ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ARCALYST 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 a 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

ARCALYST 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 ARCALYST 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. ARCALYST 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 ARCALYST 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 indicates 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

ARCALYST has not been studied in patients with hepatic impairment.

Method of administration
ARCALYST is for subcutaneous use only. It is not intended for intravenous or intramuscular use.
For preparation and additional administration instructions, 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: ARCALYST 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 ARCALYST.

In an open-label extension study, one patient developed bacterial meningitis and died. ARCALYST 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 ARCALYST to patients with a history of recurring infections or with underlying conditions that may predispose them to infections.

Because ARCALYST dampens an inflammatory response, vigilance in excluding underlying infection in unwell patients is required

Tumour necrosis factor (TNF[0]) 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. [0]Before starting treatment with ARCALYST, all patients should be evaluated for both active and inactive (latent) tuberculosis.

Combinations not recommended
The combination of ARCALYST 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.

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

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

Hypersensitivity
Although hypersensitivity reactions related to treatment with ARCALYST were not seen in the initial clinical program, if a hypersensitivity reaction occurs, administration should be discontinued 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 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 x 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 ARCALYST 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 ARCALYST 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 ARCALYST. If a patient becomes neutropenic the ANC should be monitored closely and treatment discontinuation should be considered.

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

Vaccines
Live vaccines should not be given concurrently with ARCALYST (see section 4.5). Prior to initiation of ARCALYST 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 ARCALYST 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 ARCALYST 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 ARCALYST, 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 ARCALYST. Therefore, live vaccines should not be given concurrently with ARCALYST, unless the benefits clearly outweigh the risks. Should vaccination with live vaccines be indicated after initiation of ARCALYST treatment, the recommendation is to wait for at least 6 weeks after the last ARCALYST injection and before the next one (see section 4.4).

4.6 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 fetal morphology; however a study in pregnant monkeys showed reduced levels of oestrogen (see section 5.3). The risk for the fetus/mother is unknown. Women should use effective contraceptives during treatment with ARCALYST 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.

Lactation

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 ARCALYST should be made taking into account the benefit of breast-feeding to the child and the benefit of ARCALYST 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 ARCALYST 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 ARCALYST 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 (≥1/10); common (≥ 1/100 to <1/10), uncommon (≥1/1000 to <1/100).

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

Table 2: Adverse reactions with ARCALYST in CAPS patients

MedDRA System Organ Class	**Adverse reaction**	**Frequency**
General disorders and administration site conditions	Injection site reactions, including erythema, bruising, pruritis, 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 ARCALYST (9%) than with placebo (0%). In Part B, randomised withdrawal, the incidence of infections were similar in the ARCALYST (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 rilonacept 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 rilonacept 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 ARCALYST. 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, pruritis, 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 ARCALYST in clinical studies. Nineteen of 55 patients (35%) who had received ARCALYST 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 ARCALYST 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 ARCALYST 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 x 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 EMEA 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-1β and IL-1α, 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-1β or IL-1α.

Pharmacodynamic effects
In clinical studies, CAPS patients who have uncontrolled over-production of IL-1β 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 data
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 2. 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	-2.5*	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[1].

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

[1] Based on population PK modelling
[2] 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 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 of the reconstituted 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, ARCALYST 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. 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 ARCALYST 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 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)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE ANDMANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER 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 OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics).

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

The Marketing Authorisation Holder (MAH) shall ensure that, prior to launch, all physicians who are expected to prescribe/use Arcalyst 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 Arcalyst;
- 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 Arcalyst as treatment with Arcalyst should not be initiated in patients with neutropenia;
- The need to monitor patients for changes in their lipid profiles;
- The unknown safety of Arcalyst 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.

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 2 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 2 of 13 March 2009 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the 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 EMEA

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the annual reassessment of the benefit/risk profile.

Area	**Description**	**Due date**
Clinical SO1	The Applicant 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-1ß suppression is a concern in view of the orphan nature of the condition. The Applicant will need to propose a plan to collect data 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 Applicant is requested to assess cases for whom there is loss of efficacy to determine whether this is due to changes over time in PK/PD or antibody development. The Applicant is required to 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
Clinical SO2	Further PK steady state exposure data (AUC, C_{max}, C_{min} during steady state) especially for paediatric subjects is required. The Applicant is requested to commit to a PK study in children.	01 July 2011

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ARCALYST 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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)

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

ARCALYST 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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)

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.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT LABEL

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

Solvent for ARCALYST

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.

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

ARCALYST 80 mg/ml **powder and solvent for solution for injection**
rilonacept

Read all of this leaflet carefully before you start using this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ARCALYST IS AND WHAT IT IS USED FOR

ARCALYST is used to treat adults and adolescents aged 12 years and older with severe symptoms of Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells syndrome (MWS). ARCALYST can help reduce inflammation and the signs and symptoms of your disease, such as rash, joint pain, fever, and fatigue.

ARCALYST belongs to a group of medicines called interleukin inhibitors. ARCALYST 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, ARCALYST leads to an improvement in these symptoms.

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

2. BEFORE YOU USE ARCALYST

Do not use ARCALYST
- if you are allergic (hypersensitive) to rilonacept or to any of the other ingredients of ARCALYST (listed in section 6, ‘What ARCALYST contains’);
- if you have an active, severe infection.

Take special care with ARCALYST
You should tell your doctor if you have:
- an infection;
- [0]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.
- signs of an allergic reaction such as difficulty breathing, nausea, dizziness, skin rash, palpitations, or low blood pressure.

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

Using other medicines
Please tell your doctor or pharmacist if you are using or have recently used any other medicines, including medicines obtained without a prescription.

In particular, you should tell you doctor if you are using medicines containing any of the following active substances:

- Tumour Necrosis Factor blockers.
- Other medicines that block interleukin 1.
- Any other medicines for chronic disorders, as ARCALYST can affect how the liver processes some medicines, such as warfarin. Your doctor may need to perform some tests and adjust the dose of such medicines.

Pregnancy and breast-feeding

- You are advised to avoid becoming pregnant and must use adequate contraception while using ARCALYST and for up to six weeks after the last ARCALYST treatment. It is important to tell your doctor if you are pregnant, if you think you may be pregnant or if you plan to get pregnant. Your doctor will discuss with you the potential risk of taking ARCALYST during pregnancy.
- It is not known whether ARCALYST passes into human milk. Your doctor will discuss with you the potential risks of taking ARCALYST before breast-feeding.

ARCALYST has not been tested in pregnant women.

ARCALYST should not be used during pregnancy unless clearly necessary.

The safety of ARCALYST in breast-feeding women is unknown. If you are breast-feeding you should ask your doctor or pharmacist before using ARCALYST.

Driving and using machines

Some symptoms associated with CAPS or with ARCALYST 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 ARCALYST

Always use ARCALYST exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

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

Adults (including the elderly)
The initial dose is 320 mg (corresponding to 2 injections of 2 ml solution each), given on the same day at 2 different sites, followed by a maintenance dose of 160 mg (1 injection of 2 ml) injected once weekly

Adolescents (aged 12 to 17 years old)
The prescribed dose will depend on the body weight of the patient. The initial dose is 4.4 mg/kg body weight, up to 320 mg, delivered as one or two injections. This is followed by a maintenance dose of 2.2 mg/kg, 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 ARCALYST may need to be adjusted as the child grows. Talk with your doctor before making any dose adjustments.

How to inject ARCALYST
ARCALYST is injected under the skin (subcutaneously). The first injection of ARCALYST should be given under the supervision of a trained healthcare professional. You or your caregiver will receive adequate training on how to reconstitute the powder (dissolve to make a solution), prepare the dose, and administer the injection. Detailed instructions are also provided at the end of this leaflet.

If you use more ARCALYST than you should
There are no reported overdoses in patients. In case of a possible overdose you should contact your doctor immediately.

If you forget to use ARCALYST
If you miss a dose of ARCALYST and remember within a few days, inject it as soon as you remember. The next dose should be taken at the next regularly scheduled time. Do not take a double dose to make up for the forgotten dose.

4. POSSIBLE SIDE EFFECTS

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

You must tell your doctor immediately if any of the following serious side effects occur while you are using ARCALYST:

• **Serious infections.** You should talk to your doctor immediately if you develop symptoms of an infection while being treated with ARCALYST, such as
prolonged fever (i.e. 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 ARCALYST if you develop a severe infection.

• **Allergic reactions.** If you develop signs of an allergic (hypersensitivity) reaction during treatment with ARCALYST (for example, rash, swollen face, trouble breathing), tell your doctor immediately.

Side effects may occur with certain frequencies, which are defined as follows:

- very common: affects 1 or more user in 10
- common: affects 1 to up to 10 users in 100
- uncommon: affects 1 to up to10 users in 1,000
- rare: affects 1 to up to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

<u>Very common side effects</u>
Injection-site reactions. These include redness, swelling, itching, and bruising at the injection site. Most injection-site reactions are mild and will go away in one to two days.
Upper respiratory infection
Sinus infection
Headache

<u>Common side effects</u>
Viral infection
Bronchitis
Skin, eye, or ear infection
Fatigue
Increased blood pressure
Pneumonia
Stomach/Intestinal infection
Dizziness
Flushing
Allergic reaction
Anxiety
Insomnia

<u>Uncommon side effects</u>
Meningitis
Inflammation of the eye (iritis)

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

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ARCALYST

Keep out of the reach and sight of children.

Do not use ARCALYST 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 ARCALYST solution, it is best if used immediately 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 reconstitution

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.

Medicines should not be disposed of via wastewater or household waste. Ask pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ARCALYST contains

- The active substance is rilonacept. Each vial of powder contains 220 mg rilonacept. After reconstitution, each ml of solution contains 80 mg rilonacept.

- The other ingredients in the powder are glycine, arginine hydrochloride, histidine, histidine hychloride monohydrate, polyethylene glycol 3350 and sucrose. The solvent is water for injections.

What ARCALYST looks like and contents of the pack

ARCALYST is provided as a powder and solvent for solution for injection. The powder is white to off-white and the solvent is a colourless liquid.

Powder vial: 20 ml clear type 1 glass vial with rubber stopper and lacquered flip-off aluminum seal containing 220 mg rilonacept.

Solvent: 5 ml transparent plastic (LDPE) vial 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

Marketing Authorisation HolderRegeneron 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 approved in

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

Instructions for use

STEP 1: Setting up for an injection

1. Wash your hands well with soap and water, and dry with a clean towel.

2. Put the following items on a clean table, or other flat surface, for each injection (see Figure 1):
    - 2 sterile, 3-ml disposable syringes with markings at each 0.1 ml (see Figure 2):
        - one needed for dissolving (reconstituting) ARCALYST
        - one needed for injection
    - 2 sterile disposable needles (27-gauge, ½-inch)
        - one needed for dissolving (reconstituting) ARCALYST
        - one needed for injection
    - 1 vial of ARCALYST powder for solution for injection
    - 1 vial of solvent (water for injections)

    You will also need (not provided in the prescription pack):
    - 2 alcohol wipes
    - 1 2x2 gauze pad
    - 1 puncture-resistant container for disposal of used needles, syringes and vials

    Ask your pharmacist for these supplies.

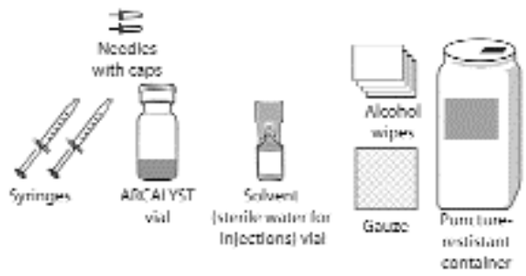

Figure 1

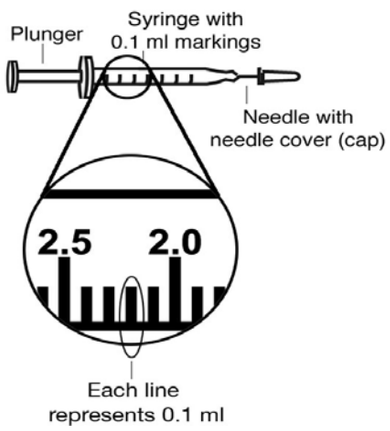

Figure 2

• Do not touch the needles or the rubber stopper on the ARCALYST 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 the 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-proof container right after use. Do not try to recap the needle.

STEP 2: Preparing the ARCALYST vial

1. Check the expiration date on the carton of ARCALYST. Do not use ARCALYST after the expiry date which is stated on the vial label and carton after EXP. The expiry date refers to the last day of that month.

2. Remove the protective plastic cap from the ARCALYST vial.

3. Clean the top of the ARCALYST vial with an alcohol wipe, wiping in one direction around the top
4. Set the vial aside.

STEP 3: Preparing the solvent vial

1. Snap off the plastic tab on the top of the solvent (water for injections) vial.

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 the syringe by pulling apart the tabs.

3. Attach the exposed top of the solvent vial to the top of a syringe by twisting the syringe onto the solvent vial (see Figure3).

Figure 3

4. Hold the vial in one hand and the syringe in the other hand and carefully turn the vial upside down. Hold the syringe at eye level.

5. Slowly pull back on the syringe plunger to the 2.5 ml line on the syringe (see Figure 4).

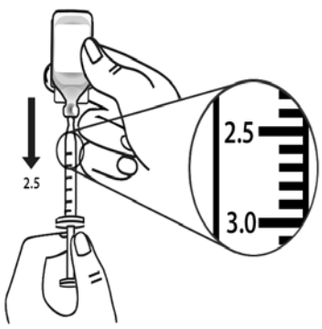

Figure 4

6. 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 5).

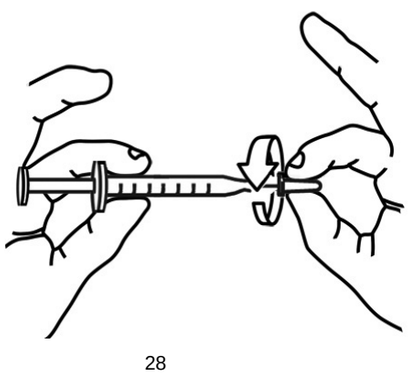

Figure 5

7. Turn the syringe so that the needle is facing straight up. Remove the needle cap. Gently tap the syringe until air bubbles rise to the top of the syringe (see Figure 6).

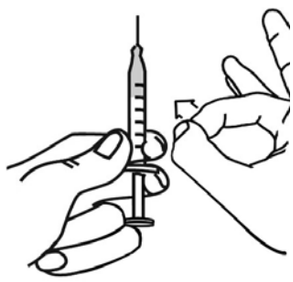

Figure 6

8. With the syringe and needle pointed upward push the syringe plunger to expel any excess solvent until the 2.3 ml line is matched (see Figure 7).

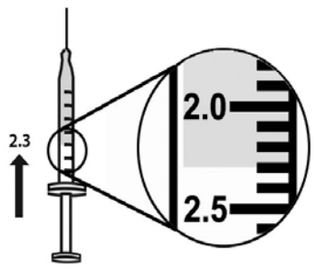

Figure 7

STEP 4: Dissolving (reconstituting) ARCALYST

1. With one hand, hold the ARCALYST vial on a firm surface.

2. With the other hand, take the syringe with the solvent and slowly insert the needle straight down through the centre of the rubber stopper of the ARCALYST vial. Direct the water stream to gently go down the side of the vial into the powder (see Figure 8).

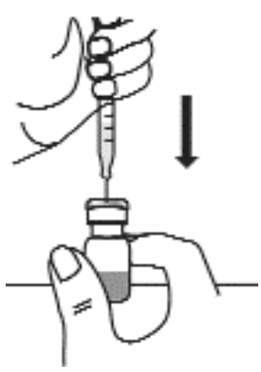

Figure 8

3. Push the plunger in all the way to inject the solvent into the vial.

4. Remove the syringe and needle from the stopper and throw away the needle, syringe, and solvent vial in the puncture-resistant container. Do not try to put the needle cover back on the needle.

5. Hold the vial containing the mixture of powder and solvent (water for injections) 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.

6. Put the vial back on the table and let the vial sit for about 1 minute.

7. Look at the vial for any particles or clumps of powder which have not dissolved.

8. 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.

9. Repeat step 8 until the powder is completely dissolved and the solution is clear.

10. The dissolved ARCALYST should be a thick, clear liquid, colourless to pale yellow in colour. Do not use the solution if it is discoloured or cloudy, or if small particles are in it (see Figure 9).

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

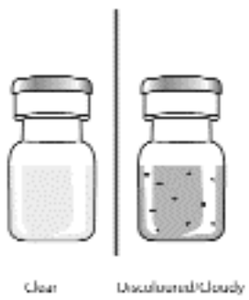

Figure 9

11. After preparing the solution, it is best if used immediately. If necessary, the product may be kept at room temperature (20 to 25°C), but should be used within 3 hours of reconstitution. Keep ARCALYST 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 powder vial with a new alcohol wipe.

2. Take a new sterile, disposable needle and attach securely to a new syringe without removing the needle cover.

3. The amount of air you draw into the syringe should equal the volume of the solution that your doctor has prescribed for you to inject.

4. To draw air into the syringe, hold the syringe at eye level. Do not remove the needle cover. 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 (see Figure 10).

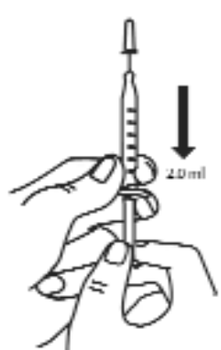

Figure 10

5. 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 11).

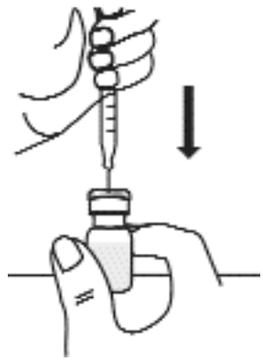

Figure 11

6. 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.

7. 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 12).

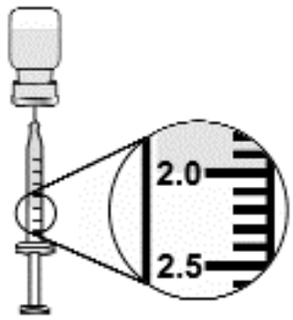

Figure 12

8. Keep the vial upside down with the needle straight up, and gently tap the syringe until any air bubbles rise to the top of the syringe (see Figure 13). It is important to remove air bubbles so that you withdraw up the correct amount of medicine from the vial.

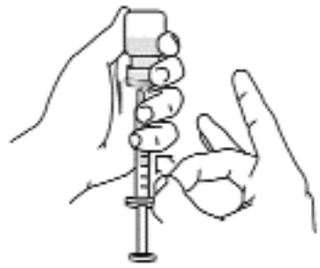

Figure 13

9. To remove the air bubbles, slowly and gently push in the plunger so only the air is pushed through the needle.

10. Check to make sure that you have the amount of medicine prescribed by your doctor in the syringe.

11. 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 ARCALYST more than one time.

12. 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. ARCALYST is given by subcutaneous injection, an injection that is given into the tissue directly below the layers of skin. It is not meant to go into any muscle, vein, or artery.

   You should change (rotate) the sites and inject in a different place each time in order to keep your skin healthy.

   Rotating 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 ARCALYST include the left and right sides of the abdomen, and left and right thighs. If someone else is giving the injection, the upper left and right arms may also be used for injection (see Figure 14):

   (Do not inject within a 2-inch area around the navel)

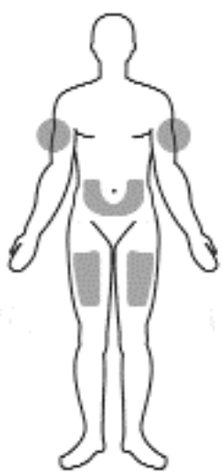

Figure 14

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.

3. Hold the syringe in one hand like you would hold a pencil.

4. With the other hand gently pinch a fold of skin at the cleaned site for injection (see Figure 15).

Figure 15

5. Use a quick “dart like” motion to insert the needle straight into the skin (90° angle) (see Figure 15). 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 16).

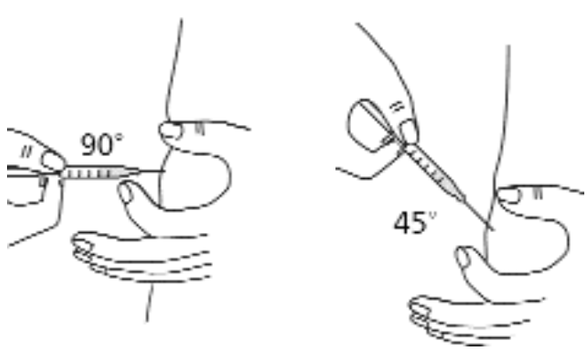

Figure 16

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 (see Figure 17).

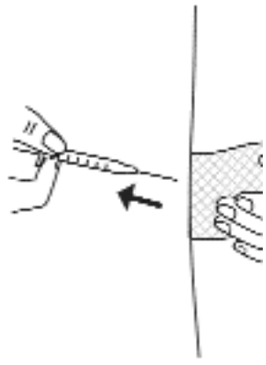

Figure 17

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.

The following information is intended for medical or healthcare professionals only:

Indication

ARCALYST 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. ARCALYST 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 ARCALYST 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)

Dose modification is not required based on advanced age.

Renal impairment

No dose adjustment is required in patients with mild, moderate or severe renal impairment, or end stage renal disease.

Hepatic impairment

ARCALYST has not been studied in patients with hepatic impairment.

Method of administration

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

The adult dose 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: ARCALYST 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, ARCALYST 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. 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 ARCALYST 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.