DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

STN: BL 125249/0

BLA APPROVAL

FEB 27 2008

Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Attention: Mierette R. Stocker
Associate Director, Regulatory Affairs

Dear Ms. Stocker:

Please refer to your biologics license application (BLA) dated May 25, 2007, received May 29, 2007, submitted under section 351 of the Public Health Service Act for Arcalyst (rilonacept).

We acknowledge receipt of your submissions dated June 26 (2), July 2, 24, and 26, August 20 and 24, September 24 and 27, October 3, 25, and 26, and December 19, 2007, and January 23 and 25, and February 13, 22, and 27, 2008.

We also acknowledge receipt of your submission dated October 26, 2007, which constituted a major amendment.

We are issuing Department of Health and Human Services U.S. License No. 1760 to Regeneron Pharmaceuticals, Tarrytown, New York, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Arcalyst (rilonacept). Arcalyst is indicated for treatment for cryopyrin-associated periodic syndromes (CAPS).

Under this license, you are approved to manufacture rilonacept drug substance at your Regeneron facility in Rensselaer, New York. The final lyophilized drug product will be manufactured at the [redacted] The final lyophilized drug product will be labeled and packaged at [redacted] You may label your product with the proprietary name Arcalyst and market it in 20-mL, single-use vials, each containing 220 mg of rilonacept.

The dating period for Arcalyst shall be 18 months from the date of manufacture when stored at 2 - 8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your formulated drug substance shall be 18 months when stored at ≤ -20°C. We have approved the stability protocols in your license

application for the purpose of extending the expiration dating period of your formulated drug substance and drug product under 21 CFR 601.12.

You currently are not required to submit samples of future lots of Arcalyst to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling text, submitted February 27, 2008, for the package insert and the patient package insert. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, **"SPL for approved STN BL 125249/0."**

Pursuant to 21 CFR 201.57(c)(18) and 201.80(f)(2), patient labeling must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling.

CARTON AND CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and container labels, submitted February 27, 2008, as soon as they are available but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission **"Product Correspondence – Final Printed Carton and Container Labels for approved STN BL 125249/0."** Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because Arcalyst for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING STUDY COMMITMENTS SUBJECT TO THE REPORTING REQUIREMENTS OF 21 CFR 601.70

We acknowledge your written commitments as described in your letters dated February 27, 2008 as outlined below:

Nonclinical

1. To conduct a study in cynomolgus monkeys examining the effects of rilonacept exposure of the pregnant female during the third trimester of development. You will submit a detailed outline of the study and rationale for review.

   Protocol Submission: by April 2008
   Study Completion: by January 2010
   Final Report Submission: by October 2010

2. To conduct a juvenile animal study in cynomolgus monkeys to assess effects on sex hormones and bone development. You will submit a detailed outline of the study and rationale for review.

   Protocol Submission: by April 2008
   Study Start: by January 2010
   Final Report Submission: by October 2010

Clinical

3. To assess the safety of long-term use of rilonacept in the pediatric patient population by establishing a pediatric registry. The registry will collect information on growth and development as well as adverse events, particularly serious infections. The duration of the study will be at least five years.

   Study Completion: by July 2013
   Final Report Submission: by January 2014

4. To conduct a pharmacokinetics (PK) study in the pediatric population.

   Study Completion: by January 2010
   Final Report Submission: by July 2010

5. To assess whether either lower maintenance doses or a longer interval between doses could be equally effective as, but potentially safer than, the approved dose. The study could be designed to randomize patients on rilonacept to blindly continue on the approved dose or to switch to a lower dose or a longer interval between doses and to assess symptom scores over, for example, 9 weeks.

Submission of supporting data: by April 2008
Study Completion (if needed): by January 2010
Final Report Submission: by July 2010

POSTMARKETING STUDY COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS OF 21 CFR 601.70

1. Pharmacovigilance: In addition to standard pharmacovigilance practices, for the first five years of marketing, particular attention will focus on reports of serious infections, pregnancy outcomes, and off-label use.

   Study Completion: by January 2014
   Final Report Submission: Quarterly reporting for the first three years, then annually

2. To assess release and shelf-life specifications for rilonacept drug substance, formulated drug substance, and drug product, as appropriate. Data and specifications assessment will be provided two years from time of approval and reported in an annual report.

   Study Completion: by April 2010
   Final Report Submission: by Annual Report 2010

3. To perform validation studies on the modified assay that measures [redacted] in rilonacept drug substance, formulated drug substance, and drug product. Using those data, to establish [redacted] content specification for drug substance, formulated drug substance, and drug product release and stability, and drug substance, formulated drug substance, drug product reference standard qualification and stability. The protocol, final report, and proposed specifications will be submitted as a CBE-30 supplement.

   Study Completion: by January 2009 ([redacted])
   Final Report Submission: by April 2009 (CBE-30)

4. To validate the [redacted] species at the concentration of intended use with alternative orthogonal analytical methods. Methods such as [redacted] should also address [redacted]. The full validation package will be submitted as an annual report. In addition, a re-assessment of specifications based on the validated method will be included in the annual report.

   Study Completion: by April 2009
   Final Report Submission: by Annual Report 2009 ([redacted])

5. To validate the DS, FDS, and DP rilonacept [redacted] assay for the new proposed acceptance criteria [redacted]

ranges). The validation protocol and report will be submitted to the Agency in the annual report.

Study Completion: by April 2009
Final Report Submission: by Annual Report 2009

6. To qualify the additional assays used for Assay qualifications reports will be submitted in the annual report.

Study Completion: by April 2009
Final Report Submission: by Annual Report 2009

7. To perform an adequate study The study will be performed prior to the next manufacturing campaign of rilonacept, and the study report will be submitted in the annual report.

Study Completion: by January 2009
Final Report Submission: by Annual Report 2009

8. To re-qualify in the test. The qualification procedures and summary data will be submitted in the annual report.

Study Completion: by April 2009
Final Report Submission: by Annual Report 2009

9. If Regeneron performs testing in lieu of testing and/or testing, a direct or indirect correlation of the two tests will be performed. Correlation studies at a that is comparable to the sensitivity of the test will be performed. Results will be submitted in the first annual report after the testing is completed.

Study Completion: by April 2009
Final Report Submission: by Annual Report 2009

10. To perform stability testing on one lot of rilonacept formulated drug substance and one lot of drug product annually for each year in which rilonacept formulated drug substance or drug product is manufactured. The ongoing stability program will continue until testing of all remaining time points from the lots used to support the approved shelf life have been reached. These stability data will be submitted in the annual report.

Additionally, lots that are manufactured following significant changes to the approved manufacturing process or facility, and lots that are reprocessed outside of the approved manufacturing process will be placed on stability.

Study Completion:	Annual reporting
Final Report Submission:	Annual reporting

Submit clinical protocols to your IND, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this BLA. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments, as appropriate:

- Postmarketing Study Commitment Protocol
- Postmarketing Study Commitment - Final Study Report
- Postmarketing Study Correspondence
- Annual Status Report of Postmarketing Study Commitments

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the February 2006 Guidance for Industry: *Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997* (see http://www.fda.gov/cder/guidance/5569fnl.htm) for further information.

PROMOTIONAL MATERIALS

You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this BLA and to the following address:

MedWatch, HFD-001
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to the following address:

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the following address:

Division of Compliance Risk Management and Surveillance
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20903

Biological product deviations sent by courier or overnight mail should also be sent to this address.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging, or labeling of rilonacept or in the manufacturing facilities.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Kathleen Davies, Regulatory Project Manager, at (301) 796-2205.

Sincerely,

MD, MPH

Curtis Rosebraugh, M.D., M.P.H.
Acting Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures (3):
Package Insert
Patient Package Insert
Carton and Immediate Container Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ARCALYST safely and effectively. See full prescribing information for ARCALYST.

ARCALYST™ (rilonacept)
Injection for Subcutaneous Use
Initial U.S. Approval: 200X

----------INDICATIONS AND USAGE----------
ARCALYST (rilonacept) is an interleukin-1 blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older. (1)

----------DOSAGE AND ADMINISTRATION----------
- Adult patients 18 yrs and older: Initiate treatment with a loading dose of 320 mg delivered as two, 2-mL, subcutaneous injections of 160 mg on the same day at two different sites. Continue dosing with a once-weekly injection of 160 mg administered as a single, 2-mL, subcutaneous injection. Do not administer ARCALYST more often than once weekly. (2)
- Pediatric patients aged 12 to 17 years: Initiate treatment with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two subcutaneous injections with a maximum single-injection volume of 2 mL. Continue dosing with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection, up to 2 mL. If the initial dose is given as two injections, they should be given on the same day at two different sites. Do not administer ARCALYST more often than once weekly. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Sterile, single-use 20-mL, glass vial containing 220 mg of rilonacept as a lyophilized powder for reconstitution. (3)

----------CONTRAINDICATIONS----------
None.

----------WARNINGS AND PRECAUTIONS----------
- Interleukin-1 blockade may interfere with immune response to infections. Serious, life-threatening infections have been reported in patients taking ARCALYST. Discontinue treatment with ARCALYST if a patient develops a serious infection. Do not initiate treatment with ARCALYST in patients with active or chronic infections. (5.1)
- Hypersensitivity reactions associated with ARCALYST administration have been rare. If a hypersensitivity reaction occurs, discontinue administration of ARCALYST and initiate appropriate therapy. (5.5)
- Live vaccines should not be given concurrently with ARCALYST. Prior to initiation of therapy with ARCALYST, patients should receive all recommended vaccinations. (5.3)

----------ADVERSE REACTIONS----------
The most common adverse reactions reported by patients with CAPS treated with ARCALYST are injection-site reactions and upper respiratory tract infections. (6.2, 6.3)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-877-REGN-777 (1-877-734-6777) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
No formal drug interaction studies have been conducted with ARCALYST. (7)

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy – No human data. Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: m/year

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ARCALYST™ (rilonacept) is an interleukin-1 blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

INJECTION FOR SUBCUTANEOUS USE ONLY.

2.2 Dosing

Adult patients 18 years and older: Treatment should be initiated with a loading dose of 320 mg delivered as two, 2 mL, subcutaneous injections of 160 mg each given on the same day at two different sites. Dosing should be continued with a once-weekly injection of 160 mg administered as a single, 2-mL, subcutaneous injection. ARCALYST should not be given more often than once weekly. Dosage modification is not required based on advanced age or gender.

Pediatric patients aged 12 to 17 years: Treatment should be initiated with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two subcutaneous injections with a maximum single-injection volume of 2 mL. Dosing should be continued with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection, up to 2 mL. If the initial dose is given as two injections, they should be given on the same day at two different sites. ARCALYST should not be given more often than once weekly.

2.3 Preparation for Administration

Each single-use vial of ARCALYST contains a sterile, white to off-white, preservative-free, lyophilized powder. Reconstitution with 2.3 mL of preservative-free Sterile Water for Injection (supplied separately) is required prior to subcutaneous administration of the drug.

2.4 Administration

Using aseptic technique, withdraw 2.3 mL of preservative-free Sterile Water for Injection through a 27-gauge, ½-inch needle attached to a 3-mL syringe and inject the preservative-free Sterile Water for Injection into the drug product vial for reconstitution. The needle and syringe used for reconstitution with preservative-free Sterile Water for Injection should then be discarded and should not be used for subcutaneous injections. After the addition of preservative-free Sterile Water for Injection, 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 withdrawal volume of up to 2 mL for subcutaneous administration. The reconstituted solution is viscous, clear, colorless to pale yellow, and essentially free from particulates. 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 in that vial should not be used.

Using aseptic technique, withdraw the recommended dose volume, up to 2 mL (160 mg), of the solution with a new 27-gauge, ½-inch needle attached to a new 3-mL syringe for subcutaneous injection. EACH VIAL SHOULD BE USED FOR A SINGLE DOSE ONLY. Discard the vial after withdrawal of drug.

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.

2.5 Stability and Storage

The lyophilized ARCALYST product is to be stored refrigerated at 2° to 8°C (36° to 46°F) inside the original carton to protect it from light. Do not use beyond the date stamped on the label. After reconstitution, ARCALYST may be kept at room temperature, should be protected from light, and should be used within three hours of reconstitution. ARCALYST does not contain preservatives; therefore, unused portions of ARCALYST should be discarded.

3 DOSAGE FORMS AND STRENGTHS

ARCALYST is supplied in sterile, single-use, 20-mL, glass vials. Each vial contains 220 mg of rilonacept as a white to off-white, preservative-free, lyophilized powder. Reconstitution with 2.3 mL of preservative-free Sterile Water for Injection is required prior to subcutaneous administration of the drug. The reconstituted ARCALYST is a viscous, clear, colorless to pale yellow, essentially free from particulates, 80-mg/mL solution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Interleukin -1 (IL-1) blockade may interfere with the immune response to infections. Treatment with another medication that works through inhibition of IL-1 has been associated with an increased risk of serious infections, and serious infections have been reported in patients taking

ARCALYST [*see Clinical Studies (14)*]. There was a greater incidence of infections in patients on ARCALYST compared with placebo. In the controlled portion of the study, one infection was reported as severe, which was bronchitis in a patient on ARCALYST.

In an open-label extension study, one patient developed bacterial meningitis and died [*see Adverse Reactions (6.3)*]. ARCALYST should be discontinued if a patient develops a serious infection. Treatment with ARCALYST should not be initiated in patients with an active or chronic infection.

In clinical studies, ARCALYST has not been administered concomitantly with tumor necrosis factor (TNF) inhibitors. An increased incidence of serious infections has been associated with administration of an IL-1 blocker in combination with TNF inhibitors. **Taking ARCALYST with TNF inhibitors is not recommended because this may increase the risk of serious infections.**

Drugs that affect the immune system by blocking TNF have been associated with an increased risk of reactivation of latent tuberculosis (TB). It is possible that taking drugs such as ARCALYST that block IL-1 increases the risk of TB or other atypical or opportunistic infections. Healthcare providers should follow current CDC guidelines both to evaluate for and to treat possible latent tuberculosis infections before initiating therapy with ARCALYST.

5.2 Immunosuppression

The impact of treatment with ARCALYST on active and/or chronic infections and the development of malignancies is not known [*see Adverse Reactions (6.3)*]. However, treatment with immunosuppressants, including ARCALYST, may result in an increase in the risk of malignancies.

5.3 Immunizations

Since no data are available on either the efficacy of live vaccines or on the risks of secondary transmission of infection by live vaccines in patients receiving ARCALYST, live vaccines should not be given concurrently with ARCALYST. In addition, because ARCALYST may interfere with normal immune response to new antigens, vaccinations may not be effective in patients receiving ARCALYST. No data are available on the effectiveness of vaccination with inactivated (killed) antigens in patients receiving ARCALYST.

Because IL-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with ARCALYST adult and pediatric patients receive all recommended vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine. (See current Recommended Immunizations schedules at the website of the Centers for Disease Control. http://www.cdc.gov/vaccines/recs/schedules/).

5.4 Lipid Profile Changes

Patients should be monitored for changes in their lipid profiles and provided with medical treatment if warranted *[see Adverse Reactions (6.7)]*.

5.5 Hypersensitivity

Hypersensitivity reactions associated with ARCALYST administration in the clinical studies were rare. If a hypersensitivity reaction occurs, administration of ARCALYST should be discontinued and appropriate therapy initiated.

6 ADVERSE REACTIONS

Six serious adverse reactions were reported by four patients during the clinical program. These serious adverse reactions were *Mycobacterium intracellulare* infection; gastrointestinal bleeding and colitis; sinusitis and bronchitis; and *Streptococcus pneumoniae* meningitis [*see Adverse Reactions (6.3)*].

The most commonly reported adverse reaction associated with ARCALYST was injection-site reaction (ISR) [*see Adverse Reactions (6.2)*]. The next most commonly reported adverse reaction was upper respiratory infection [*see Adverse Reactions (6.3)*].

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described herein reflect exposure to ARCALYST in 600 patients, including 85 exposed for at least 6 months and 65 exposed for at least one year. These included patients with CAPS, patients with other diseases, and healthy volunteers. Approximately 60 patients with CAPS have been treated weekly with 160 mg of ARCALYST. The pivotal trial population included 47 patients with CAPS. These patients were between the ages of 22 and 78 years (average 51 years). Thirty-one patients were female and 16 were male. All of the patients were White/Caucasian. Six pediatric patients (12-17 years) were enrolled directly into the open-label extension phase.

6.1 Clinical Trial Experience

Part A of the clinical trial was conducted in patients with CAPS who were naïve to treatment with ARCALYST. Part A of the study was a randomized, double-blind, placebo-controlled, six-week study comparing ARCALYST to placebo [*see Clinical Studies (14)*]. Table 1 reflects the frequency of adverse events reported by at least two patients during Part A.

Table 1: Most Frequent Adverse Reactions (Part A, Reported by at Least Two Patients)

Adverse Event	ARCALYST 160 mg (n=23)	Placebo (n=24)
Any AE	17 (74%)	13 (54%)
Injection-site reactions	11 (48%)	3 (13%)
Upper respiratory tract infection	6 (26%)	1 (4%)
Nausea	1 (4%)	3 (13%)
Diarrhea	1 (4%)	3 (13%)
Sinusitis	2 (9%)	1 (4%)
Abdominal pain upper	0	2 (8%)
Cough	2 (9%)	0
Hypoesthesia	2 (9%)	0
Stomach discomfort	1 (4%)	1 (4%)
Urinary tract infection	1 (4%)	1 (4%)

6.2 Injection-Site Reactions

In patients with CAPS, the most common and consistently reported adverse event associated with ARCALYST was injection-site reaction (ISR). The ISRs included erythema, swelling, pruritis, mass, bruising, inflammation, pain, edema, dermatitis, discomfort, urticaria, vesicles, warmth and hemorrhage. Most injection-site reactions lasted for one to two days. No ISRs were assessed as severe, and no patient discontinued study participation due to an ISR.

6.3 Infections

During Part A, the incidence of patients reporting infections was greater with ARCALYST (48%) than with placebo (17%). In Part B, randomized withdrawal, the incidence of infections were similar in the ARCALYST (18%) and the placebo patients (22%). 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 360 patients treated with rilonacept and 179 treated with placebo, the incidence of infections was 34% and 27% (2.15 per patient-exposure year and 1.81 per patient-exposure year), respectively, for rilonacept and placebo.

Serious Infections: One subject receiving ARCALYST for an unapproved indication in another study developed an infection in his olecranon bursa with ~~m~~*Mycobacterium intracellulare*. The patient was on chronic glucocorticoid treatment. The infection occurred after an intraarticular glucocorticoid injection into the bursa with subsequent local exposure to a suspected source of mycobacteria. The patient recovered after the administration of the appropriate antimicrobial therapy. One patient treated for another unapproved indication developed bronchitis/sinusitis, which resulted in hospitalization. One patient died in an open-label study of CAPS from *Streptococcus pneumoniae* meningitis.

6.4 Malignancies

[see Warnings and Precautions (5.2)].

6.5 Hematologic Events

One patient in a study in an unapproved indication developed transient neutropenia (ANC < 1 x 10^9/L) after receiving a large dose (2000 mg intravenously) of ARCALYST. The patient did not experience any infection associated with the neutropenia.

6.6 Immunogenicity

Antibodies directed against the receptor domains of rilonacept were detected by an ELISA assay in patients with CAPS after treatment with ARCALYST. Nineteen of 55 subjects (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, seven tested positive at the last assessment (Week 18 or 24 of the open-label extension period), and five subjects tested positive for neutralizing antibodies on at least one occasion. There was no correlation of antibody activity and either clinical effectiveness or safety.

The data reflect the percentage of patients whose test results were positive for antibodies to the rilonacept receptor domains in specific assays, and are highly dependent on the sensitivity and specificity of the assays. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, 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.

6.7 Lipid profiles

Cholesterol and lipid levels may be reduced in patients with chronic inflammation. Patients with CAPS treated with ARCALYST experienced increases in their mean total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. The mean increases from baseline for total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were 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.

7 DRUG INTERACTIONS

7.1 TNF-blocking agent and IL-1 blocking agent

Specific drug interaction studies have not been conducted with ARCALYST. Concomitant administration of another drug that blocks IL-1 with a TNF-blocking agent in another patient population has been associated with an increased risk of serious infections and an increased risk of neutropenia. The concomitant administration of ARCALYST with TNF-blocking agents may also result in similar toxicities and is not recommended [*see Warnings and Precautions (5.1)*].

The concomitant administration of ARCALYST with other drugs that block IL-1 has not been studied. Based upon the potential for pharmacologic interactions between rilonacept and a recombinant IL-1ra, concomitant administration of ARCALYST and other agents that block IL-1 or its receptors is not recommended.

7.2 Cytochrome P450 Substrates

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) 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 drug concentration should be performed and the individual dose of the medicinal product may need to be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies of ARCALYST in pregnant women. Based on animal data, ARCALYST may cause fetal harm. An embryo-fetal developmental toxicity study was performed in cynomolgus monkeys treated with 0, 5, 15 or 30 mg/kg given twice a week (highest dose is approximately 3.7-fold higher than the human doses of 160 mg based on body surface area). The fetus of the only monkey with exposure to rilonacept during the later period of gestation showed multiple fusion and absence of the ribs and thoracic vertebral bodies and arches. Exposure to rilonacept during this time period was below that expected clinically. Likewise, in the cynomolgus monkey, all doses of rilonacept reduced serum levels of estradiol up to 64% compared to controls and increased the incidence of lumbar ribs compared to both control animals and historical control incidences. In perinatal and postnatal developmental toxicology studies in the mouse model using a murine analog of rilonacept (0, 20, 100 or 200 mg/kg), there was a 3-fold increase in the number of stillbirths in dams treated with 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). ARCALYST should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Nonteratogenic effects. A peri- and post-natal reproductive toxicology study was performed in which mice were subcutaneously administered a murine analogue of rilonacept at doses of 20, 100, 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). Results indicated an increased incidence in unscheduled deaths of the F_1 offspring during maturation at all doses tested.

8.3 Nursing Mothers

It is not known whether rilonacept is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ARCALYST is administered to a nursing woman.

8.4 Pediatric Use

Six pediatric patients with CAPS between the ages of 12 and 16 were treated with ARCALYST at a weekly, subcutaneous dose of 2.2 mg/kg (up to a maximum of 160 mg) for 24-weeks during the open-label extension phase. These patients showed improvement from baseline in their symptom scores and in objective markers of inflammation (e.g. Serum Amyloid A and C-Reactive Protein). The adverse events included injection site reactions and upper respiratory symptoms as were commonly seen in the adult subjects.

The trough drug levels for four pediatric patients measured at the end of the weekly dose interval (mean 20 mcg/mL, range 3.6 to 33 mcg/mL) were similar to those observed in adult patients with CAPS (mean 24 mcg/mL, range 7-56 mcg/mL).

Safety and effectiveness in pediatric patients below the age of 12 have not been established.

When administered to pregnant primates, rilonacept treatment may have contributed to alterations in bone ossification in the fetus. It is not known if ARCALYST will alter bone development in pediatric patients. Pediatric patients treated with ARCALYST should undergo appropriate monitoring for growth and development. [*see Use in Specific Populations (8.1)*]

8.5 Geriatric Use

In the placebo-controlled clinical studies in patients with CAPS and other indications, 70 patients randomized to treatment with ARCALYST were ≥ 65 years of age, and 6 were ≥ 75 years of age. In the CAPS clinical trial, efficacy, safety and tolerability were generally similar in elderly patients as compared to younger adults; however, only ten patients ≥ 65 years old participated in the trial. In an open-label extension study of CAPS, a 71 year old woman developed bacterial meningitis and died [*see Adverse Reactions (6.3)*]. Age did not appear to have a significant effect on steady-state trough concentrations in the clinical study.

8.6 Patients with Renal Impairment

No formal studies have been conducted to examine the pharmacokinetics of rilonacept administered subcutaneously in patients with renal impairment.

8.7 Patients with Hepatic Impairment

No formal studies have been conducted to examine the pharmacokinetics of rilonacept administered subcutaneously in patients with hepatic impairment.

10 OVERDOSAGE

There have been no reports of overdose with ARCALYST. Maximum weekly doses of up to 320 mg have been administered subcutaneously for up to approximately 18 months in a small number of patients with CAPS and up to 6 months in patients with an unapproved indication in clinical trials without evidence of dose-limiting toxicities. In addition, ARCALYST given intravenously at doses up to 2000 mg monthly in another patient population for up to six months were tolerated without dose-limiting toxicities. The maximum amount of ARCALYST that can be safely administered has not been determined.

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

11 DESCRIPTION

Rilonacept is a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the human interleukin-1 receptor component (IL-1RI) and IL-1 receptor accessory protein (IL-1RAcP) linked in-line to the Fc portion of human IgG1. Rilonacept has a molecular weight of approximately 251 kDa. Rilonacept is expressed in recombinant Chinese hamster ovary (CHO) cells.

ARCALYST is supplied in single-use, 20-mL glass vials containing a sterile, white to off-white, lyophilized powder. Each vial of ARCALYST is to be reconstituted with 2.3 mL of Sterile Water for Injection. A volume of up to 2 mL can be withdrawn, which is designed to deliver 160 mg for subcutaneous administration only. The resulting solution is viscous, clear, colorless to pale yellow, and essentially free from particulates. Each vial contains 220 mg rilonacept (80 mg/ 1 mL after reconstitution), histidine, arginine, polyethylene glycol 3350, sucrose, and glycine at a pH of 6.5 ± 0.3. No preservatives are present.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CAPS refer to rare genetic syndromes generally caused by mutations in the NLRP-3 [Nucleotide-binding domain, leucine rich family (NLR), pyrin domain containing 3] gene (also known as Cold-Induced Auto-inflammatory Syndrome-1 [*CIAS1*]). CAPS disorders are inherited in an autosomal dominant pattern with male and female offspring equally affected. Features common to all disorders include fever, urticaria-like rash, arthralgia, myalgia, fatigue, and conjunctivitis.

In most cases, inflammation in CAPS is associated with mutations in the NLRP-3 gene which encodes the protein cryopyrin, an important component of the inflammasome. Cryopyrin regulates the protease caspase-1 and controls the activation of interleukin-1 beta (IL-1β). Mutations in NLRP-3 result in an overactive inflammasome resulting in excessive release of activated IL-1β that drives inflammation.

Rilonacept blocks IL-1β signaling by acting as a soluble decoy receptor that binds IL-1β and prevents its interaction with cell surface receptors. Rilonacept also binds IL-1α and IL-1 receptor antagonist (IL-1ra) with reduced affinity. The equilibrium dissociation constants for rilonacept binding to IL-1β, IL-1α and IL-1ra were 0.5 pM, 1.4 pM and 6.1 pM, respectively.

12.2 Pharmacodynamics

C-Reactive Protein (CRP) and Serum Amyloid A (SAA) are indicators of inflammatory disease activity that are elevated in patients with CAPS. Elevated SAA has been associated with the development of systemic amyloidosis in patients with CAPS. Compared to placebo, treatment with ARCALYST resulted in sustained reductions from baseline in mean serum CRP and SAA to normal levels during the clinical trial. ARCALYST also normalized mean SAA from elevated levels.

12.3 Pharmacokinetics

The average trough levels of rilonacept were approximately 24 mcg/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.

No pharmacokinetic data are available in patients with hepatic or 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 subjects. 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 study, reflecting the epidemiology of the disease.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of rilonacept. The mutagenic potential of rilonacept was not evaluated.

Male and female fertility was evaluated in a mouse surrogate model using a murine analog of rilonacept. Male mice were treated beginning 8 weeks prior to mating and continuing through female gestation day 15. Female mice were treated for 2 weeks prior to mating and on gestation days 0, 3, and 6. The murine analog of rilonacept did not alter either male or female fertility parameters at doses up to 200 mg/kg (this dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area).

14 CLINICAL STUDIES

The safety and efficacy of ARCALYST for the treatment of CAPS was demonstrated in a randomized, double-blind, placebo-controlled study with two parts (A and B) conducted sequentially in the same patients with FCAS and MWS.

Part A was a 6-week, randomized, double-blind, parallel-group period comparing ARCALYST at a dose of 160 mg weekly after an initial loading dose of 320 mg to placebo. Part B followed immediately after Part A and consisted of a 9-week, patient-blind period during which all subjects received ARCALYST 160 mg weekly, followed by a 9-week, double-blind, randomized withdrawal period in which patients were randomly assigned to either remain on ARCALYST 160 mg weekly or to receive placebo. Patients were then given the option to enroll in a 24-week, open-label treatment extension phase in which all patients were treated with ARCALYST 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 randomized parallel-group period (Part A) and the randomized withdrawal period (Part B) of the study are shown in Table 2. ARCALYST-treated patients had a larger reduction in the mean symptom score in Part A compared to placebo-treated patients. In Part B, mean symptom scores increased more in patients withdrawn to placebo compared to patients who remained on ARCALYST.

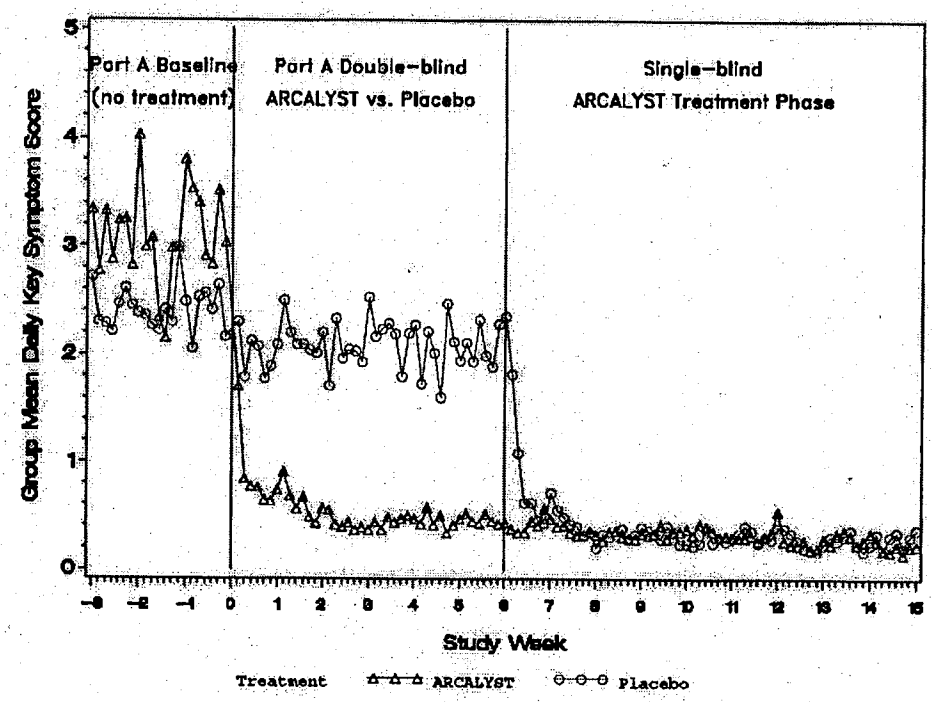
Table 2: Mean Symptom Scores

Part A	Placebo (n=24)	ARCALYST (n=23)	Part B	Placebo (n=23)	ARCALYST (n=22)
Pre-treatment Baseline Period (Weeks -3 to 0)	2.4	3.1	Active ARCALYST 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
LS* Mean Change from Baseline to Endpoint	-0.5	-2.4	LS* Mean Change from Baseline to Endpoint	0.9	0.1
95% confidence interval for difference between treatment groups	(-2.4, -1.3)**		95% confidence interval for difference between treatment groups	(-1.3, -0.4)**	

*Differences are adjusted using an analysis of covariance model with terms for treatment and Part A baseline.
** A confidence interval lying entirely below zero indicates a statistical difference favoring ARCALYST versus placebo.

Daily mean symptom scores over time for Part A are shown in Figure 1.

Figure 1: Group Mean Daily Symptom Scores by Treatment Group in Part A and Single-blind ARCALYST Treatment Phase from Week -3 to Week 15



Improvement in symptom scores was noted within several days of initiation of ARCALYST therapy in most patients.

In Part A, patients treated with ARCALYST experienced more improvement in each of the five components of the composite endpoint (joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue) than placebo-treated patients.

In Part A, a higher proportion of patients in the ARCALYST 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%) compared to the placebo group.

Serum Amyloid A (SAA) and C-Reactive Protein (CRP) levels are acute phase reactants that are typically elevated in patients with CAPS with active disease. During Part A, mean levels of CRP decreased versus baseline for the ARCALYST treated patients, while there was no change for those on placebo (Table 3). ARCALYST also led to a decrease in SAA versus baseline to levels within the normal range.

Table 3. Mean Serum Amyloid A and C-Reactive Protein Levels Over Time in Part A

Part A	ARCALYST	Placebo
SAA (normal range: 0.7 – 6.4 mg/L)	(n=22)	(n=24)
Pre-treatment Baseline	60	110
Week 6	4	110
CRP (normal range: 0.0 – 8.4 mg/L)	(n= 21)	(n=24)
Pre-treatment Baseline	22	30
Week 6	2	28

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

16 HOW SUPPLIED/ STORAGE AND HANDLING

Each 20-mL glass vial of ARCALYST contains a sterile, white to off-white, preservative-free, lyophilized powder. ARCALYST is supplied in a carton containing four vials.

The lyophilized ARCALYST product is to be stored refrigerated at 2 to 8 °C (36° to 46°F) inside the original carton to protect from light. Do not use beyond the date stamped on the label. After reconstitution, ARCALYST may be kept at room temperature, should be kept from light, and

should be used within three hours of reconstitution. ARCALYST does not contain preservatives; therefore, unused portions of ARCALYST should be discarded. Discard the vial after a single withdrawal of drug.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

The first injection of ARCALYST should be performed under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer ARCALYST, he/she should be instructed on aseptic reconstitution of the lyophilized product and injection technique. The ability to inject subcutaneously should be assessed to ensure proper administration of ARCALYST, including rotation of injection sites. (*See Patient Information Leaflet for ARCALYST™*). Arcalyst should be reconstituted with preservative-free Sterile Water for Injection to be provided by the pharmacy. A puncture-resistant container for disposal of vials, needles and syringes should be used. Patients or caregivers should be instructed in proper vial, syringe, and needle disposal, and should be cautioned against reuse of these items.

Injection-site Reactions: Physicians should explain to patients that almost half of the patients in the clinical trials experienced a reaction at the injection site. Injection-site reactions may include pain, erythema, swelling, pruritis, bruising, mass, inflammation, dermatitis, edema, urticaria, vesicles, warmth, and hemorrhage. Patients should be cautioned to avoid injecting into an area that is already swollen or red. Any persistent reaction should be brought to the attention of the prescribing physician.

Infections: Patients should be cautioned that ARCALYST has been associated with serious, life-threatening infections, and not to initiate treatment with ARCALYST if they have a chronic or active infection. Patients should be counseled to contact their healthcare professional immediately if they develop an infection after starting ARCALYST. Treatment with ARCALYST should be discontinued if a patient develops a serious infection. Patients should be counseled not to take any IL-1 blocking drug, including ARCALYST, if they are also taking a drug that blocks TNF such as etanercept, infliximab, or adalimumab. Use of ARCALYST with other IL-1 blocking agents, such as anakinra, is not recommended.

Vaccinations: Prior to initiation of therapy with ARCALYST physicians should review with adult and pediatric patients their vaccination history relative to current medical guidelines for vaccine use, including taking into account the potential of increased risk of infection during treatment with ARCALYST.

REGENERON

Manufactured and distributed by:
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U.S. License Number XXXX

3XXXXXX – v1.0
Regeneron U.S. Patent 6,927,044 B2, 6,472,179 B2, 5,844,099 and other pending patents

Patient Information

ARCALYST™ (ARK-a-list)

(rilonacept)

Injection for Subcutaneous Use

Read the patient information that comes with ARCALYST before you start taking it and each time you refill your prescription. There may be new information. The information in this leaflet does not take the place of talking with your healthcare provider about your medical condition and your treatment.

What is the most important information I should know about ARCALYST?

ARCALYST can affect your immune system. ARCALYST can lower the ability of your immune system to fight infections. Serious infections, including life-threatening infections and death have happened in patients taking ARCALYST. **Taking ARCALYST can make you more likely to get infections, including life-threatening serious infections, or may make any infection that you have worse.**

You should not begin treatment with ARCALYST if you have an infection or have infections that keep coming back (chronic infection).

After starting ARCALYST, if you get an infection, any sign of an infection including a fever, cough, flu-like symptoms, or have any open sores on your body, call your healthcare provider right away. **Treatment with ARCALYST should be stopped if you develop a serious infection.**

You should not take medicines that block Tumor Necrosis Factor (TNF), such as ENBREL® (etanercept), Humira ® (adalimumab), or Remicade® (infliximab), while you are taking ARCALYST. You should also not take other medicines that block Interleukin -1 (IL-1), such as Kineret® (anakinra), while taking ARCALYST. Taking ARCALYST with any of these medicines may increase your risk of getting a serious infection.

Before starting treatment with ARCALYST, tell your healthcare provider if you:

- think you have an infection
- are being treated for an infection
- have signs of an infection, such as fever, cough, or flu-like symptoms
- have any open sores on your body
- have a history of infections that keep coming back
- have asthma. Patients with asthma may have an increased risk of infection.
- have diabetes or an immune system problem. People with these conditions have a higher chance for infections.
- have tuberculosis (TB), or if you have been in close contact with someone who has had tuberculosis.
- have or have had HIV, Hepatitis B, or Hepatitis C

- take other medicines that affect your immune system

Before you begin treatment with ARCALYST, talk with your healthcare provider about your vaccination history. Ask your healthcare provider whether you should receive any vaccinations, including pneumonia vaccine and flu vaccine, before you begin treatment with ARCALYST.

What is ARCALYST?

ARCALYST is a prescription medicine called an interleukin-1 (IL-1) blocker. ARCALYST is used to treat adults and children 12 years and older with Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle Wells Syndrome (MWS). ARCALYST can help lessen the signs and symptoms of CAPS, such as rash, joint pain, fever, and tiredness, but it can also lead to serious side effects because of the effects on your immune system.

What should I tell my healthcare provider before taking ARCALYST?

ARCALYST may not be right for you. **Before taking ARCALYST, tell your healthcare provider about all of your medical conditions, including if you:**

- are scheduled to receive any vaccines. You should not receive live vaccines if you take ARCALYST.
- are pregnant or planning to become pregnant. It is not known if ARCALYST will harm your unborn child. Tell your healthcare provider right away if you become pregnant while taking ARCALYST.
- are breast-feeding or planning to breast-feed. It is not known if ARCALYST passes into your breast milk.

See "What is the most important information I should know about ARCALYST?"

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take other medicines that affect your immune system, such as:

- other medicines that block IL-1, such as Kineret® (anakinra).
- medicines that block Tumor Necrosis Factor (TNF), such as ENBREL® (etanercept), Humira® (adalimumab), or Remicade® (infliximab).
- corticosteroids.

See "What is the most important information I should know about ARCALYST?"

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist every time you get a new prescription.

If you are not sure or have any questions about any of this information, ask your healthcare provider.

How should I take ARCALYST?

See the "Patient Instructions for Use" at the end of this leaflet.

- Take ARCALYST exactly as prescribed by your healthcare provider.
- ARCALYST is given by injection under the skin (subcutaneous injection) one time each week.
- Your healthcare provider will tell and show you or your caregiver:
  - how much ARCALYST to inject
  - how to prepare your dose
  - how to give the injection
- Do not try to give ARCALYST injections until you are sure that you or your caregiver understands how to prepare and inject your dose. Call your healthcare provider or pharmacist if you have any questions about preparing and injecting your dose, or if you or your caregiver would like more training.
- If you miss a dose of ARCALYST, inject it as soon as you remember, up to the day before your next scheduled dose. The next dose should be taken at the next regularly scheduled time. If you have any questions, contact your healthcare provider.
- If you accidentally take more ARCALYST than prescribed, call your healthcare provider.

What are the possible side effects of ARCALYST?

Serious side effects may occur while you are taking and after you finish taking ARCALYST including:

- **Serious Infections. See "What is the most important information I should know about taking ARCALYST?"** Treatment with ARCALYST should be discontinued if you develop a serious infection.
- **Allergic Reaction.** Call your healthcare provider or seek emergency care right away if you get any of the following symptoms of an allergic reaction while taking ARCALYST:
  - rash
  - swollen face
  - trouble breathing

Common side effects with ARCALYST include:

- **Injection-site reaction.** This includes: pain, redness, swelling, itching, bruising, lumps, inflammation, skin rash, blisters, warmth, and bleeding at the injection site.
- **Upper respiratory infection.**
- **Changes in your blood cholesterol and triglycerides (lipids).** Your healthcare provider will check you for this.

These are not all the possible side effects of ARCALYST. Tell your healthcare provider about any side effects that bother you or that do not go away. For more information ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ARCALYST?

- Keep ARCALYST in the carton it comes in.
- Store ARCALYST in a refrigerator between 36°F to 46°F (2°C to 8°C). Call your pharmacy if you have any questions.
- Always keep ARCALYST away from light.
- Refrigerated ARCALYST can be used until the expiration date printed on the vial and carton.
- ARCALYST may be kept at room temperature after mixing. ARCALYST should be used within **three hours** of mixing. Keep ARCALYST away from light.
- If you need to take ARCALYST with you when traveling, store the carton in a cool carrier with a cold pack and protect it from light.

Keep ARCALYST, injection supplies, and all other medicines out of reach of children.

What are the ingredients in ARCALYST?

Active ingredient: rilonacept.

Inactive ingredients: histidine, arginine, polyethylene glycol 3350, sucrose, and glycine.

General Information about ARCALYST

Medicines are sometimes prescribed for conditions other than those listed in patient information leaflets. Do not use ARCALYST for a condition for which it was not prescribed. Do not give ARCALYST to other people even if they have the same condition. It may harm them.

This leaflet summarizes the most important information about ARCALYST. If you would like more information, speak with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ARCALYST that was written for healthcare professionals. For more information about ARCALYST, call 1-877-REGN-777 (1-877-734-6777), or visit www.ARCALYST.com.

Patient Instructions for Use

It is important for you to read, understand and follow the instructions below exactly. Following the instructions correctly will help to make sure that you use prepare and inject the medicine the right way to prevent infection.

How do I prepare and give an injection of ARCALYST?

STEP 1: Setting up for an injection

1. Choose a table or other flat surface area to set up the supplies for your injection. Be sure that the area is clean or clean it with an antiseptic or soap and water first.
2. Wash your hands well with soap and water, and dry with a clean towel.
3. Put the following items on a table, or other flat surface, for each injection (see Figure 1):

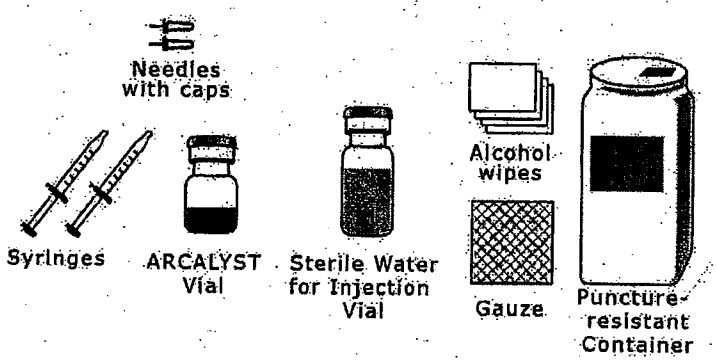

Figure 1

- 2 sterile, 3-milliliter (mL) disposable syringes with markings at each 0.1 mL (see Figure 2):
  - one needed for mixing (reconstitution) ARCALYST
  - one needed for injection

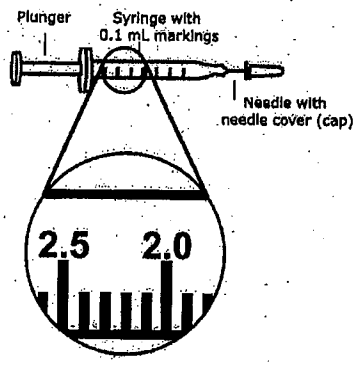

Figure 2

- 2 sterile disposable needles (27 gauge ½ inches)
  - one needed for mixing
  - one needed for injection
- 4 alcohol wipes
- 1 2x2 gauze pad
- 1 vial of ARCALYST (powder in vial)
- 1 vial of preservative-free Sterile Water for Injection
- 1 puncture-resistant container for disposal of used needles , syringes, and vials

Note:

- Do not use Sterile Water for Injection, syringes or needles other than those provided by your pharmacy. Contact your pharmacy if you need replacement syringes or needles.
- Do not to touch the needles or the rubber stoppers on the vials with your hands. If you do touch a 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 Vials

1. Check the expiration date on the carton of ARCALYST. Do not use the vial if the expiration date has passed. Contact your pharmacy for assistance.
2. Check the expiration date on the vial of Sterile Water for Injection. Do not use the vial if the expiration date has passed. Contact your pharmacy for assistance.
3. Remove the protective plastic cap from both vials.

4. Clean the top of each vial with an alcohol wipe. Use one wipe for each vial and wipe in one direction around the top of the vial (see Figure 3).

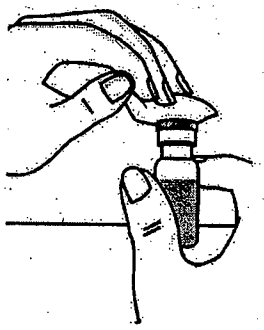

Figure 3

5. Open the wrapper that contains the 27-gauge needle by pulling apart the tabs and set it aside for later use. Do not remove the needle cover. This needle will be used to mix the water with powder. Open the wrapper that contains the syringe by pulling apart the tabs. Hold the barrel of the syringe with one hand and twist the 27-gauge needle onto the tip of the syringe until it fits snugly with the other hand (see Figure 4).

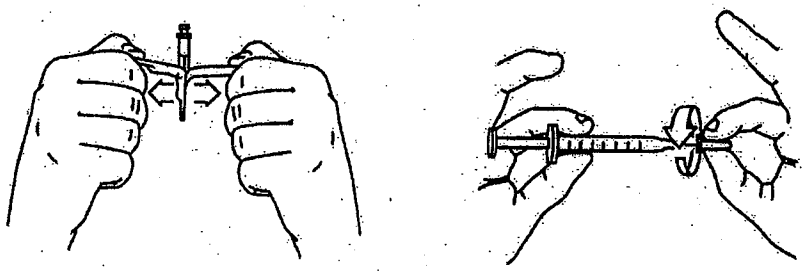

Figure 4

6. Hold the syringe at eye level. With the needle covered pull back the plunger to the 2.3 mL mark, filling the syringe with air (see Figure 5).

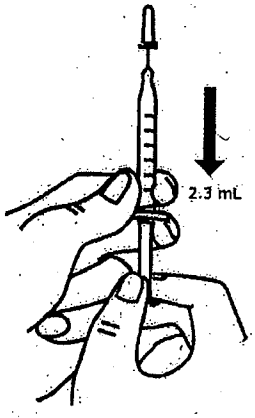

Figure 5

7. Hold the syringe in one hand, use the other hand to pull the needle cover straight off. Do not twist the needle as you pull off the cover. Place the needle cover aside. Hold the syringe in the hand that you will use to mix (reconstitute) your medicine. Hold the Sterile Water vial on a firm surface with your other hand. Slowly insert the needle straight through the rubber stopper. Do not bend the needle. Push the plunger in all the way to push the air into the vial (see Figure 6).

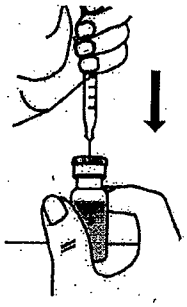

Figure 6

8. 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.
9. Make sure the tip of the needle is covered by the liquid and slowly pull back on the plunger to the 2.3 mL mark to withdraw the Sterile Water from the vial (see Figure 7).

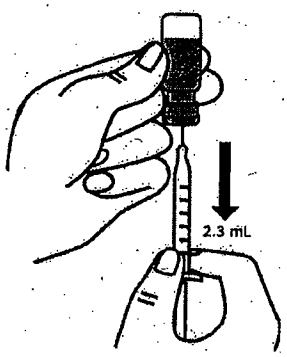

Figure 7

10. Keep the vial upside down and tap or flick the syringe with your fingers until any air bubbles rise to the top of the syringe.
11. To remove the air bubbles, gently push in the plunger so only the air is pushed out of the syringe and back into the bottle.

12. After removing the bubbles, check the syringe to be sure that the right amount of Sterile Water has been drawn into the syringe (see Figure 8).

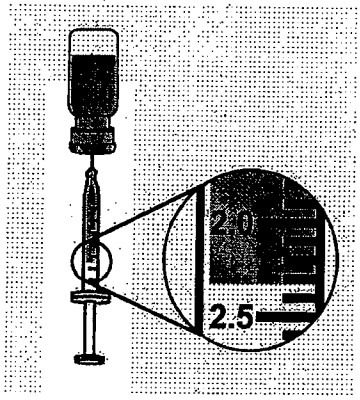

Figure 8

13. Carefully remove the syringe with needle from the Sterile Water vial. Do not touch the needle.

STEP 3: Mixing (Reconstituting) ARCALYST

1. With one hand, hold the ARCALYST vial on a firm surface.
2. With the other hand, take the syringe with the Sterile Water and the same needle, and slowly insert the needle straight down through the rubber stopper of the ARCALYST vial. Push the plunger in all the way to inject the Sterile Water into the vial.
3. Direct the water stream to gently go down the side of the vial into the powder (see Figure 9).

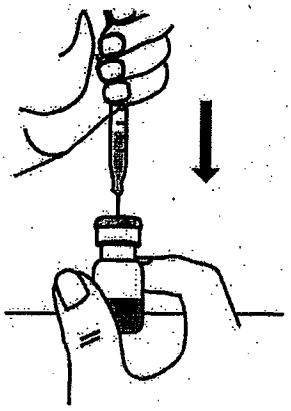

Figure 9

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

5. Hold the vial containing the ARCALYST and sterile water for injection 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 (see Figure 10).

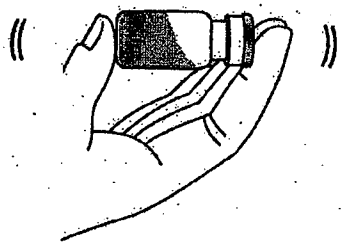

Figure 10

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 mixed ARCALYST should be thick, clear, and colorless to pale yellow. Do not use the mixed liquid if it is discolored or cloudy, or if small particles are in it (see Figure 11).

    NOTE: Contact your pharmacy to report any mixed ARCALYST that is discolored or contains particles.

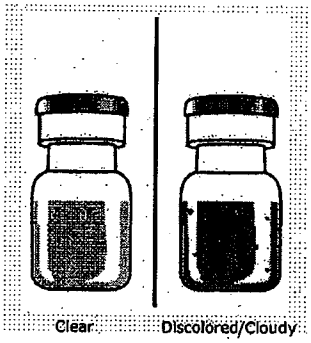

Figure 11

11. ARCALYST may be kept at room temperature after mixing. ARCALYST should be used within **three hours** of mixing. Keep ARCALYST away from light.

STEP 4: Preparing the injection

1. Hold the ARCALYST vial on a firm surface and wipe the top of the ARCALYST vial with a new alcohol wipe (see Figure 12).

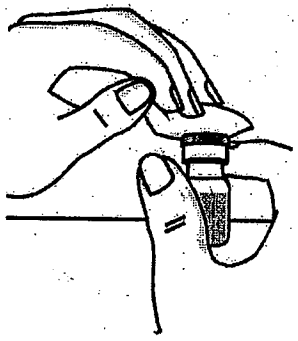

Figure 12

2. Take a new sterile, disposable needle and attach securely to a new syringe without removing the needle cover (see Figure 13).

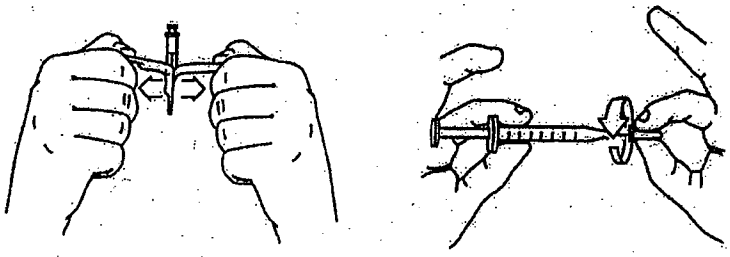

Figure 13

3. The amount of air you draw into the syringe should equal the amount of mixed ARCALYST that your healthcare provider 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 amount of mixed ARCALYST that your healthcare provider has prescribed for you to inject (see Figure 14).

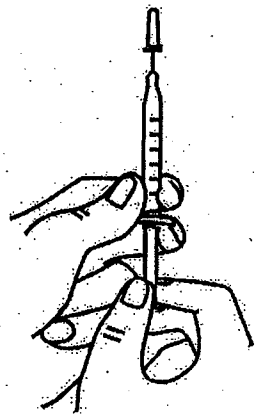

Figure 14

5. Remove the needle cover and be careful not to touch the needle. Keep the ARCALYST 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 15).

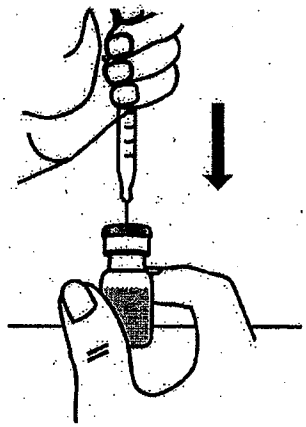

Figure 15

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 healthcare provider (see Figure 16).

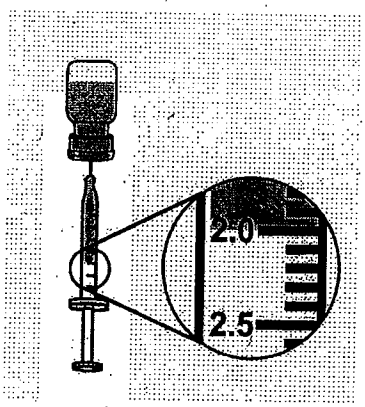

Figure 16

NOTE: The maximum adult dose of ARCALYST is 2 mL.

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 17).

   It is important to remove air bubbles so that you withdraw up the right amount of medicine from the vial.

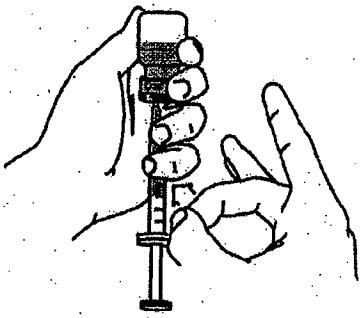

Figure 17

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 healthcare provider in the syringe.

11. Throw away the ARCALYST vial in the puncture resistant container even if there is any medicine left in the vial (see Figure 18). Do not use any vial of ARCALYST more than one time.

Figure 18

STEP 5: 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 completely absorbed. Ask your healthcare provider 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 healthcare provider 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 19):

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

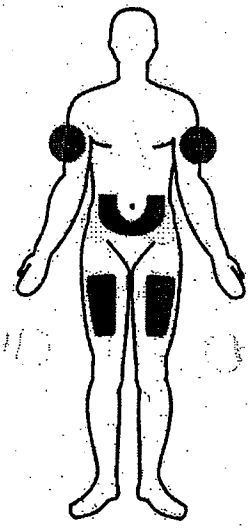

Figure 19

2. Choose the area for the injection. Clean the area in a circular motion with a new alcohol wipe. Begin at the center of the site and move outward. Let the alcohol air dry completely.
3. Take the cover off the needle and be careful not to touch the needle.
4. Hold the syringe in one hand like you would hold a pencil.
5. With the other hand gently pinch a fold of skin at the cleaned site for injection (see Figure 20).

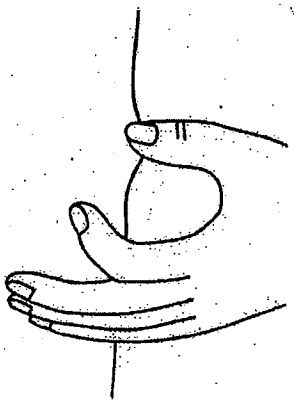

Figure 20

6. Use a quick "dart like" motion to insert the needle straight into the skin (90 degree angle) (see Figure 20). 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 degree angle (see Figure 21).

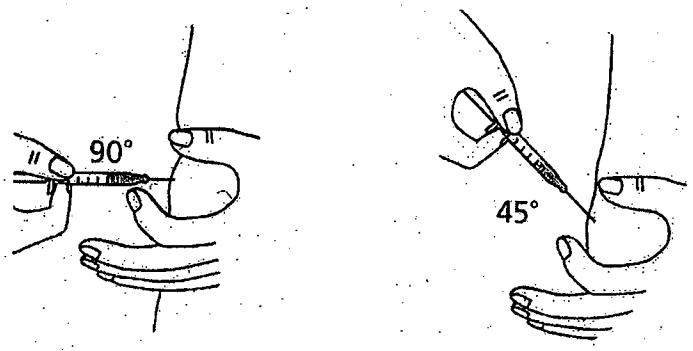

Figure 21

7. After the needle is completely in the skin, let go of the skin that you are pinching.
8. 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 (syringes, needles, vials, alcohol swabs and gauze pad).
9. If no blood appears, inject all the medicine n 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.
10. Pull the needle out of the skin, and hold a piece of sterile gauze over the injection site for several seconds (see Figure 22).

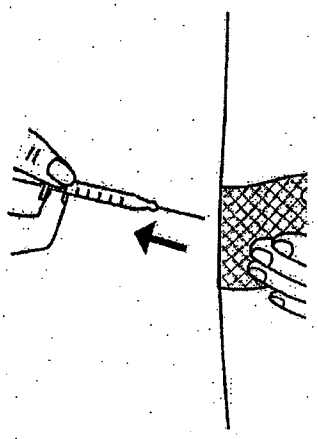

Figure 22

11. Do not replace the needle cover. Throw away the vials, used syringes and needles in the puncture-resistant container (see Figure 23). Do not recycle the container. DO NOT throw away vials, needles, or syringes in the household trash or recycle.

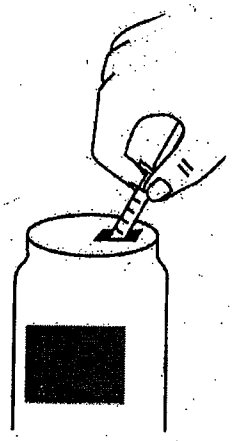

Figure 23

12. 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 healthcare provider. Follow any special state or local laws about the right way to throw away needles and syringes.
13. Used alcohol wipes can be thrown away in the household trash.

Contact your healthcare provider right away with any questions or concerns about ARCALYST.

Issued Month Year

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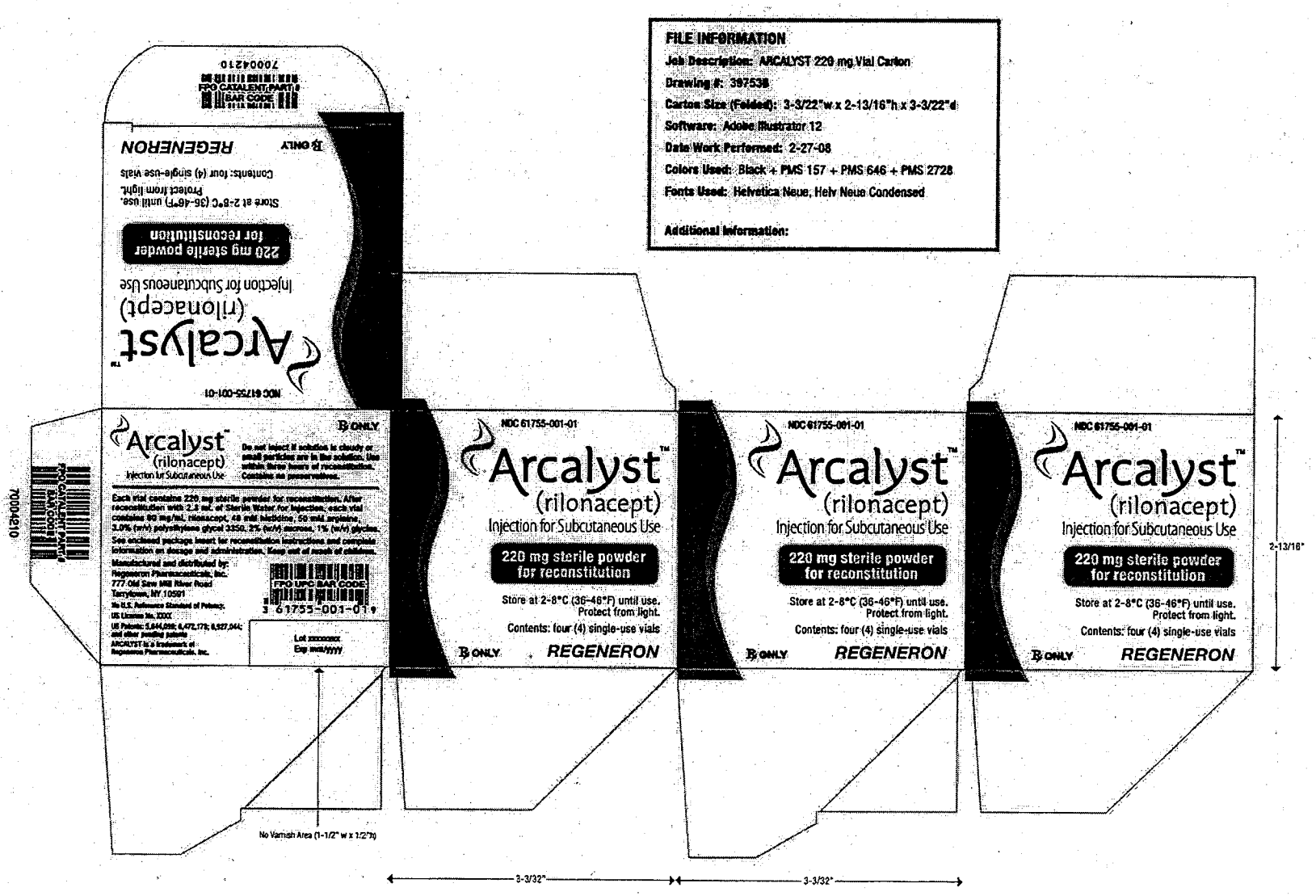
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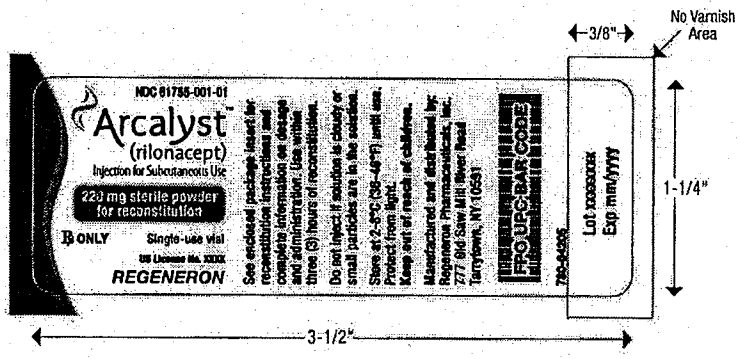
Carton Size (Folded): 3-3/22"w x 2-13/16"h x 3-3/22"d
Software: Adobe Illustrator 12
Date Work Performed: 2-27-08
Colors Used: Black + PMS 157 + PMS 646 + PMS 2728
Fonts Used: Helvetica Neue, Helv Neue Condensed
Additional Information:
NDC 61755-001-01
Arcalyst™
(rilonacept)
Injection for Subcutaneous Use
220 mg sterile powder for reconstitution
Store at 2-8°C (36-46°F) until use.
Protect from light.
Contents: four (4) single-use vials
℞ ONLY
REGENERON
No Varnish Area (1-1/2" w x 1/2"h)
2-13/16"
3-3/32"
3-3/32"



FILE INFORMATION

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Drawing #: Not Available

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Additional Information: