

**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 Rilonacept 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*

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

#### Method of administration

Rilonacept 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 rilonacept in total) given on the same day at different sites. The subsequent doses are administered as a 2 ml (160 mg of rilonacept) 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

### **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 Rilonacept 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 Rilonacept 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 Rilonacept Regeneron. If a patient becomes neutropenic the ANC should be monitored closely and treatment discontinuation should be considered.

#### Malignancies

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

#### Vaccines

Live vaccines should not be given concurrently with Rilonacept Regeneron (see section 4.5). Prior to initiation of Rilonacept 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 Rilonacept 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 Rilonacept 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 rilonacept, 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 Rilonacept 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 Rilonacept 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 rilonacept were detected by an ELISA assay in patients with CAPS after treatment with Rilonacept Regeneron in clinical studies. Nineteen of 55 patients (35%) who had received Rilonacept 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 rilonacept 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 rilonacept 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 Rilonacept 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 Rilonacept 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

Rilonacept 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. Rilonacept binds to and blocks the activity of the cytokine IL-1 and binds both IL-1 $\beta$  and IL-1 $\alpha$ , which are the primary pro-inflammatory cytokines implicated in many inflammatory diseases. Rilonacept also binds the endogenous IL-1 receptor antagonist (IL-1ra) but with a lower affinity than IL-1 $\beta$  or IL-1 $\alpha$ .

### Pharmacodynamic effects

In clinical studies, CAPS patients who have uncontrolled over-production of IL-1 $\beta$  show a rapid response to therapy with rilonacept, 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 rilonacept 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 rilonacept 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 rilonacept 160 mg weekly, followed by a 9-week, double-blind, randomised withdrawal period in which patients were randomly assigned to either remain on rilonacept 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 rilonacept 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 rilonacept 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 rilonacept after a subcutaneous injection is estimated to be approximately 50%.

The average trough levels of rilonacept 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: Rilonacept steady-state pharmacokinetic properties<sup>1</sup>

Parameter	Value <sup>2</sup>
C <sub>max</sub> (mg/l)	31.5
AUC (day mg/l)	198
CL /F (l/day)	0.808
T <sub>1/2</sub> terminal (day)	7.72

<sup>1</sup> Based on population PK modelling

<sup>2</sup> Derived 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  $\beta$ -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 riloncept.

### 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, Riloncept 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 discoloration or particulate matter. If there is discoloration 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>.