clinical studies without evidence of dose-limiting toxicities.

In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interleukin inhibitors, ATC code: L04AC04.

This medicinal product has been authorised under “Exceptional Circumstances”. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The EMA will review any new information, which may become available every year, and this SPC will be updated as necessary.

Mechanism of action

Riloncept is a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the human type I interleukin-1 receptor (IL-1RI) and IL-1 receptor accessory protein (IL-1RAcP) linked in-line to the Fc portion of human IgG1. Riloncept binds to and blocks the activity of the cytokine IL-1 and binds both IL-1 β and IL-1 α , which are the primary pro-inflammatory cytokines implicated in many inflammatory diseases. Riloncept also binds the endogenous IL-1 receptor antagonist (IL-1ra) but with a lower affinity than IL-1 β or IL-1 α .

Pharmacodynamic effects

In clinical studies, CAPS patients who have uncontrolled over-production of IL-1 β show a rapid response to therapy with riloncept, i.e. laboratory parameters such as C-reactive protein (CRP) and serum amyloid A (SAA) levels, leukocytosis, and high platelet count rapidly returned to normal.

Clinical efficacy and safety

The safety and efficacy of riloncept for the treatment of CAPS, including patients with FCAS, also known as familial cold urticaria syndrome (FCUS), and MWS was demonstrated in a randomised, double-blind, placebo-controlled study with two parts (A and B) conducted sequentially in the same patients. The efficacy portion of the study included 47 patients, 44 of whom had a diagnosis of FCAS and 3 with a diagnosis of MWS. Twelve additional patients enrolled during the open label extension in which efficacy data were collected, 8 adults with a diagnosis of FCAS and 4 adolescents (13-16 years old), 3 with FCAS and 1 with FCAS/MWS overlap. Four additional adolescents (12-17 years) all with a diagnosis of FCAS subsequently enrolled in the open label extension where efficacy assessments were not collected. The efficacy was not evaluated in patients without a confirmed NLRP3/CIAS1 gene mutation.

Part A was a 6-week, randomised, double-blind, placebo-controlled period to evaluate riloncept at a dose of 160 mg weekly after an initial loading dose of 320 mg. Immediately after Part A patients entered Part B which consisted of a 9-week, patient-blind period during which all patients received riloncept 160 mg weekly, followed by a 9-week, double-blind, randomised withdrawal period in which patients were randomly assigned to either remain on riloncept 160 mg weekly or to receive placebo. Patients were then given the option to enroll in a 24-week, open-label treatment extension phase during which all patients were treated with riloncept 160 mg weekly.

Using a daily diary questionnaire, patients rated the following five signs and symptoms of CAPS: joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue, each on a scale of 0 (none, no severity) to 10 (very severe). The study evaluated the mean symptom score using the change from baseline to the end of treatment.

The changes in mean symptom scores for the randomised parallel-group period (Part A) and the randomised withdrawal period (Part B) of the study are shown in Table 3. Patients treated with riloncept

experienced an 84% reduction in the mean symptom score in Part A compared to 13% for placebo-treated patients ($p < 0.0001$). In Part B, mean symptom scores increased more in patients withdrawn to placebo compared to patients who remained on rilonacept.

Improvement in key symptom scores was noted within one day of initiation of rilonacept therapy in most patients. Patients treated with rilonacept experienced more improvement in each of the five components of the composite endpoint than placebo-treated patients.

The mean number of symptomatic “flare” days (defined as a day in which the mean symptom score reported on the patient diary was greater than 3) during the 21-day pre-treatment baseline period and the on-treatment endpoint period, in Part A, decreased from 8.6 at baseline to 0.1 at endpoint for the group on rilonacept, compared to a change from 6.2 to 5.0 for the placebo group ($p < 0.0001$ vs. placebo).

A significantly higher proportion of patients in the rilonacept group compared to the placebo group experienced improvement from baseline in the composite score by at least 30% (96% vs. 29% of patients), by at least 50% (87% vs. 8%) and by at least 75% (70% vs. 0%) ($p < 0.0001$).

In Part A and Part B, physician’s and patient’s global assessment of disease activity and patients’ assessment of the degree of limitation of their daily activities due to their disease were significantly improved for patients treated with rilonacept compared with those on placebo.

Mean levels of C reactive protein (CRP) were significantly decreased versus baseline for the rilonacept-treated patients, while there was no change for those on placebo. Rilonacept also led to a significant decrease in serum amyloid A (SAA) versus baseline to levels within the normal range.

During the open-label extension, reductions in mean symptom scores, serum CRP, and serum SAA levels were maintained for up to one year.

Table 3: Mean Symptom Scores in Adults (age 18 and older)

Part A	Placebo (n=24)	Rilonacept (n=23)	Part B	Placebo (n=23)	Rilonacept (n=22)
Pre-treatment Baseline Period (Weeks -3 to 0)	2.4	3.1	Active Rilonacept Baseline Period (Weeks 13 to 15)	0.2	0.3
Endpoint Period (Weeks 4 to 6)	2.1	0.5	Endpoint Period (Weeks 22 to 24)	1.2	0.4
Mean Change from Baseline to Endpoint	-0.3	-2.6*	Mean Change from Baseline to Endpoint	0.9	0.1**
p-value for within group comparison of change from Baseline	NS	$p < 0.0001$	p-value for within group comparison of change from Baseline	$p < 0.0001$	NS

* $p < 0.0001$, comparison of rilonacept vs. placebo

** $p < 0.001$, comparison of rilonacept vs. placebo,

NS = not significant

An assessment of efficacy with respect to age group and diagnosis was obtained by comparing KSS at the end of the 24 week open label extension with KSS at baseline using time averaged daily mean scores. The

results for the adults who entered the study in Part A are provided separately from the results of the adults who entered directly into the open label extension; the results for the four adolescents who entered directly into the open label extension are provided individually.

Table 4: Key symptom scores by age and diagnosis following 24-week open label extension

Group	Age group (range)	Diagnosis	Baseline Mean KSS	Week 24 Mean KSS	Reduction from Baseline
Adults who entered in Part A	18 - <65 (24, 63)	FCAS n=31	2.9	0.7	75.9%
	≥ 65 (67, 78)	FCAS n=10	2.4	0.4	77.3%
	18 - <65 (22, 45)	MWS n=3	3.3	0.2	90.5%
Adults who entered in OLE	18 - <65 (18, 56)	FCAS n=8	2.3	0.2	93.0%
Adolescents who entered in OLE	13	FCAS	2.4	0.4	85.6%
	15	FCAS	0.3	0.0	100%
	16	FCAS	2.8	0.0	100%
	13	FCAS/MWS	0.7	0.0	95.7%

5.2 Pharmacokinetic properties

Bioavailability of riloncept after a subcutaneous injection is estimated to be approximately 50%.

The average trough levels of riloncept were approximately 24 µg/ml at steady state following weekly subcutaneous doses of 160 mg for up to 48 weeks in patients with CAPS. The steady state appeared to be reached by 6 weeks.

Table 5: Riloncept steady-state pharmacokinetic properties¹

Parameter	Value ²
C _{max} (mg/l)	31.5
AUC (day mg/l)	198
CL /F (l/day)	0.808
T _{1/2} terminal (day)	7.72

¹Based on population PK modelling

²Derived values are presented.

Special populations

No pharmacokinetic data are available in patients with hepatic impairment. As with other large proteins elimination of rilonacept is expected to be via proteolytic catabolism and target mediated clearance.

Consequently, impaired liver function is not expected to affect the pharmacokinetics of rilonacept in a clinically significant way.

Results of a single-dose study in patients with end-stage renal disease (ESRD) indicate that the rate of elimination of rilonacept was not decreased. Renal elimination of rilonacept is therefore considered to be a minor pathway for clearance. No dose adjustment is needed in patients with renal impairment.

No study was conducted to evaluate the effect of age, gender, or body weight on rilonacept exposure. Based on limited data obtained from the clinical study, steady-state trough concentrations were similar between male and female patients. Age (26-78 years old) and body weight (50-120 kg) did not appear to have a significant effect on trough rilonacept concentrations. The effect of race could not be assessed because only Caucasian patients participated in the clinical studies in CAPS, reflecting the epidemiology of the disease.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated-dose toxicity.

Animal studies were conducted to assess reproductive toxicity. In mice, a murine analogue of rilonacept had no effect on fertility. A study of embryo-foetal development was conducted with rilonacept in monkeys at doses up to approximately 4 times the human dose. Decreases in β -estradiol levels were seen in the treated groups, the significance of this finding is unknown. In a prenatal and postnatal reproductive toxicology study in which mice were dosed subcutaneously, with a murine analogue of rilonacept at doses of 20, 100 or 200 mg/kg three times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area), there were no treatment-related effects.

Genotoxicity or long term animal studies have not been performed to evaluate the mutagenic or carcinogenic potential of rilonacept.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Glycine

Arginine hydrochloride

Histidine

Histidine hydrochloride monohydrate

Polyethylene glycol 3350

Sucrose

Solvent

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

Vial

2 years.

Diluted solution

From a microbiological safety point of view, the product should be used as soon as possible but within 3 hours of reconstitution, because it does not contain a preservative. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2 to 8°C.

6.4 Special precautions for storage

Store in a refrigerator. Do not freeze.

Keep the vials in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder vial

20 ml clear type I glass vial with rubber stopper and lacquered flip-off aluminium seal containing 220 mg rilonacept.

Solvent vial

LDPE vials containing 5 ml water for injections

Each pack contains:

4 vials of powder for solution for injection

4 vials of solvent

8 disposable 3 ml syringes

8 disposable 27 gauge, ½-inch needles

6.6 Special precautions for disposal and other handling

Instructions for reconstitution

Using aseptic technique, Rilonacept Regeneron powder should be reconstituted with 2.3 ml of solvent (water for injections) prior to administration.

The 2.3 ml of solvent should be withdrawn from the solvent vial attached directly to a 3 ml syringe and then injected into the powder vial for reconstitution using the 27 gauge, ½-inch needle (to obtain a final reconstitution volume of 2.75 ml). The needle and syringe used for reconstitution with solvent should then be discarded and should not be used for subcutaneous injections. After the addition of solvent, the vial contents should be reconstituted by shaking the vial for approximately one minute and then allowing it to

sit for one minute. The resulting 80 mg/ml solution is sufficient to allow a withdrawable volume of up to 2 ml for subcutaneous administration.

The reconstituted solution is viscous, clear and colourless to pale yellow. Prior to injection, the reconstituted solution should be carefully inspected for any discolouration or particulate matter. If there is discolouration or particulate matter in the solution, the product must not be used.

Instructions for administration

Using aseptic technique, the recommended dose volume, up to 2 ml (160 mg) of the solution, should be withdrawn with a new 27 gauge, ½-inch injection needle attached to a new 3 ml syringe for subcutaneous injection.

Sites for subcutaneous injection, such as the abdomen, thigh, or upper arm, should be rotated. Injections should never be made at sites that are bruised, red, tender, or hard.

The initial administration of Riloncept Regeneron by a patient or caregiver should be under the guidance of a trained healthcare professional. For subsequent self-administration by patients, appropriate instruction in proper injection technique should be provided and ability to apply that technique ascertained.

Disposal

Each vial should be used for a single dose only. The vial should be discarded after withdrawal of the solution.

Patients or their caregivers should be instructed on the appropriate procedure for disposal of the vials, needles, and syringes.

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

7. MARKETING AUTHORISATION HOLDER

Regeneron UK Limited
40 Bank Street
E14 5DS London
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/582/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 October 2009
Date of latest renewal:

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>.

Medicinal product no longer authorised

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Regeneron Pharmaceuticals, Inc.
81 Columbia Turnpike, Rensselaer,
New York 12144
USA

Name and address of the manufacturer responsible for batch release

Brecon Pharmaceuticals Ltd.
Pharos House
Wye Valley Business Park
Brecon Road, Hay-on-Wye
Hereford HR3 5PG
United Kingdom

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).

• **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

The Marketing Authorisation Holder (MAH) shall ensure that, prior to launch, all physicians who are expected to prescribe/use Riloncept Regeneron are provided with a physician information pack containing the following:

- The Summary of Product Characteristics
- Physician information
- Patient Alert Card

The physician information should contain the following key messages:

- The risk of serious infections, including opportunistic bacterial, viral and fungal infections in patients treated with Riloncept Regeneron;
- The risk of acute injection-related reactions;
- The need to instruct patients on proper techniques for self-administration when the patient is willing and capable to do so, and guidance for Health Care Professionals on how to report administration errors;

- The identified or potential risk of immunogenicity that might lead to immune-mediated symptoms;
- The need for Health Care Professionals to perform an annual clinical assessment of patients regarding a potential increased risk for the development of malignancies;
- The need to measure neutrophil counts prior to initiating treatment, after 1 to 2 months and periodically thereafter while receiving Riloncept Regeneron as treatment with Riloncept Regeneron should not be initiated in patients with neutropenia;
- The need to monitor patients for changes in their lipid profiles;
- The unknown safety of Riloncept Regeneron in pregnant and lactating women, thus the need for physicians to discuss this risk with patients if they become or plan to become pregnant;
- The proper patient management as regards the interaction with vaccination;
- The possibility to include patients in the registry study to facilitate the collection of long term efficacy and safety data;
- The role and use of patient alert card.

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

PSURs

The PSUR cycle for the medicinal product should follow a half-yearly cycle until otherwise agreed by the CHMP.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OBLIGATION TO CONDUCT POST-AUTHORISATION MEASURES**

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
The MAH shall submit an updated risk management plan (RMP) that adequately describes the additional pharmacovigilance activity of performing an embryo-foetal developmental toxicity study in cynomolgus monkeys to further investigate the	Within a month following the notifications of

potential risk of foetal defects.	the Commission Decision
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- SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES**

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
The MAH is requested to provide regular safety and efficacy data from the Global Registry for both adults and children. The fact that a limited number of paediatric patients were included in the clinical studies combined with the lack of data on the effect of long term IL-1 β suppression is a concern in view of the orphan nature of the condition. The continued collection of data should be maintained from the registry on safety and efficacy in children; particularly risk of infection and possible impairment of immune reactions such as response to vaccinations and growth. In addition the MAH is requested to assess cases for which there is loss of efficacy to determine whether this is due to changes over time in PK/PD or antibody development. The MAH shall provide updates on the recruitment rates and any intermediary results with the PSURs. The patients should be included in the Registry until both following conditions are met: 5 years recruitment period and 200 patients included.	With PSUR
Further PK steady state exposure data (AUC, C _{max} , C _{min} during steady state) especially for paediatric subjects is required. The MAH is requested to perform a PK study in children.	30 September 2012

Medicinal product no longer authorised

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rilonacept Regeneron 80 mg/ml powder and solvent for solution for injection
rilonacept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of powder contains 220 mg rilonacept. After reconstitution, each ml of solution contains 80 mg rilonacept.

3. LIST OF EXCIPIENTS

Also contains: glycine, arginine hydrochloride, histidine, histidine hydrochloride monohydrate polyethylene glycol 3350, sucrose, and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection.

Contains:

4 vials of powder containing 220 mg rilonacept

4 vials of 5 ml solvent

8 disposable 3 ml syringes

8 disposable 27-gauge, 1/2-inch needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use.

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.
Keep the vials in the outer carton 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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Regeneron UK Limited
40 Bank Street
E14 5DS London
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/582/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

POWDER VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Rilonacept Regeneron 80 mg/ml powder for solution for injection
rilonacept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 220 mg of rilonacept. When reconstituted, each ml solution contains 80 mg of rilonacept.

3. LIST OF EXCIPIENTS

Also contains: glycine, arginine hydrochloride, histidine, histidine hydrochloride monohydrate
polyethylene glycol 3350, sucrose

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection.
220 mg rilonacept

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

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.
Keep the vial in the outer carton 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

Regeneron UK Limited
40 Bank Street
E14 5DS London
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/582/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT LABEL

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

Solvent for Rilonacept Regeneron

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUMEN OR BY UNIT

5 ml

6. OTHER

Water for injections.

Medicinal product no longer authorised

B. PACKAGE LEAFLET

Medicinal product no longer authorised

Package leaflet: Information for the user

Rilonacept Regeneron 80 mg/ml powder and solvent for solution for injection rilonacept

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 further questions, ask your doctor or pharmacist.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

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

1. What Rilonacept Regeneron is and what it is used for

Rilonacept Regeneron is used to treat adults and adolescents aged 12 years and older with severe symptoms of Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).

Rilonacept Regeneron belongs to a group of medicines called interleukin inhibitors. Rilonacept Regeneron blocks the activity of substances including interleukin-1 beta (IL-1 beta). In patients with CAPS, the body produces excessive amounts of IL-1 beta. This may lead to symptoms such as fever, headache, fatigue, skin rash, or painful joints and muscles. By blocking the activity of IL-1 beta, Rilonacept Regeneron leads to an improvement in these symptoms.

If you have any questions about how Rilonacept Regeneron works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you use Rilonacept Regeneron

Do not use Rilonacept Regeneron:

- if you are allergic to rilonacept or any of the other ingredients of this medicine (listed in section 6).
- if you have an active, severe infection.

Warnings and precautions

Talk to your doctor before using Rilonacept Regeneron.

You should tell your doctor if you have:

- an infection;
- tuberculosis or you have been in close contact with someone who has had tuberculosis;
- a history of infections that keep coming back;
- been scheduled to receive any vaccines.

Children and adolescents

Riloncept Regeneron is not recommended for children younger than 12 years of age.

Other medicines and Riloncept Regeneron

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

In particular, you should tell your doctor if you are using any of the below medicines.

- Other medicines that block interleukin-1, such as anakinra or canakinumab.
- Medicines called Tumour Necrosis Factor (TNF) inhibitors (such as etanercept, adalimumab, or infliximab) predominantly used in rheumatoid and autoimmune disease.
- Any other medicines for chronic disorders, as Riloncept Regeneron can affect how the liver processes some medicines, such as warfarin (a blood thinner). Your doctor may need to perform some tests and adjust the dose of such medicines.

Pregnancy and breast-feeding

Riloncept Regeneron has not been tested in pregnant women and should not be used during pregnancy unless clearly necessary. You should not become pregnant and must use birth control while using Riloncept Regeneron and for at least six weeks after your last dose. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

The safety of Riloncept Regeneron in breast-feeding women is unknown. If you are breast-feeding you should ask your doctor for advice before using Riloncept Regeneron.

Driving and using machines

Some symptoms associated with CAPS or with Riloncept Regeneron treatment, such as a spinning sensation (known as vertigo), may affect your ability to drive or use machines. If you feel a spinning sensation, do not drive or operate any tools or machines until you are feeling normal again.

Ask your doctor, nurse or pharmacist for advice before taking any medicine.

3. How to use Riloncept Regeneron

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

Riloncept Regeneron is intended for subcutaneous use. This means that it is injected through a short needle into the fatty tissue just under the skin.

How much Riloncept Regeneron to use

Adults (including the elderly)

- The starting dose is 2 injections of 2 millilitres (ml) solution each, given on the same day at 2 different areas of the body.
- After that, the recommended dose is 1 injection of 2 ml injected once weekly.

Adolescents (aged 12 to 17 years old)

The dose will depend on the body weight of the patient and will be different for each patient. Your doctor will tell you how much medicine to inject.

- The starting dose is 4.4 milligrams per kilogram of body weight, up to 320 milligrams (mg), given as one or two injections.
- After that, the recommended dose is 2.2 milligrams per kilogram, up to 160 mg, once weekly on the same day of the week.

In both cases your doctor will calculate the corresponding volume to inject. The dose of Riloncept Regeneron may need to be adjusted as the child grows. Talk with your doctor before making any dose adjustments.

How to inject Riloncept Regeneron

Riloncept Regeneron is injected under the skin (subcutaneously). The first injection of Riloncept Regeneron should be given under the supervision of a trained healthcare professional. You or your caregiver will receive adequate training on how to mix the powder (dissolve to make a solution), prepare the dose, and administer the injection.

Please read the section “INSTRUCTIONS FOR USE OF RILONACEPT REGENERON POWDER FOR SOLUTION FOR INJECTION” at the end of this leaflet. If you have questions, contact your doctor, nurse, or pharmacist.

If you use more Riloncept Regeneron than you should

If you accidentally inject more Riloncept Regeneron than the recommended dose, you should contact your doctor right away.

If you forget to use Riloncept Regeneron

If you miss a dose of Riloncept Regeneron and remember within a few days, inject it as soon as you remember. The next dose should be injected at the next regularly scheduled time. Do not inject a double dose to make up for the forgotten dose. Do not inject Riloncept Regeneron more frequently than once weekly.

4. Possible side effects

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

You must tell your doctor right away if any of the following serious side effects occur while you are using Riloncept Regeneron:

- **Serious infections.** Tell your doctor right away if you develop symptoms of an infection while being treated with Riloncept Regeneron, such as:

- fever lasting longer than 3 days, or any other symptoms possibly related to an infection, such as prolonged cough, prolonged headache or localised redness, warmth or swelling of your skin.

You must stop treatment with Riloncept Regeneron if you develop a severe infection.

• **Allergic reactions.** If you develop signs of an allergic (hypersensitivity) reaction during treatment with Riloncept Regeneron (such as chest tightness, wheezing, trouble breathing, severe dizziness or light-headedness, swelling of lips, or rash during or after the injection) then stop taking Riloncept Regeneron and tell your doctor right away.

Very common side effects (affects 1 or more users in 10)

- Reactions at injection site (such as redness, swelling, itching, and bruising at the injection site)
- Upper respiratory infection
- Sinus infection
- Headache

Common side effects (affects 1 to up to 10 users in 100)

- Viral infection
- Bronchitis
- Skin, eye, or ear infection
- Tiredness (fatigue)
- Increased blood pressure
- Pneumonia
- Stomach/Intestinal infection
- Dizziness
- Flushing
- Allergic reaction
- Anxiety
- Being unable to sleep (insomnia)

Uncommon side effects (affects 1 to up to 10 users in 1,000)

- Meningitis
- Inflammation of the eye (iritis)

Changes in your blood cholesterol levels or in your blood counts may also occur. These will be monitored by your doctor.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Riloncept Regeneron

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 carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator. Do not freeze.

Keep the vials in the outer carton in order to protect from light.

After preparing the Riloncept Regeneron solution, it is best if used right away because it does not contain a preservative. If necessary, the product may be kept at room temperature, but should be used within 3 hours of mixing.

The solution is viscous, clear and colourless to pale yellow. Prior to injection, the solution should be carefully inspected for any discolouration or particulate matter. If there is discolouration or particulate matter in the solution, the product must not be used.

Do not throw 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 Riloncept Regeneron contains

- The active substance is riloncept. Each vial of powder contains 220 mg riloncept. After reconstitution, each ml of solution contains 80 mg riloncept.
- The other ingredients in the powder are glycine, arginine hydrochloride, histidine, histidine hydrochloride monohydrate, polyethylene glycol 3350 and sucrose. The solvent is water for injections.

What Riloncept Regeneron looks like and contents of the pack

- Riloncept Regeneron is provided as a powder for solution for injection in a glass vial. The powder is white to off-white.
- Solvent is provided in a 5 ml transparent plastic vial containing 5 ml water for injections. The solvent is a colourless liquid.

Each pack contains:

4 vials of powder for solution for injection
4 vials of solvent
8 disposable 3-ml syringes
8 disposable 27-gauge, ½-inch needles

Marketing Authorisation Holder

Regeneron UK Limited
40 Bank Street
E14 5DS London
United Kingdom

Manufacturer

Brecon Pharmaceuticals Ltd
Wye Valley Business Park
Hay-on-Wye
HR3 5PG Hereford
United Kingdom

This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

Medicinal product no longer authorised

INSTRUCTIONS FOR USE OF RILONACEPT REGENERON POWDER FOR SOLUTION FOR INJECTION

See also section 3, “**How to inject Riloncept Regeneron.**”

Read these instructions all the way through before beginning.

Supplies needed:

The following items are included in each Riloncept Regeneron dose pack:

- 8 sterile, 3-ml disposable syringes
- 8 sterile, disposable needles (27-gauge, ½-inch)
- 4 vials of Riloncept Regeneron powder
- 4 vials of sterile water (solvent)

You will also need to obtain these items from your pharmacist, which are not included in the Riloncept Regeneron dose pack:

- Alcohol wipes
- Gauze pads
- A puncture-resistant container for disposal of used needles, syringes, and vials

Ask your pharmacist for these supplies.

General guidelines when giving a Riloncept Regeneron injection:

- Check the expiration date (month and year) on the Riloncept Regeneron carton and vial. It is stated on the vial label and carton after “EXP”. Do not use Riloncept Regeneron after the expiry date. The expiry date refers to the last date of the month.
- Do not touch the needles or the rubber stopper on the Riloncept Regeneron vial with your hands. If you do touch the rubber stopper, clean it with a fresh alcohol wipe.
- If you touch a needle or the needle touches any surface, throw away the entire syringe into your puncture-resistant container and start over with a new syringe.
- Do not reuse needles or syringes.
- To protect yourself and others from possible needle sticks, it is very important to throw away every syringe, with the needle attached, in the puncture-resistant container right after use. **Do not try to recap the needle.**

STEP 1: Setting up for an injection

1. Wash your hands thoroughly.
2. Put the following items on a clean flat surface (see Figure 1):
 - 2 sterile, 3-ml disposable syringes
 - one used for adding the sterile water (solvent) to the Riloncept Regeneron powder
 - one used for injection
 - 2 sterile, disposable needles (27-gauge, ½-inch)
 - one used for adding the sterile water (solvent) to the Riloncept Regeneron powder

- one used for injection
- 1 vial of Rilonacept Regeneron powder
- 1 vial of sterile water (solvent)
- 3 alcohol wipes
- 1 gauze pad
- 1 puncture-resistant container for disposal of used needles, syringes and vials

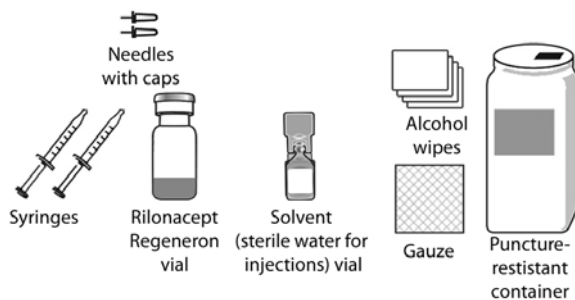


Figure 1

STEP 2: Preparing the vial of Rilonacept Regeneron powder

1. Remove the plastic cap from the Rilonacept Regeneron vial.
2. Clean the top of the Rilonacept Regeneron vial with a fresh, never-used alcohol wipe, wiping in one direction around the top.
3. Set the vial aside.

STEP 3: Filling a syringe with sterile water for injection (solvent)

1. Snap off the plastic tab on the top of the vial containing sterile water for injection (solvent).
2. Open the wrapper that contains a 27-gauge needle by pulling apart the tabs. Place the capped needle on a clean surface. Open the wrapper that contains a syringe by pulling apart the tabs.
3. Attach the exposed top of the sterile water vial to the top of a syringe by twisting the syringe onto the vial of sterile water (solvent) (see Figure 2).



Figure 2

4. Hold the vial with the sterile water (solvent) in one hand and the syringe in the other hand. Carefully turn the vial upside down. While holding the syringe at eye level, slowly pull the syringe plunger back to the 2.5-ml line so that the sterile water (solvent) moves from the vial into the syringe (see Figure 3).

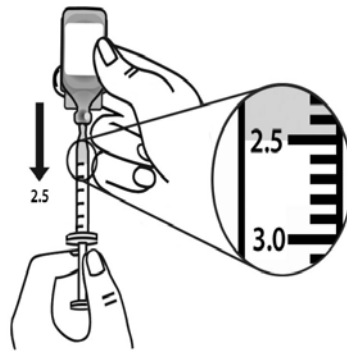


Figure 3

5. Remove the vial from the syringe. Hold the barrel of the syringe with one hand and twist the 27-gauge needle onto the tip of the syringe with the other hand until it fits snugly (see Figure 4).

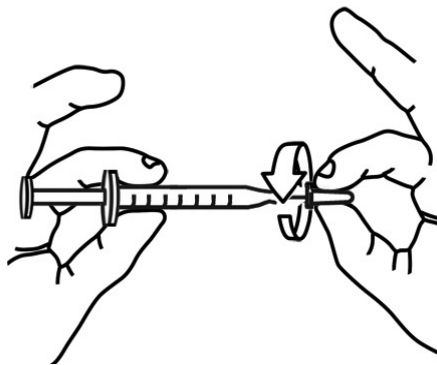


Figure 4

6. Turn the syringe so that the needle is facing straight up. Pull the needle cap straight off. Do not twist the needle or the cap as you pull it off. Gently tap the syringe until air bubbles rise to the top of the syringe (see Figure 5).



Figure 5

7. Point the syringe and needle straight upward. The sterile water should be at the 2.3-ml line (see Figure 6). If there is more sterile water in syringe, then push the syringe plunger to force out sterile water until the water reaches the 2.3-ml line.

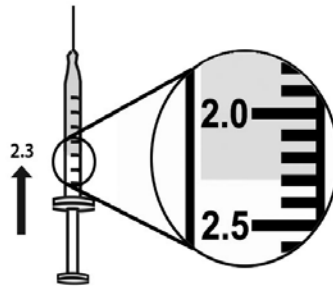


Figure 6

STEP 4: Dissolving Rilnacept Regeneron powder with the sterile water for injection (solvent)

1. With one hand, hold the Rilnacept Regeneron powder vial on a firm surface.
2. With the other hand, take the syringe with the sterile water (solvent) and slowly insert the needle straight down through the centre of the rubber stopper of the Rilnacept Regeneron powder vial. Push the syringe plunger down all the way so that the sterile water (solvent) in the syringe flows into the vial (see Figure 7).

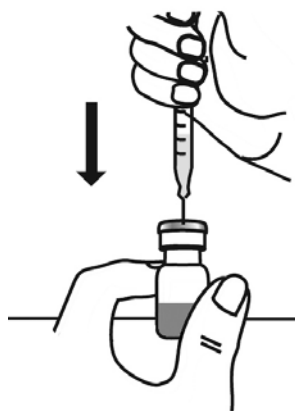


Figure 7

3. Remove the syringe and needle from the stopper and throw away the syringe attached to the needle and sterile water (solvent) vial in the puncture-resistant container. Do not try to put the needle cover back on the needle.
4. Hold the vial containing the mixture of powder and sterile water (solvent) sideways (not upright) with your thumb and a finger at the top and bottom of the vial, and quickly shake the vial back and forth (side-to-side) for about 1 minute.
5. Put the vial back on the table and let the vial sit for about 1 minute.
6. Check if the vial contains any particles or clumps of powder that have not dissolved.
7. If the powder has not completely dissolved, shake the vial quickly back and forth for 30 seconds more. Let the vial sit for about 1 minute.
8. Repeat step 7 until the powder is completely dissolved and the solution is clear.
9. The dissolved Riloncept Regeneron solution should be a thick, clear liquid, colourless to pale yellow. Do not use the solution if it is discoloured or cloudy, or if it contains small particles (see Figure 8).

NOTE: Contact your pharmacy to report any dissolved Riloncept Regeneron that is discoloured or contains particles.



Figure 8

10. It is best to move to the next step and inject the medicine immediately after dissolving the Rilonacept Regeneron powder in the sterile water (solvent). If necessary, the product may be kept at room temperature (20 to 25°C) for no more than 3 hours. Keep Rilonacept Regeneron away from light.

STEP 5: Preparing the injection

1. Hold the vial with the solution on a firm surface and wipe the top of the vial with a new alcohol wipe.
2. Open a wrapper containing a new, sterile, disposable needle. Open a wrapper containing a new, disposable syringe. Attach the needle securely to the syringe without removing the needle cover.
3. Hold the syringe upright at eye level. With the needle cover on, pull back the plunger on the syringe to the mark that is equal to the volume of the solution that your doctor has prescribed for you to inject, filling the syringe with air (see Figure 9).

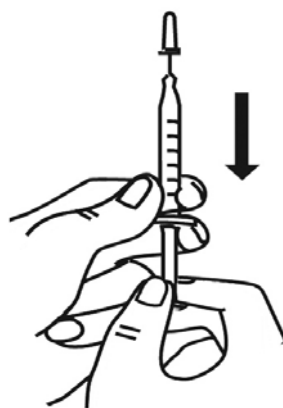


Figure 9

4. Remove the needle cover and be careful not to touch the needle. Keep the vial on a flat surface and slowly insert the needle straight down through the stopper. Push the plunger down and inject all the air into the vial (see Figure 10).

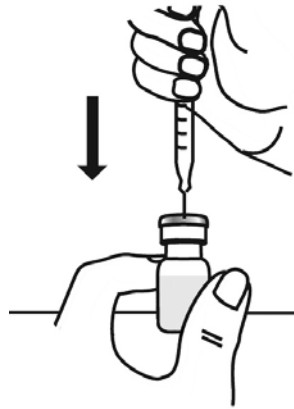


Figure 10

5. Hold the vial in one hand and the syringe in the other hand and carefully turn the vial upside down so that the needle is pointing straight up. Hold the vial at eye level.
6. Keep the tip of the needle in the liquid and slowly pull back on the plunger to the mark on the syringe that matches the amount of medicine prescribed by your doctor (see Figure 11).

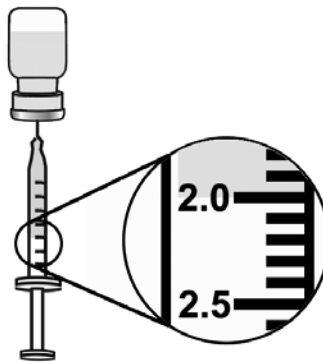


Figure 11

7. Tap the syringe until the air bubbles rise to the top of the syringe. Then slowly and gently, push in the plunger so that all of the air is pushed through the needle.
8. Check to make sure that you have the amount of medicine prescribed by your doctor in the syringe.
9. Throw away the vial in the puncture-resistant container even if there is some medicine left in the vial. Do not use any vial of Riloncept Regeneron more than one time.

10. Hold the syringe and needle in your hand ready for injecting. Do not touch the needle with your hands or allow it to come into contact with any surfaces. Proceed with the injection as described in Step 6 below.

STEP 6: Giving the injection

1. Rilonecept Regeneron is injected into the tissue directly below the layers of skin. It is not meant to go into any muscle, vein, or artery.

Where to inject

Inject in a different place each time in order to keep your skin healthy.

Changing injection sites helps to prevent irritation and allows the medicine to be better absorbed. Ask your doctor any questions that you have about rotating injection sites.

- Do not inject into skin that is tender, red, or hard. If an area is tender or feels hardened, choose another site for injection until the tenderness or “hardening” goes away.
- Tell your doctor about any skin reactions including redness, swelling, or hardening of the skin.
- Areas where you may inject Rilonecept Regeneron include the left and right sides of the abdomen, and left and right thighs. If someone else is giving you the injection, the upper arms may also be used for injection (see Figure 12):

(Do not inject within a 5-cm area around the navel.)

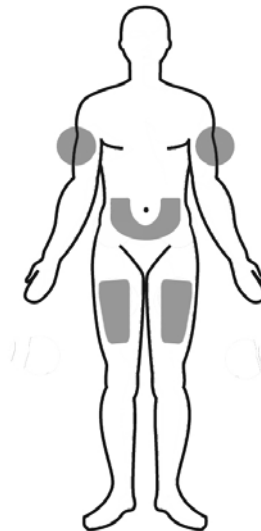


Figure 12

2. Choose the area for the injection. Clean the area in a circular motion with a new alcohol wipe. Begin at the centre of the site and move outward. Let the alcohol air dry completely. Do not touch this area again before injecting.

3. Hold the syringe in one hand like you would hold a pencil.
4. With the other hand gently pinch a fold of skin around the site that you cleaned for injection.
5. Use a quick “dart like” motion to insert the needle straight into the skin (90° angle) (see Figure 13a). Do not push down on the plunger while inserting the needle into the skin. For small children or persons with little fat under the skin, you may need to hold the syringe and needle at a 45° angle (see Figure 13b).

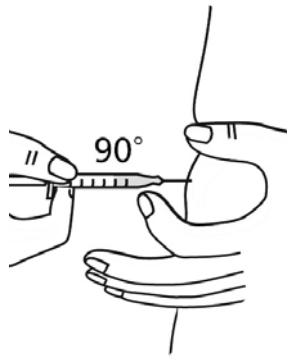


Figure 13a (Adults)

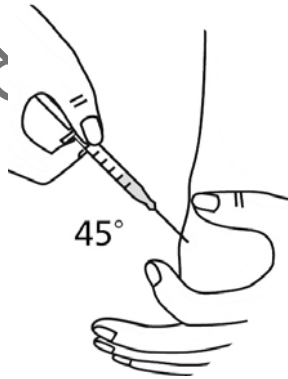


Figure 13b (Small Children, Thin Patients)

6. After the needle is completely in the skin, let go of the skin that you are pinching.
7. With your free hand hold the syringe near its base. Gently pull back the plunger. If blood comes into the syringe, the needle has entered a blood vessel. Remove the needle, discard the syringe and needle. Start over with ‘STEP 1: Setting up for an injection’ using new supplies.

8. If no blood appears, inject all the medicine in the syringe at a slow, steady rate, pushing the plunger all the way down. It may take up to 30 seconds to inject the entire dose.
9. Pull the needle out of the skin, and hold a piece of sterile gauze over the injection site for several seconds.
10. Do not replace the needle cover. Throw away the vials, used syringes and needles in the puncture-resistant container. Do not recycle the container. Do not throw away vials, needles, or syringes in the household rubbish.
11. Keep the puncture-resistant container out of reach of children. When the container is about two-thirds full, dispose of it as instructed by your doctor or pharmacist.
12. Used alcohol wipes can be thrown away in the household rubbish.

Medicinal product no longer authorised

The following information is intended for medical or healthcare professionals only and is provided as a tear-off leaflet:

Indication

Riloncept Regeneron is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) with severe symptoms, including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), in adults and children aged 12 years and older.

Posology

Adults

Treatment in adults should be initiated with a loading dose of 320 mg. Dosing should be continued with a once-weekly injection of 160 mg. Riloncept Regeneron should not be given more often than once weekly.

Paediatric population (12 to 17 years old)

Treatment should be initiated with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg. Dosing should be continued with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg (see Table 1). Dosing in children must be adjusted as the child grows. The patient or care giver should be advised to speak to the treating physician before adjusting the dose. The experience in children is limited. In the clinical program for CAPS, 8 adolescents aged 12-17 were treated for up to 18 months.

Paediatric population (up to 12 years old)

No data are available on the use of Riloncept Regeneron in children with CAPS under 12 years of age, therefore it is not recommended in this paediatric age group.

Elderly (65 years old or older)

Available data indicate that dose modification is not required based on advanced age. However, clinical experience in patients above 65 years is limited, therefore caution is recommended.

Renal impairment

No dose adjustment is required in patients with mild, moderate or severe renal impairment, or end stage renal disease. However, clinical experience in such patients is limited.

Hepatic impairment

Riloncept Regeneron has not been studied in patients with hepatic impairment.

Method of administration

Riloncept Regeneron is for subcutaneous use only. It is not intended for intravenous or intramuscular use.

The adult loading dose should be administered as two 2 ml subcutaneous injections (320 mg of riloncept in total) given on the same day at different sites. The subsequent doses are administered as a 2 ml (160 mg of riloncept) subcutaneous injection once a week.

For paediatric patients, the dose is delivered as one or two (for loading dose) subcutaneous injections with a maximum single-injection volume of 2 ml.

For convenience, the corresponding dose volume for weekly injection in paediatric patients is presented in Table 1 below.

Table 1: Rilonacept Regeneron dose volume (after reconstitution) by body weight for paediatric patients, aged 12-17 years

Weight range (kg)	Dose volume (ml)
23.6 to 27.2	0.7
27.3 to 30.8	0.8
30.9 to 34.4	0.9
34.5 to 38.1	1
38.2 to 41.7	1.1
41.8 to 45.4	1.2
45.5 to 49.0	1.3
49.1 to 52.6	1.4
52.7 to 56.3	1.5
56.4 to 59.9	1.6
60.0 to 63.5	1.7
63.6 to 67.2	1.8
67.3 to 70.8	1.9
70.9 or greater	2

Special precautions for storage

Store in a refrigerator. Do not freeze.

Keep the vials in the outer carton in order to protect from light.

After reconstitution, if necessary the product may be kept at room temperature, but should be used within three hours of reconstitution because it does not contain a preservative.

Reconstitution and administration instructions

Instructions for reconstitution

Using aseptic technique, Rilonacept Regeneron powder should be reconstituted with 2.3 ml solvent (water for injections) prior to administration.

The 2.3 ml of solvent should be withdrawn from the solvent vial attached directly to a 3-ml syringe and then injected into the powder vial for reconstitution with 27-gauge, ½-inch needle (to obtain a final reconstitution volume of 2.75 ml). The needle and syringe used for reconstitution with solvent should then be discarded and should not be used for subcutaneous injections. After the addition of solvent, the vial contents should be reconstituted by shaking the vial for approximately one minute and then allowing it to sit for one minute. The resulting 80 mg/ml solution is sufficient to allow a withdrawable volume of up to 2 ml for subcutaneous administration.

The reconstituted solution is viscous, clear and colourless to pale yellow. Prior to injection, the reconstituted solution should be carefully inspected for any discolouration or particulate matter. If there is discolouration or particulate matter in the solution, the product must not be used.

Instructions for administration

Using aseptic technique, the recommended dose volume, up to 2 ml (160 mg) of the solution should be withdrawn with a new 27-gauge, ½-inch injection needle attached to a new 3-ml syringe for subcutaneous injection.

Sites for subcutaneous injection, such as the abdomen, thigh, or upper arm, should be rotated. Injections should never be made at sites that are bruised, red, tender, or hard.

The initial administration of Riloncept Regeneron by a patient or caregiver should be under the guidance of a trained healthcare professional. For subsequent self-administration by patients, appropriate instruction in proper injection technique should be provided and ability to apply that technique ascertained.

Disposal

Each vial should be used for a single dose only. The vial should be discarded after withdrawal of the solution.

Patients or their caregivers should be instructed on the appropriate procedure for disposal of the vials, needles, and syringes.

Medicinal product no longer authorised